New insights in the enigma of nociception and pain assessment.

An evaluation of integrated paincare pathways, digital opportunities and nociceptive reflex testing.

Dissertation submitted for the degree of doctor of Medical Sciences
at the University of Antwerp to be defended by

Davina Wildemeersch

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Faculty of Medicine and Health Science
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Nieuwe inzichten in het beoordelen van nociceptie en pijn.
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Summary

Pain is a complex medical problem. Acute pain is typically initiated through a noxious stimulus, which causes the activation of specialized somatic or visceral nociceptors and transmission of nociceptive signals to the brain through spinal pathways. As pain persists, however, the underlying pathology may evolve to a chronic disease, amplifying the response to pain, decreasing treatment success, and often leading to sensitization.

The negative physiologic and psychological consequences of unrelieved pain are significant and can be long-lasting with severe consequences on overall well-being. The stress response induced by pain may include increased heart and breathing rates affecting the increasing demand for oxygen and other nutrients to vital organs. A prolonged stress state can result in detrimental multisystem effects such as stiffness, loss of muscle and joint flexibility, sleeping difficulties, anxiety, and depression. Pain adversely affects the health-related quality of life and well-being, both in the short and long term. According to the US Centers for Disease Control and Prevention, prevalence rates of chronic pain vary between 11% and 40%. A systematic review comprising studies done in the UK reported a pooled chronic pain prevalence rate of 43.5%, with the rate of moderate-to-severe disabling pain ranging from 10.4% to 14.3%. The Global Burden of Disease Study 2019 reaffirmed that the high prominence of pain and pain-related diseases is still the leading cause of disability and disease burden globally [Lancet 2020 data 1990-2019]. This includes especially lower back pain and headache besides other musculoskeletal disorders but also underlines biopsychosocial predispositions (such as depression, anxiety, and opioid use disorders) for the development of other types of chronic pain including persistent postsurgical pain (PPSP).

Improved pain measurements, especially in non-communicative patients, may be an important step in the prevention and early treatment of this debilitating disease. During the past decade many new, more objective pain assessment tools have been developed, driven by increased awareness of suboptimal pain assessment. However, these novel tools often lack proper validation for clinical use. Furthermore, daily routine use is usually rather complex. In addition, early identification of patients at risk of developing chronic (postsurgical) pain and including them in a patient-centric holistic perioperative care pathway, including physical and psychological functioning evaluation as well as patient satisfaction and wellbeing assessment, are essential for the prevention and treatment of chronic pain.

This dissertation describes the development, implementation, and re-evaluation of transmural perioperative care pathways for individuals at risk for pain chronification, and how these can contribute to improved pain care. Furthermore, two objective nociceptive reflex assessment tools were validated during surgery and intensive care treatment, aiming to optimize nociceptive assessment. These two assessments embrace the greater goal of persistent pain prevention and optimal procedure-related pain treatment using a biopsychosocial approach.

For monitoring nociception and pain in analgosedated patients, the novel pupillometric index (PPI) was designed to assess the level of intraoperative analgesia. We were among the first to evaluate the pupil dilation reflex (PDR) using a PPI protocol during routine surgical procedures in 2018 (chapter 3.1).[1] After opioid administration, propofol-sedated patients needed a higher stimulation intensity to obtain a pupillary reflex in response to the standardized automated nociceptive stimulus. Consequently, PPI score showed a reduction after opioid analgetic treatment. Moreover, the

elicitation of PDR by this low-intensity standardized noxious stimulation protocol was performed without changes in vital signs before and after opioid administration in adults under propofol-based general anesthesia (chapter 3.2). In addition, in children under general anesthesia, PPI assessments appeared to be feasible (chapter 3.3).[2] Subsequently, PPI was further evaluated during surgical procedures under general anesthesia using sufentanil (chapter 3.4)[3] and remifentanil (chapter 3.5)[ahead of print]. Both studies showed no additional value of an opioid administration protocol depending on PPI monitoring results in outpatient surgery. In sedated critically ill patients, PDR and nociception flexion reflex (NFR) are identified as non-invasive and well-tolerated monitoring tools (chapter 4.1).[4] However, results regarding the shift from NFR threshold monitoring in a perioperative setting to the mechanically ventilated, analgosedated critically ill remains unclear.

Furthermore, we focused on the design and implementation of holistic pain care for patients undergoing elective surgery. In our preliminary evaluation of a web-based psychological screening tool in adolescents undergoing minimally invasive pectus surgery (chapter 5.1)[5], we showed that perioperative online screening of psychological symptoms and trait characteristics could further inventorize patients at risk for prolonged pain conditions. Moreover, we showed that allocating patients to the appropriate level of care preoperatively and immediately after surgery may improve long-term outcome variables (chapter 5.2).[6] Internet-based technologies and feasible, objective monitoring tools can help clinicians screen surgical patients for risk factors and initiate early treatment if necessary (chapters 5.1 and 5.2).[5,6]

One of the major difficulties of integrated nociceptive evaluation in the analgosedated patient, in general, is that many devices are characterized by a laborious and often time-consuming set-up, making the translation from the clinical lab to daily practice cumbersome or even impossible. Nevertheless, they might have the potential to further improve individual pharmacological treatment and outcome measurements as intraoperative nociception monitoring guidance may reduce intraoperative opioid administration and therefore might be a viable strategy to titrate opioids intraoperatively.[7] However, to date, there is a paucity of evidence regarding the impact of opioid minimization or total avoidance on long-term analgetic use and outcomes (chronic pain, functionality, wellbeing). Up to now, despite advances in nociception monitoring technology and availability in recent years, their limitations override their benefits in routine anesthesia care. Future research should focus on defining how the balance between nociception and analgesia may affect patient-related outcome measurements (PROMs), and consequently, identify a critical balance where we positively or negatively affect patient outcomes. Consecutively, timing, frequency, and amount of analgetic titration and its impact on patients' recovery can be evaluated. Additionally, when focusing on our patients' recovery, postoperative rehabilitation, and well-being should play a more central role as primary outcome parameters taking the entire biopsychosocial package into account, in contrast to solely focusing on nociceptive monitoring, which appears up to now to be just a drop in the ocean.

When embracing the knowledge and know-how to design, implement and evaluate novel pain care pathways in real-world situations, interdisciplinary teams providing biopsychosocial care will better understand and combat the burden of chronic pain.

Samenvatting

Pijn is een complex medisch probleem. Acute pijn wordt meestal geïnitieerd door een schadelijke prikkel, die de activering van gespecialiseerde somatische of viscerale nociceptoren en nadien via spinale paden de hersenen bereikt. Naarmate de pijn echter aanhoudt, kunnen de pijnklachten evolueren naar een chronische ziekte, waardoor de reactie op pijn verder wordt versterkt. Het behandelsucces neemt verder af en vaak ontstaat sensitisatie.

De negatieve fysiologische en psychologische gevolgen van pijn zijn aanzienlijk en kunnen langdurig zijn, met ernstige gevolgen voor het algehele welzijn. De stressreactie die door pijn wordt veroorzaakt, kan een verhoogde hart- en ademhalingssnelheid omvatten die de toenemende vraag naar zuurstof en andere voedingsstoffen voor vitale organen beïnvloedt. Een langdurige stresstoestand kan leiden tot nadelige multisysteemeffecten zoals stijfheid, verlies van spier- en gewrichtsflexibiliteit, slaapproblemen, angst en depressie. Pijn heeft een negatieve invloed op de gezondheidsgerelateerde kwaliteit van leven en welzijn, zowel op korte als op lange termijn. Volgens het Amerikaanse Center of Disease Controle and Prevention variëren de prevalentiecijfers van chronische pijn tussen 11% en 40%. Een systematische review bestaande uit studies uitgevoerd in het VK rapporteerde een gepoolde prevalentie van chronische pijn van 43,5%, met een percentage van matige tot ernstige invaliderende pijn variërend van 10,4% tot 14,3%. In 2019, bevestigde de Global Burden of Disease Study opnieuw dat de grote aanwezigheid van pijn en pijngerelateerde ziekten wereldwijd nog steeds de belangrijkste oorzaak is van invaliditeit en ziektelast [Lancet 2020 data 1990-2019]. Dit omvat met name lage rugpijn en hoofdpijn naast andere musculoskeletale aandoeningen, maar onderstreept ook biopsychosociale predisposities (zoals depressie, angst en opioïdengebruik) voor de ontwikkeling van andere soorten chronische pijn, waaronder aanhoudende postoperatieve pijn (PPSP).

Verbeterde pijnmetingen, vooral bij niet-communicatieve patiënten, kunnen een belangrijke stap zijn in de preventie en vroege behandeling van deze slopende ziekte. In de afgelopen tien jaar zijn er veel nieuwe, meer objectieve instrumenten voor pijnbeoordeling ontwikkeld, gedreven door een groter bewustzijn voor suboptimale pijnbeoordeling. Deze nieuwe tools missen echter vaak de juiste validatie voor klinisch gebruik. Bovendien is het dagelijks routinematig gebruik meestal nogal complex. Essentieel voor de preventie en behandeling van chronische pijn, is een vroege identificatie van patiënten die het risico lopen chronische (postoperatieve) pijn te ontwikkelen en hen op te nemen in een patiëntgericht holistisch peri-operatief zorgtraject, dat onder andere evaluatie van fysiek en psychologisch functioneren en beoordeling van patiënttevredenheid en welzijn incorporeerd.

Dit proefschrift beschrijft de ontwikkeling, implementatie en herevaluatie van transmurale perioperatieve zorgtrajecten voor personen die risico lopen op pijnchronificatie, en hoe deze kunnen bijdragen aan verbeterde pijnzorg. Verder werden twee objectieve nociceptieve reflexbeoordelingstools gevalideerd tijdens chirurgie en intensive care-behandeling met als doel de nociceptieve beoordeling te optimaliseren. Deze twee beoordelingen omarmen het grotere doel voor geoptimaliseerde pijnpreventie en proceduregerelateerde pijnbehandeling met behulp van een biopsychosociale benadering.

Voor het monitoren van nociceptie en pijn bij geanalgoseerde patiënten werd de nieuwe pupillometrische index (PPI) ontworpen om het niveau van intraoperatieve analgesie te beoordelen.

Wij waren een van de eersten die de pupilverwijdingsreflex (PDR) evalueerden met behulp van een PPI-protocol tijdens routinematige chirurgische ingrepen in 2018 (hoofdstuk 3.1).[1] Na toediening van opioïden hadden met propofol gesedeerde patiënten een hogere stimulatie-intensiteit nodig om een pupilreflex op te wekken als reactie op de gestandaardiseerde geautomatiseerde nociceptieve stimulus. Bijgevolg vertoonde de PPI-score een verlaging na behandeling met opioïde analgetica. Bovendien werd de opwekking van PDR door dit gestandaardiseerde stimulatieprotocol met lage intensiteit uitgevoerd zonder veranderingen in vitale parameters voor en na toediening van opioïden bij volwassenen onder algemene anesthesie op basis van propofol (hoofdstuk 3.2). Daarnaast bleken bij kinderen onder algehele narcose PPI-beoordelingen haalbaar (hoofdstuk 3.3).[2] Vervolgens werd tijdens chirurgische ingrepen onder algehele narcose de PPI verder geëvalueerd met het gebruik van sufentanil (hoofdstuk 3.4)[3] en remifentanil (hoofdstuk 3.5) [ahead of print]. Beide onderzoeken toonden geen toegevoegde waarde aan van een pupil reflex gebaseerd analgetisch protocol bij poliklinische chirurgie. Aanvullend onderzoek bij gesedeerde ernstig zieke patiënten, werden PDR en nociceptieve flexie reflex (NFR) metingen geïdentificeerd als niet-invasieve en goed verdragen monitoringinstrumenten (hoofdstuk 4.1).[4] De resultaten met betrekking tot de verschuiving van NFR-drempelmetingen in een perioperatieve setting naar de mechanisch beademde kritisch zieke blijven echter onduidelijk.

Verder hebben we ons gericht op het ontwikkelen en implementeren van holistische pijnzorg voor patiënten die een electieve operatie ondergaan. In onze evaluatie van een webgebaseerd psychologisch screeningsinstrument bij adolescenten die minimaal invasieve pectuschirurgie ondergaan (hoofdstuk 5.1),[5] hebben we aangetoond dat perioperatieve online screening van psychologische voorbeschiktheden mogelijk is. Bovendien hebben we aangetoond dat het preoperatief en direct na de operatie toewijzen van patiënten aan het juiste niveau van zorg de uitkomstvariabelen op de lange termijn kan verbeteren (hoofdstuk 5.2).[6] Op eHealth gebaseerde technologieën en haalbare, objectieve monitoringtools kunnen zorgverleners helpen om chirurgische patiënten te screenen op risicofactoren en zo nodig een vroegtijdige behandeling te starten (hoofdstukken 5.1 en 5.2).[5,6]

Een van de grootste moeilijkheden van geïntegreerde nociceptieve evaluatie bij de geanalgoseerde patiënt is dat vele apparaten worden gekenmerkt door een moeizame en vaak tijdrovend opzet, waardoor de vertaling van het klinische lab en onderzoekssetting naar de dagelijkse praktijk omslachtig of zelfs onmogelijk wordt. Desalniettemin hebben ze mogelijk het potentieel om de individuele farmacologische behandeling en zorguitkomsten verder te verbeteren, aangezien een geoptimaliseerde intraoperatieve nociceptiemonitoring de potentie heeft de intraoperatieve opioïdentoediening te verminderen en dus een toekomststrategie zou kunnen zijn om opioïden intraoperatief te titreren.[7] Tot op heden is er echter een gebrek aan wetenschappelijk bewijs met betrekking tot de impact van opioïdenminimalisatie of totale vermijding op het langdurig analgetisch gebruik en de levenskwaliteit (chronische pijn, functionaliteit, welzijn). Tot nu toe hebben hun beperkingen, ondanks de technologische vooruitgang in het evalueren van nociceptie en de beschikbaarheid van de toestellen in de afgelopen jaren, voorrang op hun voordelen in de routinematige anesthesiologische zorg. Toekomstig onderzoek moet zich richten op het definiëren van hoe de balans tussen nociceptie en analgesie patiëntgerelateerde uitkomstmetingen (PROM's) zou kunnen beïnvloeden. Het is pas als er een kritische balans identificeerd kan worden dat onderzoek zich kan richten op hoe, wat, waar en wanneer we de patiëntuitkomsten positief of negatief beïnvloeden. Achtereenvolgens kunnen timing, frequentie en hoeveelheid van analgetische

titratie en de impact ervan op het herstel van de patiënt worden geëvalueerd. Bovendien zouden, wanneer we ons richten op het herstel van onze patiënten, de postoperatieve revalidatie en het welzijn een meer centrale rol moeten spelen als primaire uitkomstparameter, rekening houdend met het gehele biopsychosociale pakket, in tegenstelling tot de uitsluitende focus op nociceptieve monitoring, dat tot op heden enkel een druppel op een hete plaat blijkt te zijn.

Door de kennis en knowhow te omarmen voor het ontwikkelen, implementeren en evalueren van nieuwe pijnzorgpaden in reële situaties, zullen interdisciplinaire teams die biopsychosociale zorg bieden, chronische pijn beter begrijpen en uiteindelijk samen bestrijden.

List of abbreviations

APPI	Antwerp Personalized Pain Initiative
BIS	Bispectral index
BP	Blood pressure
BPS	Behavior Pain Scale
CDC	Centers for Disease Control and Prevention
CPOT	Critical Care Observation Tool
CPQ	Coping Pain Questionnaire
CSQ	Coping Strategy Questionnaire
CT	Computed tomography
DALYs	Disability- adjusted life years
EMG	Electromyography
ERP	Enhanced Recovery Program
EW	Edinger-Westphal nucleus
fNIRS	Functional Near-Infrared Spectroscopy
GA	General anesthesia
GABA	γ-Aminobutyric acid
GBD	Global Burden of Disease Study
HADs	Hospital Anxiety and Depression Scale
HR	Heart rate
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
ICU	Intensive care unit
mA	Milli Ampère
MIRP	Minimally invasive repair of pectus
mm	Millimeter
MPI	Multidimensional Pain Inventory
MRI	Magnetic Resonance Imaging
ms	Milli seconds
NFR	Nociception flexion reflex
NMB	Neuromuscular blockade
NoL	Nociceptive Level Index
NRS	Numeric Rating Scale
OR	Operation room
PC	Pectus carinatum
PDR	Pupil dilation reflex
PE	Pectus excavatum
PONV	Postoperative nausea and vomiting
PPI	Pupillary pain index
PPSP	Peristent postsurgical pain
PROMs	Patient Related Outcome Measurements
PTSD	Posttraumatic stress disorder
QoL	Quality of life
RASS	Richmond Agitation Sedation Scale
RR	Respiratory rate
RSES	Rosenberg self-esteem scale
STAI	State-Trait Anxiety Inventory
TBI	Traumatic brain injury
TCA	Target controlled anesthesia
TIVA	Total intravenous anesthesia
USA	United States of America
USD	US dollar
VAS	Visual Analogue Scale

Chapter 1. Introduction

The continuum of pain

According to multiple studies, chronic pain exerts an enormous personal and economic burden, affecting more than 30% of people worldwide.[8] Unlike acute pain as a symptom, which has a clear protective value, persistent or chronic pain is not simply an extension of acute pain but is considered a disease itself, involving distinct mechanisms and inquiring a dedicated medical treatment.[9,10] As such, the management plan for chronic pain is shifting from an often purely medically oriented approach to a holistic, biopsychosocial approach.[11] Furthermore, pain can not only be classified by time in acute or chronic pain but can also be subdivided in three major categories according to the mechanism of origin, all with a distinct impact on assessment and management likewise: nociceptive pain arises from tissue injury, neuropathic pain develops after nerve injury, while nociplastic pain emerges from a sensitized nervous system.[12]

In practice, however, the different types of pain mechanisms within and between patients overlap considerably. Moreover, many mechanisms at play in chronic pain are activated in the very beginning of pain, early after an injury or operation, and some patients may be predisposed or vulnerable to developing chronic pain even after a relatively small acute injury. Therefore, when the understanding of pain mechanisms advances, many experts consider pain as a continuum rather than arbitrary, separate categories.[12,13]

Efforts to capture pain in a concise definition

In 1978, pain was defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".[14] This definition has become accepted globally by healthcare professionals and for many years provided a framework to better understand pain according to a medical point-of-view and with biopsychosocial interest.[15,16] In 2018, with the final publication in 2020, the definition of pain was adapted based on current evidence-based knowledge (Table 1).[17]

The revised definition underlines more than ever the multidimensional aspects of pain.[18] It reflects the extended range of pain intensity, quality, and duration for diverse pathophysiologic pain mechanisms and meanings. By describing pain and nociception as two entities, chronic pain can be defined more as a disease in itself.[9] Yet, the International Classification of Diseases (ICD) did not systematically include a comprehensive classification of chronic pain, based on the biopsychosocial definition, until the latest ICD-11 version.[19] Implementation of pain codes, subdividing chronic pain according to localization (such as visceral, musculoskeletal, orofacial, or widespread pain), and pathology (such as pain related to cancer or after surgery or trauma) in the ICD-11, will further lead to improved classification and diagnostic coding, thereby advancing the recognition of chronic pain as a health condition in its own right.[20]

Recognizing pain in its diversity and complexity, the revised IASP definition is valid and guides acute, subacute, and chronic pain complaints (time classification) and for different pain processes, e.g., nociceptive, neuropathic, and nociplastic subtypes (pathophysiological classification).[12,13,17,21] Additionally, the practice and study of pain and its management pose numerous ethical challenges,[22,23] including the need for effective communication to validate pain. The revised definition underlines that verbal description is only one of several ways to express pain, thus preventing the exclusion of minorities where verbal communication is difficult or impossible (e.g., infants, cognitively impaired people or unconscious patients).[24]

Table 1: Definition of pain (2020), according to the International Association for the Study of Pain.

Revised IASP definition of pain (2020). *Raja, S. N., et al. "The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain (2020).*

PAIN

An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.

Notes

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- A person's report of an experience as pain should be respected. *
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

*The Declaration of Montréal, a document developed during the First International Pain Summit on September 3, 2010, states that "Access to pain management is a fundamental human right."

From noxious stimulation and activation of nociceptors to pain sensation

In contrast to pain as a biopsychosocial entity,[17,25,26] nociception is the biological process by which intense stimuli are detected by nociceptors (specialized pain receptors), a subpopulation of peripheral nerve fibers. These stimuli can be thermal, mechanical, or chemical.[27] Nociceptors are excited only when stimulus intensities reach the noxious range, suggesting properties that enable them to detect and respond to potentially injurious stimuli selectively. There are two major classes of nociceptors. The first includes medium-diameter myelinated afferent Aδ- fibers that mediate acute, well-localized "first" or fast pain. These myelinated afferents differ considerably from the larger diameter and rapidly conducting Aβ fibers that respond to innocuous mechanical stimulation (i.e., light touch, non-noxious stimuli). The second class of nociceptor includes small-diameter unmyelinated C-fibers that convey poorly localized, "second" or slow pain. Both these classes of primary afferent nerve fibers (Aδ and C) project to neurons in the dorsal horn of the spinal cord, which is organized in different laminae (see Figure 1.1).

Mainly laminae I, II (outer part of the substantia gelatinosa), V and VI are involved in the reception, processing, and rostral transmission of nociceptive information. Most nociceptive Aδ and C fibers

terminate in superficial laminae I and II, while non-nociceptive information via Aβ fibers terminates in laminae III-VI.

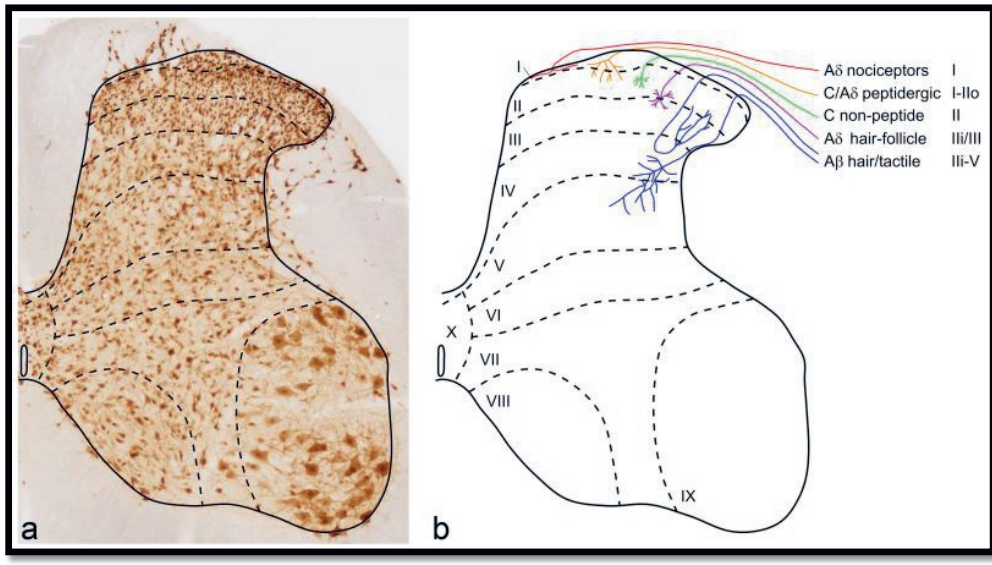


Figure 1.1 Laminar organisation of the dorsal horn and primary afferent inputs. Furthermore, interneurons and sets of projection neurons within the laminae receive convergent input from Aβ and Aδ fibers (adapted from Andrew Todd. Neuronal circuitry for pain processing in the dorsal horn. Nat Rev Neurosci. 2010).[28]

When the dorsal horn neurons of multiple ascending pathways carry the pain message to the supraspinal region, the sensory-discriminative (somatosensory cortex) and emotional (anterior cingulate gyrus and insular cortex) aspects of pain experience arise (see Figure 1.2). Finally, a powerful descending control mechanism influences both positive and negative pain message transmission at the level of the spinal cord.[29]

Recently, the concept of pain under general anesthesia has been questioned because of the absence of attentional modulation or cortical large-scale network integration.[30,31] Furthermore, general anesthetics have a complex, multifaceted effect, and the brain may contain a central pain suppression system.[32]

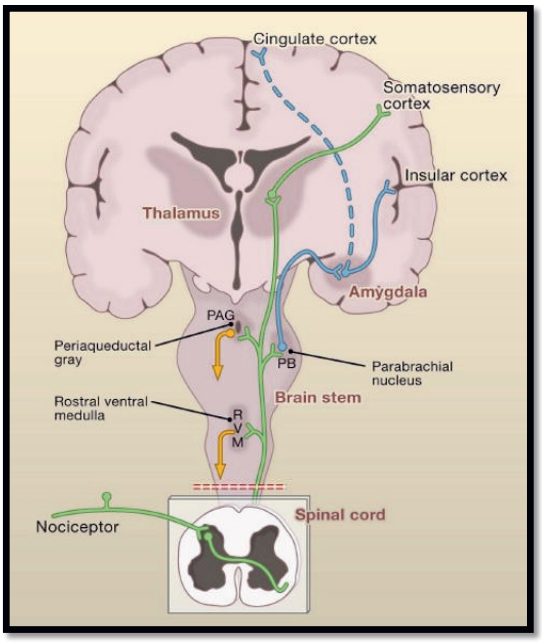


Figure 1.2. Anatomy of the ascending pain pathway. Primary afferent nociceptors convey noxious information via the dorsal horn of the spinal cord up to the somatosensory cortex. This ascending information accesses central neurons (medulla and midbrain), engaging the descending feedback (orange) that further regulates the output from the spinal cord (adapted from Basbaum et al., 2009).[33]

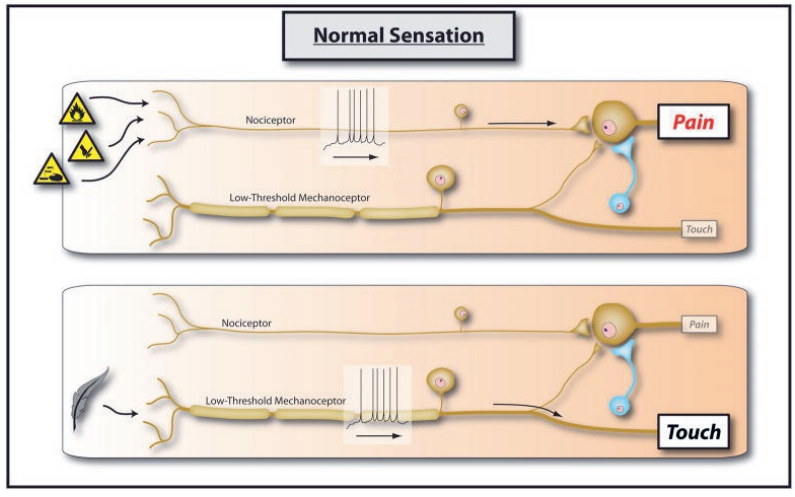
The transition from acute to chronic pain: neuropathic pain features and sensitization characteristics

Moving from a protective to a maladaptive function

As mentioned earlier, pain is categorized according to duration and pathophysiology. Acute pain implies a painful condition with rapid onset or a short course, by definition less than three months. It fulfills an early-warning physiological protective purpose, essential to detect and minimize contact with damaging or noxious stimuli. This acute nociceptive pain plays an adaptive and protective role and demands immediate attention and action, which occurs by the withdrawal reflex it activates, and the intrinsic unpleasantness of the sensation elicited.[34,35] This injury initiates an inflammatory response to clear damaged tissue, eliminate pathogens, and promote repair.[36] However, there is also pain that is not protective but rather maladaptive, resulting from abnormal nervous system functioning. This often chronic pain sensation is rather a disease state of the nervous system. It can occur after damage to the nervous system itself (neuropathic pain), but also in conditions in which there is no such preceeding damage or inflammation (nociplastic pain).[12] Chronic pain, nociceptive – neuropathic or even nociplastic, is defined as continuous, long-term pain lasting more than 12 weeks or after the expected healing time.[37]

A changed pain sensibility: introduction to the concept of sensitization

Persistent noxious stimulation resulting in the activation of polymodal nociceptors can result in enhanced responsiveness, lowered pain threshold, and development of a "background activity". All these changes are classified as peripheral sensitization.[38] Moreover, this sensitization process can spread and last for hours. Peripheral sensitization is linked to the release of inflammatory mediators such as cytokines and neuropeptides,[36] and manifests clinically as local hypersensitivity. This hypersensitivity can be located around the damaged tissue (primary hyperalgesia) but can spread beyond the injury site, where it is called secondary hyperalgesia.[39] Heightened sensory sensitivity after unavoidable tissue damage plays a protective role as it assists in tissue healing by discouraging physical contact and movement.[34] Subsequently, peripheral sensitization may trigger central sensitization of the central nervous system by upregulating glutamate receptors, downregulating GABA receptors, the primary excitatory and inhibitory neurotransmitters, and modifying different ion channels.[40,41] These neuroinflammatory changes sensitize laminae neurons which generally respond to pain-specific stimuli, to also respond to non-noxious input.[42] The latter can be clinically evaluated as allodynia, possibly leading to spontaneous pain. In other words, central sensitization, in contrast to peripheral sensitization, co-opts novel inputs to nociceptive pathways, including those that do not usually drive them, such as large low-threshold mechanoreceptor myelinated fibers to produce Aβ fiber–mediated pain (see Figure 1.3). Primarily this central sensitization has provided a mechanistic explanation for many of the temporal, spatial, and threshold changes in pain sensibility in acute and chronic clinical pain settings. It has highlighted the fundamental contribution of central nervous system changes in the generation of abnormal pain sensitivity. This central sensitization further contributes to the occurrence of neuropathic and nociplastic pain.[43]



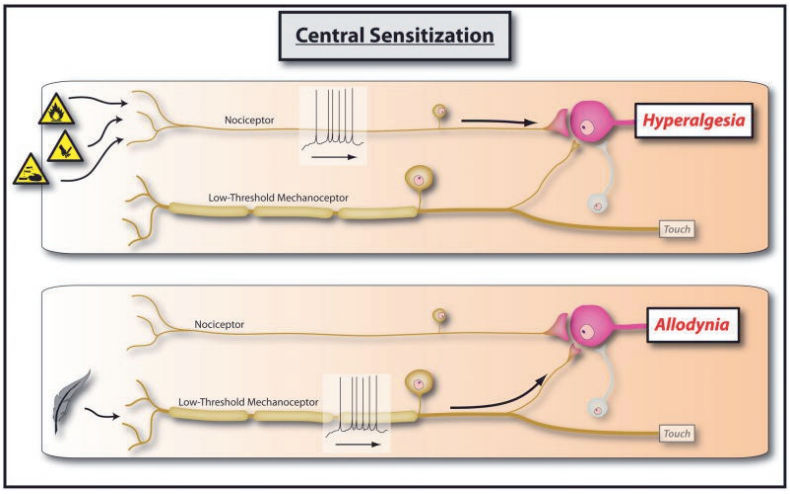


Figure 1.3. Normal sensation versus central sensitization. Typically, the somatosensory system is organized such that primary sensory neurons that encode low-intensity stimuli (feather brush) only activate those central pathways that lead to innocuous sensations (e.g., only pressure when alarming high). At the same time, high-intensity stimuli that activate nociceptors (all-or-nothing response) only activate the central pathways that lead to pain. These two parallel pathways do not functionally intersect in normal sensation. In central sensitization, somatosensory pathways increase synaptic efficacy and reduce inhibition. Through central amplification, the pain response to noxious stimuli enhances in amplitude, duration, and spatial extent (hyperalgesia), while strengthening of usually ineffective synapses recruits subliminal inputs such that inputs in low-threshold sensory inputs can now activate the pain circuit (allodynia). Thus, the two parallel sensory pathways converge (adapted from Woolf, 2011).[44]

Chronic pain after surgery: definition and pain characteristics

An essential culprit of chronic pain is surgery. Although acute pain is almost ubiquitous after surgery, it can usually be controlled well and most will resolve after a few days.[45] However, for some patients, acute postoperative pain persists beyond the usual tissue healing time and transitions into a chronic pain state.[46] The transition to chronic pain conditions still eludes explanation. Still, persistent pain after surgery provides a unique experiment that invites not only epidemiological investigation but also basic research into the mechanisms of transition. Chapman and Vierck[47] proposed five mechanisms elucidating the transition from acute to chronic pain: (1) persistent noxious signaling in the periphery in some but not all patients,[48] (2) neuroinflammatory mediated central sensitization, (3) compromised inhibitory modulation of noxious signaling in medullary-spinal pathways, (4) descending facilitatory modulation, and (5) maladaptive brain remodeling in function, structure, and connectivity. These mechanisms may be responsible individually or in a combined way.

According to the ICD, persistent postoperative pain has greater intensity or different pain characteristics than preoperative pain and is a continuum of acute postoperative pain that may even develop after an asymptomatic period.[9] Macrae and colleagues defined chronic or persistent postsurgical pain (PPSP) as pain developed after surgery for at least two months, and for which other causes have been excluded.[49] Kehlet and colleagues defined it simply as postoperative pain that persists for over three months after surgery.[26] The 11th ICD edition defines PPSP as pain developing or increasing in intensity after a surgical procedure, in the area of the surgery, at three months post-

surgery, and not better explained by another cause such as infection, malignancy, or a pre-existing pain condition.[37]

PPSP is often described as itching or burning; even electric or shooting pain characteristics are reported, representing a neuropathic quality of pain. Other clinical neuropathic descriptors such as hyperalgesia (increased sensitivity to painful stimuli), dysesthesia (unpleasant, abnormal sense of touch) or allodynia (sensitivity to ordinarily non-painful stimuli) are frequently seen in patients with PPSP, suggesting nerve damage during surgery, with the development of a peripherally and centrally (spinal cord and brain) sensitized nervous system.[50] It appears that both occur via unique mechanisms after an incision[51] and can result from ongoing prolonged inflammation.[52]

Chronic pain is a growing public health challenge with a profound negative impact

Pain conditions, especially musculoskeletal conditions (arthritis, osteoarthritis, back pain), are the top reasons patients seek care,[53] an important reason for disability,[54-56] and the biggest driver of healthcare costs.[57] Moreover, opioid prescription for pain treatment can contribute to addiction.[58] The personal impact of suffering, disability, depression, suicide, and other problems is incalculable.

Epidemiology

The global prevalence rates of chronic pain vary between 11% and 40%, with a study by the United States Centers for Disease Control and Prevention (US CDC) estimating the point prevalence at 20%.[59] Similar data have been found in Europeans, with approximately one in five adults affected, equivalent to 96 million people in Europe.[60] A systematic review comprising studies performed in the United Kingdom reported a pooled chronic pain prevalence rate of 43.5%, with moderate-to-severe disabling pain ranging from 10.4% to 14.3%.[61] The Global Burden of Disease Study (GBD) 2016 reaffirmed that the high prominence of pain and pain-related diseases is the leading cause of disability and disease burden globally.[62] Even more recent data from the GBD published in 2020 underlines that pain is still contributing to the most significant number of additional DALYs (disability-adjusted life years) over the last 30-year period (1990-2019), with low back pain in the top ten for ages 10–24 years and 50-74 years and top five ranking in the 25-49 age group.[56]

A review by the Belgian scientific institute of public health showed similar results, up to 24% of the Belgian population (corresponding to 1 million actual patients) suffers from chronic pain syndromes.[63] These findings are confirmed by a Belgian health survey (28%) and are in line with other extensive population surveys.[64]

The incidence of PPSP, which can cause substantial functional impairment, is approximately 10% after all surgeries in the USA.[49] European data collected for PPSP and reviewed by Fletcher and colleagues reported a similar incidence of moderate-to-severe PPSP at 12 months post-surgery of 11.8%.[45] The incidence can differ depending on the type of surgery. However, the wide variability in the incidence (5–85%) is mainly attributable to methodological differences in data collection and variable definitions of PPSP.[65] Moreover, the rates of pain do not seem to differ according to admission reason, either medical or surgical pathology, and this is likely related to the various etiologies of pain.[66]

Over 230 million people undergo surgery yearly worldwide,[64] with more than 2 million in Belgium [Zorg en Gezondheid - opnames], representing a vast potential for PPSP development. Early recognition of patients at risk of developing chronic (postoperative) pain is an essential first step in preventing and treating this debilitating disease.[26,46,67]

Risk factors

Fortunately, only some experience PPSP following surgical intervention. This variability is a function of multiple risk factors throughout the preoperative, intraoperative, and postoperative periods (Figure 1.4, for a comprehensive review see the LANCET paper of Wu & Raja, 2011).[67]

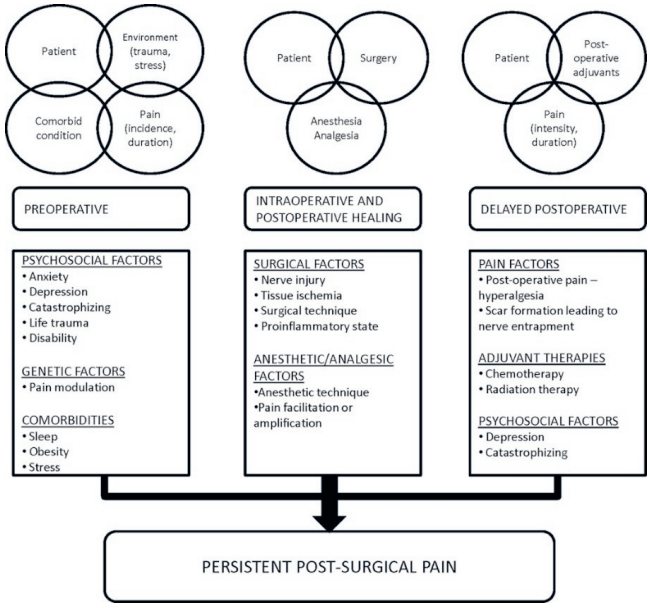


Figure 1.4. Overview of biopsychosocial risk factors in the development of PPSP (adapted from Wu and Raja, 2011).[67]

Psychological, social, and economic factors may be prominent in chronic pain conditions. As extensively studied by Vlaeyen and Linton, the expectation of pain, fear, past memories, social environment, work, and physical activity levels all affect the response to noxious stimuli.[68,69] PPSP is thought to result from an interaction between biological and psychological variables. Psychosocial factors have been identified as consistent predictors of acute and chronic postoperative pain, exerting at least moderate effects on these outcomes. Factors identified involve negative affectivity, stress and distress, and poor coping, suggesting that perceptual/cognitive, emotional, and behavioral factors play critical roles in influencing postoperative pain and should be managed adequately.[70] But also, different physiological factors (see Figure 1.4) may play a tremendous role in the development of PPSP. Especially severe postoperative pain has been identified as an independent risk factor.[71] Moreover, pain intensity has often been reported as unexpectedly high even after rather 'minor' surgical procedures.[72] The authors concluded that to reduce this number, patients should be monitored closely and treated, if necessary, regardless of the surgery's complexity level.

Additionally, sensitivity to physiological nociceptive and clinical pain differs considerably between individuals. Increasingly, this variability is recognized as an indication of heritable susceptibility to the generation and experience of pain.[73] Functional genetic polymorphisms of catecholamine-O-methyltransferase are associated, for example, with altered sensitivity to pain induced in an experimental environment.[74]

A continuous inflammatory response, such as after inguinal mesh hernia repair, can contribute to maintaining inflammatory pain in some patients.[75] However, PPSP closely resembles neuropathic pain in most affected patients.[76-78] In many surgical procedures associated with chronic pain, major nerves cross the surgical field. Hence, damage to these nerves is probably an important prerequisite for the development of PPSP.[79-81] Since the increasing knowledge of the role of nerve damage in the development of PPSP, surgical techniques continue to evolve to decrease the risk of nerve damage. For example, laparoscopic herniorrhaphy can decrease the risk of nerve damage and pain compared with open surgery.[82] Similar results were found for nerve-sparing mastectomy and minimally invasive thoracoscopy.[81,83] Studies in animals and humans indicate that some of the acute neuroplastic responses (central sensitization) following tissue injury can be prevented by aggressive early pain relief.[84] Furthermore, many anesthesiologists are familiar with fast-track surgery protocols, in which researchers found evidence that the perioperative pain evoked by a surgery-induced stress response must be reduced to the minimum for beneficial effects on the outcome.[85] Thus, further optimizing perioperative pain management can reduce the incidence of PPSP; however, evidence remains elusive, with most pharmacological interventions being unfortunately unhelpful in preventing PPSP.[86,87]

Clinical impact

Biopsychosocial repercussions

The stress response evoked by acute pain can have deleterious consequences. Increased circulating catecholamines can cause arteriolar vasoconstriction, impair tissue perfusion, and reduce tissue-oxygen partial pressure.[88] Other responses triggered by pain include catabolic hypermetabolism resulting in hyperglycemia, lipolysis, and breakdown of muscle cells to provide protein substrate. This catabolic stimulation and hypoxemia may further impair wound healing and increase the risk of wound infection. Furthermore, pain suppresses natural killer cell activity, a critical function in the immune system, with a decrease in the number of cytotoxic T cells and a reduction in neutrophil phagocytic activity.[89] However, cytotoxicity and consequent cell death pathways are critical components of the immune response to defend against infection, disease, or injury.[90,91] On the other hand, pain pathways leading from immune activation to inflammation and their contribution to the generation of neuropathic pain are relatively well documented.[92] As described before, mediators released by immune cells, such as cytokines, sensitize nociceptive signaling in the peripheral and central nervous systems,[93,94] and subsequently, the development of sensitization may further complicate pain conditions. Moreover, at least partially, immune pathogenesis of neuropathic pain has been suggested.[92,95] Therefore, as described earlier, acute pain should be considered a major risk factor for developing debilitating chronic, persistent, often neuropathic pain. Furthermore, higher postoperative pain scores are associated with more postoperative complications and vice versa.[96] Patients who developed major complications were more likely to report pain.[97]

Numerous studies indicate that patients with chronic pain are more likely to develop psychological disorders than those without chronic pain.[98] Chronic pain has been associated with increased rates of major depressive disorder,[99] suicidal ideation, and suicide attempts.[100] Cognitive processes such as memory and attention have been shown to be impaired in up to two-thirds of patients with chronic pain.[101] In patients with chronic pain, overall quality of life is decreased.[102] Quality of life (QoL) is affected by the aforementioned sequelae, including mental health and sleep, but also by decreased social interactions and daily activities such as personal relationships and employment status.[103,104] The frequency of interference with social life, work, and daily activities is increased in chronic pain patients and further increases with the severity of pain.[105,106] The multidimensional negative impact of chronic pain leads to poorer QoL compared to the general population and patients with other long-term conditions.[107] Thus, as stated, it is crucial to effectively manage pain in its early stages before it progresses and further affects patients' well-being. The presence of pain is, moreover, a social issue, affecting not only the quality of life of an individual patient, but also their friends and families, their colleagues, and society in general.[103,108]

Populations at risk for persistent pain development

Evidence suggests that critically ill patients experience stressful and unpleasant experiences such as pain, fear, and sleep problems during their ICU admission.[109,110] This biopsychosocial stress affects the quality of life even after ICU discharge.[111,112] Among these adverse experiences, acute pain has emerged as a leading stressor for ICU patients, with nearly 50% of interviewed patients rating their pain intensity as moderate to severe,[113,114] and numbers further increase up to 80% during standard care procedures.[115] Studies have demonstrated that ICU survivors rate ICU-related procedures such as arterial line insertion, chest tube, and drain removal as the most painful.[116,117] Other procedures rated as uncomfortable include mechanical ventilation, endotracheal tube suctioning, and repositioning.[118,119] Even after discharge pain and psychosocial comorbidities may persist. A study by Granja noted that 17% of patients remembered experiencing severe pain six months after an ICU stay and 18% were at risk of developing post-traumatic stress disorder (PTSD).[120,121] In addition, Schelling et al. conducted a long-term follow-up questionnaire study (median, 4 years) of 80 patients who had been treated in the ICU for acute respiratory distress syndrome. [122,123] They concluded that patients who recalled pain and other traumatic situations while in the ICU had a higher incidence of chronic pain (38%) and PTSD symptoms (27%), and a lower health-related quality of life (21%). PTSD profoundly impacts the individual's quality of life and has been associated with several adverse health outcomes, including pain.[124,125]

Awareness should further grow to screen for pain and PTSD symptoms and contributing factors in ICU survivors and start care for them accordingly, given the potential negative impact on quality of life.[121] Studies performed in surgical, trauma, and medical ICUs report that a protocolized approach to assess and manage pain, agitation, and delirium, [126,127] is associated with a reduced duration of mechanical ventilation, ICU-acquired infections, length of stay, and costs in ICU and hospital as well as 30-day mortality.[128] Accordingly, the guidelines recommend protocolized pain screening and assessing analgesic needs first to palliate the current under-recognition and treatment of pain.[129,130]

Not only the presence of pain and its biopsychosocial impact, as described before, may negatively affect all patient-related outcome measurements (PROM), but also the suboptimal use of strong (mainly opioid) analgesics can contribute to adverse outcomes.[131] The prolonged administration of large amounts of long-working opioid analgesics has been associated with longer durations of

mechanical ventilation and total hospital stay,[132] chronic opioid use[133] and increased mortality.[134,135] Nevertheless, pain is frequent during hospital stays, as described above. Therefore, it is recommended to use individually titrated preemptive analgesics in such circumstances rather than prolonged administration of large amounts of long-working opioid analgesics.

In summary, we could say that pain and pain management are inextricably linked with psychosocial well-being and even psychiatric conditions such as delirium in ICU-admitted patients (see Figure 1.5). Therewith, improved biopsychosocial pain management is clearly associated with better patient outcomes in the ICU.

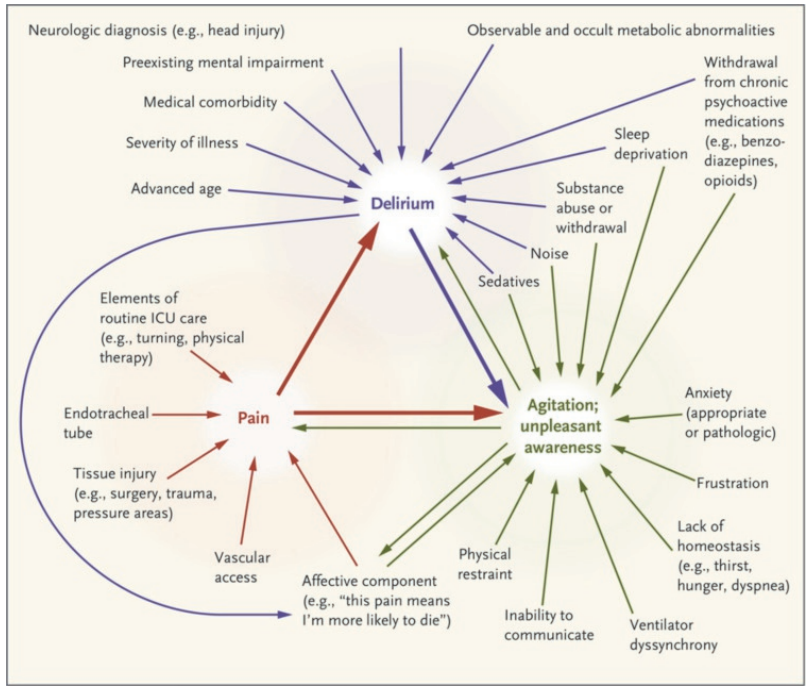


Figure 1.5. Interaction between pain, delirium, and agitation. Adapted from Reade et al. The new England Journal of Medicine. 2014.[136] Overview of the "ICU triad", which recognizes that pain, agitation, and delirium — and therefore approaches to their management — are inextricably linked.

Also, in pediatric populations, there is a growing awareness of the potential PPSP development and its implications.[137,138] Yet, the 12-month incidence of PPSP in children ranges from 11% to 54%, which is like the adult literature.[139] A recently published narrative review of epidemiologic, perioperative, and psychosocial factors contributing to the transition of acute to chronic postoperative pain in youth underlines the same biopsychosocial character as seen in adults.[140] Pediatric PPSP is also associated with pain-related distress and comorbid mental health outcomes, such as anxiety and depression. But not only youth factors may play a role in the development and maintenance of PPSP, but also parent factors, such as cognitive appraisals of a child's pain expression and pain catastrophizing, converge and lead to chronic pain disability. Since the first publication on the incidence evaluation of PPSP in children in 2011,[141] still only a handful of other studies have reported

on this topic and are mainly focused on major spinal surgery. Williams and colleagues highlighted some procedure-specific incidence of PPSP in children.[137] For scoliosis surgery, PPSP incidence ranges between 19% at three months and 10% and 15% at 1 to 5 years postoperatively. Also, they reported incidence rates of up to 16% after childhood thoracotomy with a follow-up period of up to 30 years. A systematic review and meta-analysis on the prevalence and predictors of PPSP in children executed by Rabbits and colleagues included 628 participants across all surgery types and found a median prevalence of PPSP across studies of 20% reported 12 months after surgery.[142] However, compared to adult studies, data are far less available on the precise incidence of PPSP after different specific surgical interventions. Furthermore, data collection is complicated because investigations in children often involve a range of age-specific procedures, a different PPSP definition usage, high dropout rates, and long durations between the time of surgery and the outcome survey. Despite this recently increased interest in PPSP incidence, potential risk factors identification, and outcome evaluation in children undergoing surgery, there is fewer data to guide clinicians on the specific management of PPSP in the pediatric population.[137]

Opioids

Natural products such as opium have been described as anesthetics since early civilization. Still, the first public demonstration of modern anesthesia happened on 16 October 1846 and is known as the "ether day".[143] Later, synthetic opioids were introduced during the Second World War. The use of fentanyl in anesthesia was described for the first time in 1962 after its synthesis by Paul Janssen in 1960.[144] The initiation of the so-called balanced anesthesia (a term introduced by Lundy in 1926;[145] a concept in which a combination of drugs are used to produce general anesthesia, with each drug chosen for a specific effect was possible due to the possibility of administrating high doses of opioids and the hemodynamic stability associated with their use during surgery.[146] Quickly, it led to the generalization of its perioperative use. Since the 1960s, a shift has been seen to more balanced multimodal anesthesia with the association of a hypnotic, an analgetic, and a muscle-blocking agent, up to the modern multimodal general anesthesia, including NMDA-receptor antagonists, with or without local anesthetics.[147] All these innovations were satisfying with good procedural (surgical) conditions, rapid recovery, and cardiovascular stability, and opioids remain the most potent drugs used to control severe (cancer) pain.[148,149] However, since the improvement of knowledge and monitoring techniques, the decreased use of opioids due to their described side effects is often requested.[150,151] Whereas not only the presence of pain has profound negative clinical repercussions, also the increased use of mainly opioid analgetics can be associated with adverse effects. In the short term, opioid use may lead to sedation, urinary retention, ileus, postoperative nausea and vomiting (PONV), or respiratory depression.[150,151] These, in turn, will adversely affect the hospitalization duration and well-being. Even more, many studies have questioned the use of high-dose opioids highlighting the immune effects, the lack of evidence of specific activation of pain pathways under general anesthesia, or the risk of opioid-induced hyperalgesia.[152-154]

Moreover, even in the perioperative setting, the interface between the legitimate medical use of opioids to provide adequate analgesia and the phenomena associated with abuse and addiction continues to challenge the clinical community.[155] Furthermore, the consequences of long-term opioid use, such as persistent opioid-induced constipation, dependence, and opioid-induced hyperalgesia, can impact the user's quality of life and functionality.[153,154] The risks of opioid-related adverse events and opioid misuse (use of opioids in another manner than directed on the prescription, i.e., greater amounts, more often or more extended usage) relate to higher dose prescription and longer

treatment duration.[156] In addition, the use of opioids can not only negatively affect the prescribed individual itself but also carries a risk of diversion, which raises the possibility of misuse and overdose in individuals other than the prescription recipient.

Although opioids have been regarded for millennia as among the most effective pain treatments despite the known short-term side effects, their long-term use in the management of (sub)acute severe pain and chronic non-cancer pain has become more and more controversial.[148] Today, many arguments arise for opioid-free anesthesia, thereby reducing some adverse side effects of opioids, such as PONV and gastrointestinal tract delay particularly present in abdominal surgery patients and morbidly obese, especially in fast-track regimens or outpatient surgery.[157] However, rather than debating on whether or not to abandon opioids in anesthesia in general, a patient-centric approach might be more prudent in which the opioid treatment is optimized individually to prevent complications of both over- and under-dosing during the whole perioperative period.[158] Concerns related to long-term effectiveness, safety, and abuse driven by the magnitude of the USA opioid crisis,[159,160] have evolved over decades, driving a more restrictive perspective, and leading to a greater willingness to endorse this strategy. Preventing an opioid crisis of US proportions across Europe is still debatable.[161]

The attitudes towards the long-term us of opioids have shifted repeatedly in response to clinical and epidemiological observations, and events in the legal and regulatory communities.[162,163] In March 2016, the US CDC released a guideline targeted at primary care clinicians prescribing opioids for pain outside of active cancer treatment, palliative care, and end-of-life care,[164] and therefore interested the surgical patient. These US CDC recommendations intended to improve communication between clinicians and patients and empower them to make informed, person-centered decisions related to pain care together.[165] Since the release of the US CDC opioid prescribing guideline in 2016, new evidence has emerged on the benefits and risks of opioid prescription for both acute and chronic pain. The latest guideline, published in 2022, even broadens the scope from primary care physicians to all clinicians providing pain care for outpatients aged ≥18 years.[135] Moreover, it has expanded its guidance on non-opioid options for pain, added recommendations that apply specifically to starting or increasing opioid dosages, and outlined situations when clinicians should consider tapering to a reduced or discontinued opioid therapy. The 2022 guideline can further help inform risk-benefits treatment decisions and assist all clinicians involved in opioid therapy in meeting patients' unique needs.[166] Future challenges may also focus on guideline implementation in routine practice. Up to now, little is known about the extent to which clinicians are following prescribing practices outlined in the guideline.[163]

Socioeconomic impact of pain

Pain is often an unexpectedly high humanitarian cost of necessary surgery. The economic cost of chronic pain, which includes a significant proportion of PPSP, exceeds the cost of heart disease, cancer, and diabetes in the USA.[57] Chronic pain is probably one of the diseases with the most significant negative impact on the individual's quality of life and their wider society: sleep, work, and relationships are compromised, and depression and anxiety are common.[167] As such, the socio-economic benefits of early identification of at-risk patients and earlier treatment after correct and repeated pain assessment can be high. Chronic pain syndromes prevent a significant number of individuals from participating in socio-economic activities, and their numbers could be dramatically decreased through early individualized coaching and treatment programs for individuals at risk.[168]

Although chronic pain can be invisible to employers, its impact can be immense.[169] Chronic pain can cause loss of productivity at the workplace, underperformance or even absence of the employee. More than a fifth of chronic pain patients are unemployed.[170] And those still at work are twice as often absent from work as their colleagues.[60,171] In addition, a systematic review executed by Patel and colleagues[172] reported a negative association between chronic pain and work-related outcomes. This negative association also appeared consistent across different European populations regardless of country (and social security policies) and pain etiology. Chronic pain patients may even form a burden to colleagues, leading to a detrimental effect on their mental health and a decline in morale across the workplace.[173,174] The European Working Conditions Survey (EWCS) conducted a survey in 2017 on job quality in correlation to the health and well-being of workers and its impact on absenteeism and presenteeism (i.e., unhealthy employees are physically present at work but unable to perform at total capacity). It also noted that presenteeism increased costs and was associated with lower productivity.[175] Although chronic pain significantly impacts workforce participants and productivity, it is not adequately acknowledged nor addressed for PPSP since most of the research focuses on persistent musculoskeletal pain.

The financial burden of chronic pain is tremendous. Health economists from Johns Hopkins University reported that the annual cost of chronic pain in the US amounts to $635 billion a year, which is more than the yearly costs for heart disease ($309 billion), cancer ($243 billion), and diabetes ($188 billion) combined.[57] For this study, the researchers estimated the annual economic costs of chronic pain in the USA by assessing the incremental costs of health care due to pain and the indirect pain costs from lower productivity. They compared health care costs for persons with chronic pain with those not reporting chronic pain. A report (Nr. 48C) by the Belgian Health Care Knowledge Centre focusing on chronic low back pain indicated that the total medical cost in Belgium varies from 81 to 167 million euros.[176] However, according to the literature, the direct medical expenses paid by the health insurance sector account for only 10% to 30% of the overall costs for the patient and society. Belgium's total direct and indirect costs could be prudently estimated at between 270 million and 1.6 billion euros. Furthermore, given the rising prevalence of chronic pain conditions, as mentioned before, the direct and indirect costs incurred from managing adverse events with long-term opioid use are likely to be multiplied, contributing to the socioeconomic burden of chronic pain.[177]

In conclusion, pain can be conceptualized as a public health challenge for several reasons. First is the extent of the problem: chronic pain prevalence rates vary (11-40%) worldwide, with a point prevalence of around 20%.[59,60] In Belgium in 2018, 12% of the population reported suffering from low back pain, and 7.8% from neck pain. Its occurrence increases with age up to 24% of people over 75 years of age reporting back pain.[178] Furthermore, in Belgium, between 2008 and 2018, the age-adjusted prevalence of low back pain and neck pain increased in both genders (26% in men and 3.9% in women, and 23% in men and 20% in women, respectively). As such, chronic pain contributes substantially to morbidity, mortality, disability, demands on the healthcare system, and a significant economic burden for society.[179] As previously mentioned, the prevalence of chronic pain is growing and is likely to continue to do so. Second, there are substantial disparities in pain prevalence and seriousness and rates of undertreatment across population groups, including the elderly,[180,181] children,[182-184] racial, ethnic,[185] and other minorities.[186] Recent figures, however, clearly indicate the rising prevalence of chronic pain syndromes in younger people[187], including survivors of cancer[188], as well as of chronic pain after surgery[189] or chronic back pain.[190] Thirdly, because pain is omnipresent

across the general population, imposes a differential burden on vulnerable subgroups, and is affected by conditions in the social, physical, and economic environments, a comprehensive pain prevention and management strategy at the population health level is needed,[191] and can be further refined on an individual basis according to patient setting and pain type. Fourth, pain is costly[57] – not just in terms of healthcare expenditures and disability compensation but also in terms of lost school/work days, lost productivity and employment, reduced incomes, and lost potential and quality of life.[192] Managing adverse events with long-term opioid usage also contributes to the socioeconomic burden.[177] The impact of pain on public health can be decreased by applying new multi-disciplinary knowledge from basic, clinical, and translational research, epidemiologic studies, and analysis of care patterns and costs.

Translating pain theory to practice for surgical and ICU patients

Suboptimal pain management could result from lacking or insufficient implementation of practical guidelines considering pain treatment,[193] but a correct pain assessment also plays an even more crucial role. Reports documenting the inability of healthcare professionals to use evidence-based anchor points for assessing and treating pain continue to appear in the literature.[194-197] Additionally, clinicians' personal beliefs, attitudes, and fears can directly influence how they and their patients respond to the varied dimensions of pain.[198,199]

Up to now, there has been much effort to prevent many medical conditions, including pain, and the insights into pain pathophysiology and treatment are increasing tremendously, as described earlier. Nevertheless, the challenge remains for developing and wide rollout of effective, evidence-based approaches to improve post-surgical outcomes in daily clinical practice. Prevention and recognition of PPSP with identification of risk factors as part of a proposed multidisciplinary biopsychosocial care pathway using pharmacological and non-pharmacological strategies have yet to be implemented and evaluated.[200]

Patients planned for elective surgery may be good candidates for preoperative inclusion in a biopsychosocial surgical care pathway preventing the development of severe postoperative pain and PPSP because of its clear ‘nociceptive starting point’. Furthermore, the additional use of more objective nociceptive assessment tools can tailor pain treatment more individually, diminishing various adverse effects after noxious stimulation.

Improved outcome: how to measure

Many guidelines are available to improve outcomes after painful procedures.[201,202] Among others, the improved outcome can be defined as a decrease in nociceptive input (including pain) during surgery, noxious procedures, and during the postprocedural period, leading to less discomfort, promoting early mobilization and rehabilitation with less persistent pain.[203-205] Patient-reported outcome measurements (PROMs) are used to assess a patient’s health status and can be completed pre- and post-event.[206] In recent years, PROMs are increasingly being used to assess health interventions' effects and improve the quality of care.[207]

When we think about improving outcomes, focussing on pain prevention for surgical or ICU admitted patients, we evaluate the possibilities to optimize pain assessment further. The IASP definition indicates that the measurement of choice is the subjective pain survey in conscious patients. Behavior analysis is a good alternative in different unconscious patient populations. And in addition, even more objective nociceptive assessment strategies could give the caregiver supplementary

information about the individual nociceptive-anti-nociceptive balance. Moreover, the presence of pain can also be viewed as a domain of quality of life and well-being.

Pain intensity assessment: gold standards

Pain severity evaluation can be divided into (1) a unidimensional pain intensity assessment and a (2) pain-related interference (activities, disability) query, which is more multi-dimensional. Current gold standard pain intensity assessment tools rely on individual self-reporting using pain rating scales. Visual analogue scales (VAS)[208] and subtypes such as the (Wong-Baker) faces pain scale[209], the verbal rating scales (VRS), and the numeric rating scale (NRS)[210] are valid, reliable, and appropriate for use in clinical practice (Figure 1.6).[211-213]

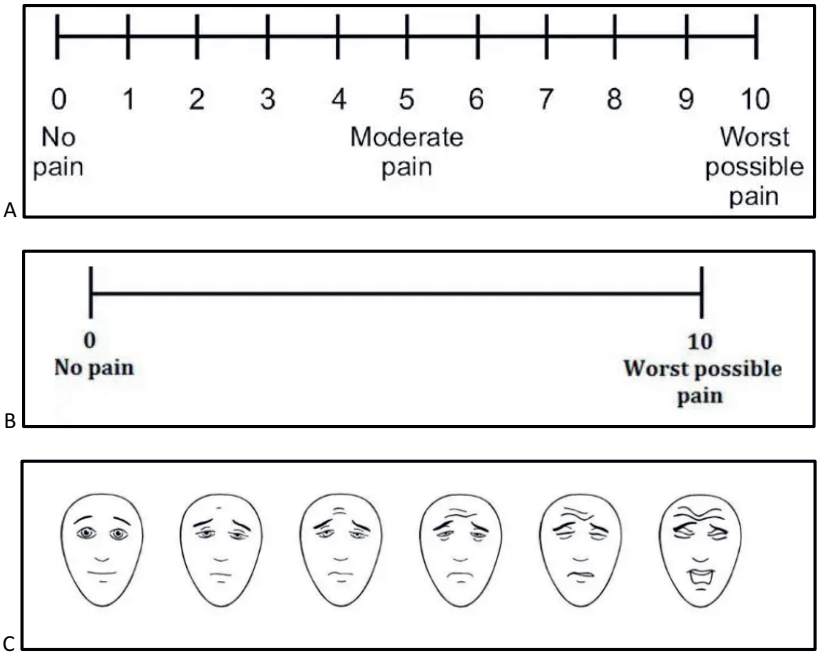


Figure 1.6. Overview of commonly used pain intensity assessment scales, adapted from the European Pain Federation (accessed in Jan 2023). (a) Numeric Rating Scale (NRS), (b) Visual Analogue Scale (VAS), (c) Faces Pain Scale. The latter uses six faces to measure pain in children, usually between 3 and 8 years old. The child is asked to point to the face that best represents their pain intensity.

The VAS and NRS, on which patients rate their current pain intensity on an 11-level scale from 0 ("no pain") to 10 ("worst possible pain"), has become the most widely used instrument for pain assessment. However, both tools require a communicative conscious patient. Therefore, its use has led to an essential and informative dispute about whether self-report pain intensity measures should be considered the gold standard.[214,215] Hence, clinicians must rely on alternative, more observative (behavioral) techniques for pain evaluation. The Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) are the most valid and reliable behavioral pain scales for assessing pain in patients receiving sedatives or who are unable to communicate (Figure 1.7).[216-219]

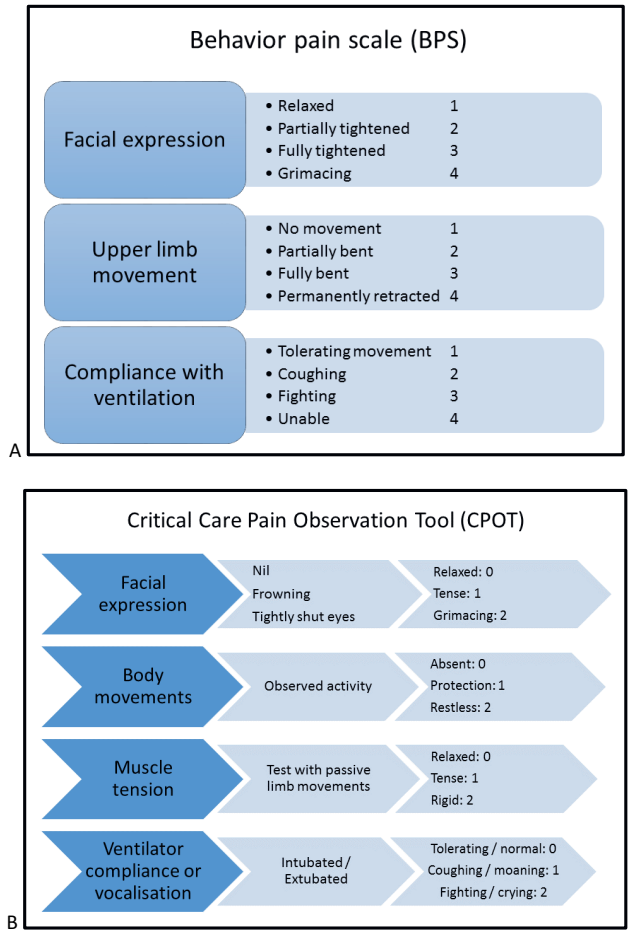


Figure 1.7. Observational pain evaluation tools in non-communicative patients: (a) Behavior Pain Scale (BPS) after Payen et al.[216] (b) Critical Care Pain Observation Tool (CPOT) after Gélinas et al.[220]

Though no scale is suitable for all patients, Dalton and McNaull advocate a universal adoption of an 11-level scale for clinical assessment of pain intensity in adult patients.[221] Standardization may promote collaboration and consistency among caregivers in multiple settings. Using a pain scale with 0 being no pain and 10 being the worst pain imaginable, a numerical value can be assigned to the patient's perceived pain intensity. Asking patients to rate their present pain, their pain after an intervention, and their pain over the past 24 hours will enable healthcare providers to see if the pain is worsening or improving.[197] Also, inquiring about the pain level acceptable to the patient will help clinicians understand the patient's goal of therapy.

Pitfalls in the use of gold standard assessment tools: unidimensional, timing, medication use

In conscious patients, subjective self-reporting pain values are frequently unidimensionally assessed as described above.[210,222,223] This contrasts with the multidimensional, biopsychosocial nature of pain. A first step towards this model is pain assessment methods that rely on pain intensity and the perception of pain and pain-related symptoms by either the patient or a professional caregiver.[224] A

more global pain evaluation may also include a judgment if the pain prevents the patient from moving appropriately or from performing the necessary activities to expedite recovery,[225] as a multidimensional pain assessment is essential for adequate pain management after painful interventions such as surgery.[226]

As many critically ill patients may be unable to self-report their pain, one would easily assume that vital signs could be a valuable tool to assess pain in these patients. Vital signs (e.g., blood pressure (BP), heart rate (HR), respiratory rate (RR)) are easily accessible in the OR and ICUs, and professional caregivers consider them essential in pain assessment.[227] However, multiple studies recommend avoiding the use of vital signs as a primary assessment for pain in the ICU.[228] Vital signs were found to increase, decrease, or remain stable during painful procedures,[118,119] and should therefore never be used as the sole indicator of pain. Moreover, correlations of vital sign fluctuations with behavioral pain scores and self-reports of pain are weak or absent.[229,230] Changes in vital signs may also occur from fear, anxiety, and other psychological stressors. HR and RR increased in traumatic brain injured (TBI) patients during a painful procedure, but only RR correlated with pain self-report in 13 ICU patients with TBI.[231] Considering that vital sign utility for pain assessment is poor, they are not considered valid pain indicators and should be used cautiously. Furthermore, a challenge remains for evaluating patients needing muscle relaxation. In this specific patient group that receives neuromuscular blockers in an ICU or OR environment, a motor function evaluation (as part of the BPS and CPOT) is impossible.

Likewise, during surgery, opioids are titrated frequently in the function of hemodynamic parameters and movement response on nociceptive stimulation such as endotracheal intubation or skin incision.[232] Nociceptive assessment or analgesia management evaluation in daily clinical routine is, in contrast to the other two components of anesthesia (hypnosis, immobility), frequently based on very unspecific clinical 'endpoints' such as movement, tearing, or vital signs.[233] Some anesthesiologists use the bispectral index (BIS) monitors for sedation depth monitoring and correlate it to analgesia management. However, these more integrated devices correlate insufficiently with evaluating the nociceptive-anti-nociceptive balance during anesthesia.[234] Sedation depth can, at most, be better controlled as a specific confounding variable in pain evaluation.[235] Therefore, objective, and reproducible assessment remains a challenge in these patients and demands the application of innovative and integrated diagnostic paradigms. However, individually tailored analgesia during analgosedation should enable maintaining an individual nociceptive-anti-nociceptive balance and may be superior in avoiding adverse effects as described earlier. Pain is by its nature, subjective and hence unmeasurable in anesthetized subjects. In contrast to pain, nociception is not a subjective feeling but a physiological encoding and processing of nociceptive stimuli (chapter 1). What can be monitored is therefore 'nociception' or the (patho)physiological response to it. Moreover, pain and nociception may exist without each other.[236]

Pain as a component of well-being

Endeavors to measure pain more multidimensionally resulted in the EuroQol self-report survey introduced by the EuroQol group in 2009. The original 3-level EQ-5D (EQ-5D-3L) includes five dimensions with three levels of problems per dimension. Since 2010, a more sensitive version with five levels of problems per dimension (EQ-5D-5L) has become available. Meanwhile, population value sets have been developed for both questionnaire versions. The EQ5D provides a useful PROMs tool

to assess the impact of health interventions on the generic health-related quality of life.[237] A standardized valuation study protocol was developed by the EuroQol Group to create standard value sets for the EQ-5D-5L. A list of all currently available standard value sets for the EQ-5D-5L can be found on the euroqol website [https://euroqol.org].[238] The valuation for Belgium was published by Bouckaert in 2021 (from collected data in 2018-2020).[239] A map EQ-5D-3L descriptive system data to value sets for the EQ-5D-5L was published recently.[240]

The EuroQol 5 Dimensions 5 Levels (see https://euroqol.org for further information) descriptive tool measures health-related quality of life across five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Figure 1.8). Pain and discomfort measured by the EQ-5D-5L are consistently reported among the top dimensions having the most negative impact on health-related quality of life across countries (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/).

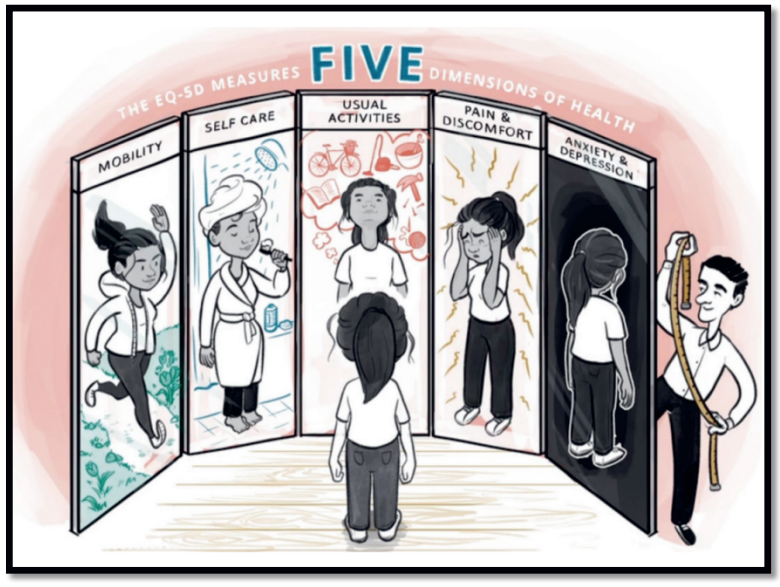


Figure 1.8. EQ-5D, is an instrument to describe and value health. The descriptive assessment tool assesses health-related quality of life in five dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. (Figure adapted from EQ-5D-5L Belgian value set; questionnaires in different languages are available on Euroqol.org.)

Role of e-Health in a changing health care environment

Definition and possibilities

E-Health, telehealth, digital health, or telemedicine was defined by the World Health Organisation (WHO) in 2010 as "the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment, and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities".[241] Many terms and definitions are used interchangeably. E-Health encompasses all domains such as tele-expertise, telemonitoring, Tele assistance, mHealth, and teleconsultation.

There is a growing demand for simplification and acceleration of administrative tasks in the healthcare sector and e-Health technology has become increasingly popular to meet this need.[242] Moreover, e-Health has an enormous potential to optimize patient-centered care, and improve healthcare cost, safety, and quality of care.[243] There is a growing demand for simplifying and accelerating administrative tasks in the healthcare sector, and e-Health technology has become increasingly popular.[242] Moreover, these technologies have an enormous potential to optimize patient-centered care, and improve healthcare cost, safety, and quality of care.[243]

After an intensive treatment program during hospitalization, patients are frequently discharged with fewer painkillers, and a check-up consultation is often only scheduled after several weeks or months.[244,245] Patients often have difficulty distinguishing acute from chronic pain at home and lack knowledge on analgetic medication to self-medicate accordingly.[246] They also frequently incorrectly reduce the prescribed pain treatment due to a fear of side effects or addiction. As a result, patients risk insufficient pain relief after being discharged from hospitalization.[247,248] Digital technologies offer extensive possible solutions to such post-hospitalization issues. Not only can the use of e-Health tools be implemented before surgery, during a hospital stay, or after discharge, different intervention types can be applied as well, such as education or supportive websites, telemonitoring (electronic questionnaires or electronic symptom alert system with the usage of wearables), or telerehabilitation (physiotherapy at home) covering all biopsychosocial medical aspects. The implementation of this innovation, as recently concluded by Van der Meij et al., may lead to improved PROMs compared to the standard of care, spending more time doing what matters the most.[249-251]

In the field of anesthesiology and pain medicine, e-Health interventions are used to preoperatively inform patients,[252] enhance patient recovery[251,253] provide healthcare provider education, [254,255] or collect and share medical data.[256,257] There is a growing body of evidence that it can improve health outcomes across a range of areas.[258-261]

Despite the evident benefits of e-Health technologies, the adoption of new care models is often challenged by unfamiliarity with program eligibility, leading most healthcare providers by default to the care option with which they are familiar, and patients' reluctance to try out new approaches of care. However, the SARS-COV-19 pandemic has tremendously accelerated the development and expansion of (new) healthcare services to rapidly respond to the needs of people not only diagnosed with the SARS-CoV-19 virus but all individuals in need of healthcare. According to a KCE report concluded two years after the first lockdown in Belgium, professionals and patients consider e-health as a feasible intervention, and they are willing to expand it to other pathologies.[262] As there is no way back, this digital era will hopefully catalyze further extension. Investing resources to endorse collaboration frameworks and facilitate the development of care paths for acute and chronic medical conditions besides preventive care should be encouraged. According to one survey, the majority of European doctors believe that telemedicine is here to stay.[263]

UZA@home®: a hospital-wide digital, interactive patient portal

The studies described in this dissertation have been performed at the Antwerp University Hospital (Universitair Ziekenhuis Antwerpen, UZA), which has developed and implemented the integrated UZA@home® platform (see https://home.uza.be). The surgical care pathways in this thesis included remote patient evaluation and gave a boost to its further development in a pre-Covid-era. Further adaptations and updates are regularly developed. Recently, the platform is even accessible using the UZA@home® application, which can be downloaded from the App Store or Google Play Store.

In the meantime, further accelerated by the COVID-19 pandemic, UZA@home® has grown into a hospital-wide digital, interactive patient portal. The platform supports and guides patients during different care processes in the hospital. Even more, after hospital (same day) admission or ambulant visit, patients can recover in their home environment and further followed up digitally when necessary. The secure platform is now even part of the electronic patient file so that healthcare professionals have a good overview of all information and can pool knowledge. The platform also offers the prospect of digitally monitoring patients in a 'digital hospital' in the long term. A smart solution that contributes to the continuity of care with the current shortages of healthcare professionals. Procedure-specific questionnaires are available, besides objectively obtained parameters via platform-linked devices, and a patient diary noting updates concerning pain, sleep, and daily activity. The semi-objective diary information is greatly enhanced with objective and functional data captured by non-invasive medical grade monitoring devices (telemetry), offering a continuous insight into the patient's global functioning, and providing objective outcome parameters. Blood pressure and heart rate are continuously monitored (as functional parameters for the global physical condition of the patient and the rehabilitation process), sleep quality is monitored through the application of a telemetric device, oxygen saturation is repeatedly measured with a finger probe and daily motion is continuously recorded via a Bluetooth-operated medical graded activity tracker.

In conclusion, UZA@home® supports and guides patients digitally during multiple care processes in UZA. Up to now, different digital functionalities are possible such as telemonitoring, video consultation, or medical file oversight and possibilities are further growing. The goal is to provide patients with everything they need to actively take control of their treatment and to offer them the best care as close to home as possible. We are evolving towards a dynamic model with frequent – mainly digital – contact moments.

Efforts in the prevention of pain after surgery: development of a perioperative pain care pathway

Several preventive, pre-emptive, multimodal pain management approaches are described in the literature to reduce rates of PPSP.[26,51,264-266] Despite continuous advances in these techniques over the past 25 years, developing optimal individual peri- and postoperative pain management remains a challenge for researchers and healthcare providers,[46,204] as stated earlier. As showed by Katz and colleagues,[200] the development and implementation of biopsychosocial surgical care pathways can provide the opportunity to impact patients' pain trajectories, preventing the transition from acute to chronic pain and reducing suffering, disability, and health care costs. The adequate identification and treatment of patients at risk for PPSP via a well-designed perioperative pain care pathway, including tele-monitoring, can offer the physician and researcher an innovative platform for early assessment and treatment if necessary.

Up to now, anchor points for further biopsychosocial pathway design are needed to transform the management of pain in postsurgical patients by providing seamless care beginning preoperatively and continuing throughout the hospital stay and after patients' hospital discharge. Finally, the next steps are to determine the efficacy of these multidisciplinary biopsychosocial pathways in preventing PPSP and positively affecting many PROMs.

Prevention should start as early as possible, ideally preoperatively. Literature shows only two research groups[267,268] that developed, implemented, and evaluated a practically valuable risk factor screening questionnaire for adults planned for elective surgery. Kalkman and colleagues concluded that severe postoperative pain in the early postoperative phase could be predicted using a small set of variables that can be easily queried in the preoperative phase.[267] Alternatively, Althaus et al. developed a risk index for the prediction of chronic postoperative pain.[268] Five predictors were defined, including severe postoperative pain. Results are promising in the identification of high-risk patients who can benefit most from an optimized individual pain management strategy. Until today, no publications have been found on external validation of these questionnaires.

Efforts in the prevention of pain after noxious stimulation: addition of a more objective nociceptive monitoring tool

To facilitate painful care or (surgical) procedures, general anesthesia (GA) or monitored sedation is often necessary. The primary goal of GA is to render the patient unconscious and unable to feel pain while controlling autonomic reflexes. GA requires an adequate balance between hypnosis, analgesia, and neuromuscular blockade (NMB) while maintaining hemodynamic and respiratory dynamics in a safe range.[269] Technological monitoring assures detection and alarm of complications, but clinical observation is essentially based on the anesthetist's skills and experience.[270] Appropriate monitoring devices recommended in anesthetic standards are described in the WHO International Standards for a safe practice of Anesthesia, published in 2018.[269] These standards include routine monitoring of (1) anesthesia depth (e.g., processed electroencephalography for hypnosis, newly researched pain monitors for analgesia, peripheral neuromuscular transmission monitor for NMB evaluation), (2) hemodynamics (pulse oximeter, electrocardiography, blood pressure), (3) respiratory dynamics (oxygen supply, pulse oximeter, auscultation, clinical observation), and for (4) temperature monitoring. In this manner, the monitors supplement clinical observation to achieve optimal drug doses for complete anesthesia-hemodynamics-respiratory management. In response to this guideline, Hendel and colleagues[271] underlined that practical and evidence-based stepping stones

must also be offered to support those who cannot yet reach this patient safety ideal, and the global anesthesia community has been asked to embrace a bare minimum for safe practice.[272]

When investigating the idea of optimizing nociception monitoring, it is worth considering that the understanding of nociception in the analgosedated unconscious person is more controversially discussed than (conscious) pain. Nevertheless, measuring nociception is still very difficult in a clinical environment, which is a hindrance to the reliable validation of nociceptive (reflex) monitors.[236] Despite many difficulties, monitoring nociception remains an important goal as it may contribute to the decrease of intraoperative stress responses beyond simply controlling the hemodynamics. In addition, the evaluation of opioid-sparing strategies during surgery, permitting the reduction or total avoidance of intraoperative opioid use is ultimately relevant and could boost clinical research in this complex topic.[273] Furthermore, these monitors could be integrated into closed-loop systems for analgesic administration. Nowadays, computer-controlled drug delivery is done by open-loop target-controlled infusion (TCI) systems, mainly for sedatives, and is a first step toward automation of drug delivery.[274] However, in the control loop, the anesthesiologist is compiled to select the initial target doses or concentrations and adjust them accordingly to the peri-operative evaluation of the patient's state. The effect of the drugs on each patient is estimated by the clinicians based on monitoring devices, clinical expertise, and previous experience. While this strategy is manually closed by the anesthesiologist, closed-loop control systems use direct measurements from anesthesia monitors to automatically adapt the infusion rates. The measured response of the patient is used as feedback for the controller.[275] It is only then that the anesthesiologist receives other high-level roles and can focus on high-rated tasks in ORs and in ICUs, such as adaptation of the treatment for PPSP at-risk individuals. As such, it is possible that patients with a higher likelihood of severe postoperative pain could benefit more from this more targeted pre-emptive analgesia strategy. This technology could be implemented broadly in operation theaters, ICUs, and other wards where communication between patients and caregivers is impaired.[4,236,276]

As known, ICU-admitted patients experience pain because of painful interventions and barriers to effective verbal communication limit a self-report of pain. Therefore, as described earlier, behavioral and physical responses can be used in the pain assessment.[277] However, clinicians are advised to identify patients at risk for chronic pain conditions by using structured, valid, reliable, and feasible tools to assess pain, and optimally manage nociceptive as well as pain-derived symptoms. Ideally, a structured program for this optimal care and follow-up is used.[278] A survey in the Netherlands by van der Woude revealed that most ICUs are already using a standardized pain score in conscious patients by NRS or VAS.[279] Although non-teaching hospitals used pain assessment tools more often than teaching hospitals. More important is the conclusion that in patients unable to self-report, pain is not routinely measured with a validated behavioral pain assessment tool, and certainly not using more objective indices. Consequently, more research and effort are needed for a more widespread acceptance of (1) the problem and (2) the usage of validated (behavior) pain assessment tools in non-communicative patients.

Chapter 2. Research aims & hypotheses

This thesis focuses on the possibilities for the prevention of postprocedural chronic pain. From one point of view, we looked at the possibilities of optimizing the nociceptive-anti-nociceptive balance assessment during surgery or ICU admission in unconscious patients. In the past decades, a variety of monitoring systems were developed in this balance evaluation (see **Appendix A** for an overview of the available monitoring tools and extensive background information on this subject). These are, among others, based on electromyography (EMG) response, evaluation of the autonomic state and autonomic reactions, and spinal reflex pathways. In the latter two categories, the pupil dilation reflex (PDR) evaluation and the nociceptive flexion reflex (NFR) measurement (see **Appendix B** for introduction into the two reflex measurements applied and discussed in this thesis) were evaluated as practically useful with promising results.[280-284] By extension, adequate pain management can only be executed if validated patient-specific assessment strategies are used. Moreover, this involves a correct identification of known biopsychosocial risk factors for persistent pain (after surgery) and multidisciplinary collaboration in a holistic care program. Consequently, this research project elaborates on this perioperative multidisciplinary approach through the development, implementation, and evaluation of surgical-specific biopsychosocial pain care programs.

Note that for some readers, a primary reading of the appendices A & B might be supportive for a better understanding of the content of the following chapters. The appendices can be found at the end of this book and contain supplementary information on the applied objective monitoring tools.

Research synopsis

This PhD project focuses on the following research questions in specific patient populations covering a majority of the patients hospitalized for surgery, admission in the ICU, or at (high) risk for chronic pain development (see Figure 2.1).

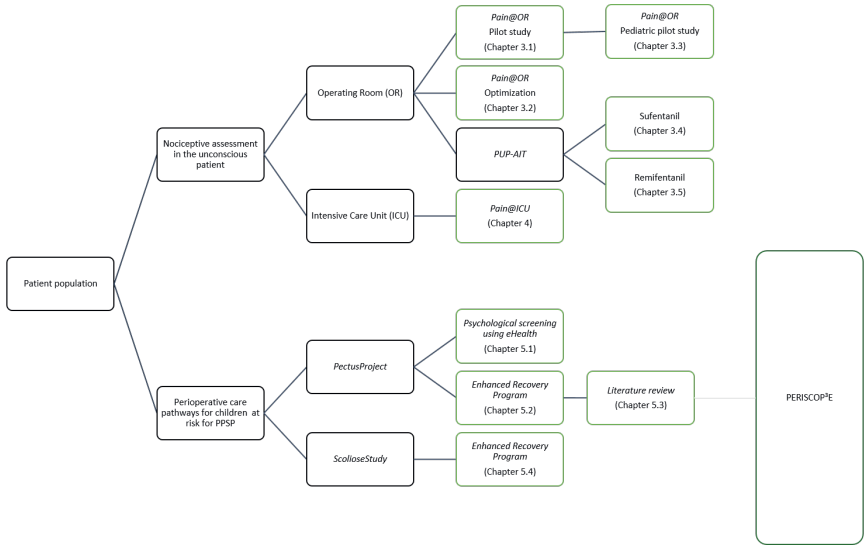


Figure. 2.1. Research project overview per category. Publications are shown in green, and attached as separate chapters. OR: operating room, ICU: intensive care unit, PPSP: persistent postsurgical pain, PUP-AIT: PUPil dilation reflex Assessment for Intraoperative analgesic Titration. *Note: Telemonitoring studies were executed in the pre-covid period.*

The following research questions address objective nociceptive assessment tools in a real-life setting in adult unconscious patients during surgery or intensive care treatment.

1. Is the pupil dilation reflex (PDR) using a pupillary pain index protocol feasible in anesthetized patients?
2. Is the PDR using a pupillary pain index protocol feasible in critically ill ventilated patients?
3. Can we measure a nociceptive flexion reflex (NFR) in these critically ill ventilated patients?

The following research questions address the development, implementation, and re-evaluation of transmural perioperative care pathways for patients at high risk for severe and/or persistent pain after elective surgery. The related studies focused on adolescents undergoing major thoracic (pectus) or spinal (scoliosis) surgery.

1. Can PROMs on pain and analgetic usage be favorably influenced using a biopsychosocial perioperative care protocol during the surgical trajectory?
2. Are screening questionnaires concerning psychological traits and state characteristics via a patient-specific online platform of potential use?
3. Is telemonitoring surveyance a feasible and representative manner to evaluate pain, sleep and daily activities during postoperative rehabilitation?

Overview of study populations and settings

Elective surgical procedures under general anesthesia: OR-population ('Operating Room')

As previously stated (chapter 1), the under-treatment of postoperative pain is generally known as a major delay in the postoperative recovery, rehabilitation, and discharge from the hospital, and the presence of analgesic side effects or the lack of adequate pain management will affect the hospitalization length adversely. Although several pre-emptive, multimodal pain treatment methods are described in the literature to reduce this dilemma[131] and continuous progress in these techniques, the development of an optimal individual perioperative pain management remains a challenge for researchers and care providers.[204]

Studies under this part of the research project are:

- **Pain@OR pilot study.** Pupillary dilation reflex and pupillary pain index evaluation during general anesthesia: a pilot study (see chapter 3.1).
- **Pain@OR optimization.** Pain assessment by pupil dilation reflex in response to noxious stimulation in anesthetized adults (see chapter 3.2).
- **Pain@OR Kids.** Evaluation of the pupil dilation reflex as a model for objective perioperative pain assessment in children and adolescents (see chapter 3.3).
- **PUP-AIT**. PUPil dilation reflex Assessment for Intraoperative analgesic Titration [PUP-AIT]. A single-center, randomized, double-blind trial comparing PDR-based opioid administration with the standard of care evaluating pain, opioid dosages, and PROMs. Note that this research project was divided into two studies with an identical study protocol but using two different opioids, remifentanil, and sufentanil. Study results after using 2 different commonly used opioids were published separately (see chapters 3.4 and 3.5).

Critically ill, mechanically ventilated patients: ICU-population ('Intensive Care Unit')

As described in the previous chapter, the negative physiological and psychological consequences of untreated pain in ICU patients are well-known, frequently present, and could be long-term in nature.[120] Therefore, it should be emphasized that this risk group deserves the attention of researchers and clinicians to optimize the current pain management strategies.

One study was performed under this part of the global research project:

Pain@ICU. Objective nociceptive assessment in ventilated ICU patients: A feasibility study using pupillometry and the nociceptive flexion reflex (see chapter 4.1).

A transmural perioperative care pathway in patients undergoing elective surgery prone to PPSP development

This thesis attempts to shed light on an intensive, biopsychosocial pain assessment in adolescents undergoing thoracic wall deformity surgery or spinal fusion surgery. The increasing interest in PPSP in children has heightened the need for risk factor identification and adequate early treatment. Attempts to address this question have been hampered by the difficulty of structured, holistic, long-term patient follow-up.[137]

Minimally invasive pectus surgery ('PectusProject')

Pectus excavatum (PE) occurs in 1 out of 400 to 1000 live births and is the most common chest wall deformity (80-90%); additionally, it affects four times more males than females. Pectus carinatum (PC) is the second most common anterior chest deformity (15%), with an even more pronounced male predominance.[285] The presence of PE and PC is reflected in a psychological component (low self-esteem) and clinical repercussions such as restrictive pulmonary disease, reduced exercise tolerance and cardiac compression in mainly adolescent patients. The surgical procedure has a long history. The minimally invasive NUSS-bar or MIRP-approach (minimally invasive repair of pectus), however, has only recently been introduced by Nuss for pectus excavatum patients.[286] In 1998, he described this technique as an alternative to the classic recovery described by Ravitch in 1949.[287] Moreover, it is only in the past decade that the Abramson technique has been used for pectus carinatum patients as a more minimally invasive surgical technique.[288] The reduced blood loss, smaller incision, and shorter operating time are just several of the advantages of this relatively new method. Despite the use of 'minimally invasive techniques', this procedure is associated with considerable postoperative pain.[289] Adequate analgesia, therefore, contributes significantly to perioperative success, with high patient satisfaction and reduction of surgical complications. The under-treatment of postoperative pain is generally known as a major delay in the postoperative recovery phase and rehabilitation with a delay in hospital discharge. Moreover, not surprisingly, it is suggested as a vital factor of patient dissatisfaction.[290] Despite the recognition of the above problem, a significant percentage of patients still experiences mild to moderately severe pain in the acute postoperative period.[291] Not only the presence of pain but also other discomforts such as nausea and vomiting are frequent, can dominate the early recovery period and may cause a prolonged hospitalization duration. [292,293] Notwithstanding the recent increase in scientific interest in pain management and PROMs,[294] to provide adequate pain management and antiemetic treatment remains challenging for every healthcare provider.

Studies that were performed under this part of the research project are:

- **Psychological screening using e-/m-Health**. Preliminary Evaluation of a Web-Based Psychological Screening Tool in Adolescents Undergoing Minimally Invasive Pectus Surgery: Single-Center Observational Cohort Study (see chapter 5.1).
- **Enhanced Recovery Program.** Implementation of an enhanced recovery pathway for minimally invasive PECTUS surgery: a population-based cohort study evaluating short- and long-term outcomes using mobile health technology (see chapters 5.2 and 5.3).

Posterior spinal fusion surgery due to idiopathic scoliosis ('ScolioseStudy')

By analogy, the **ScolioseStudy** was designed, implemented, and evaluated with a comparable patient population, namely adolescents planned for idiopathic scoliosis correction.

Adolescent idiopathic scoliosis (AIS) is a three-dimensional deformation of the spine affecting 1-3% of adolescents with a female predominance (8:1).[295,296] AIS is the most common type of spinal deformity and is a benign condition, but is frequently associated with back pain and psychosocial difficulties. It is of interest to compare PectusProject outcome variables with this spin-off trial, especially on persistent postsurgical pain, since recent data have shown that after major spinal fusion, 10 to 19% still experiences pain.[137]

One study was performed under this part of the global research project:

- **Enhanced Recovery Program.** Introduction of an enhanced recovery program for young adults undergoing posterior spinal fusion surgery for idiopathic scoliosis: a single-center pilot study evaluating short-term outcomes (see chapter 5.4).

A protocol for perioperative risk factor screening in the prevention of persistent pain after surgery (PERISCOP^{3}E)

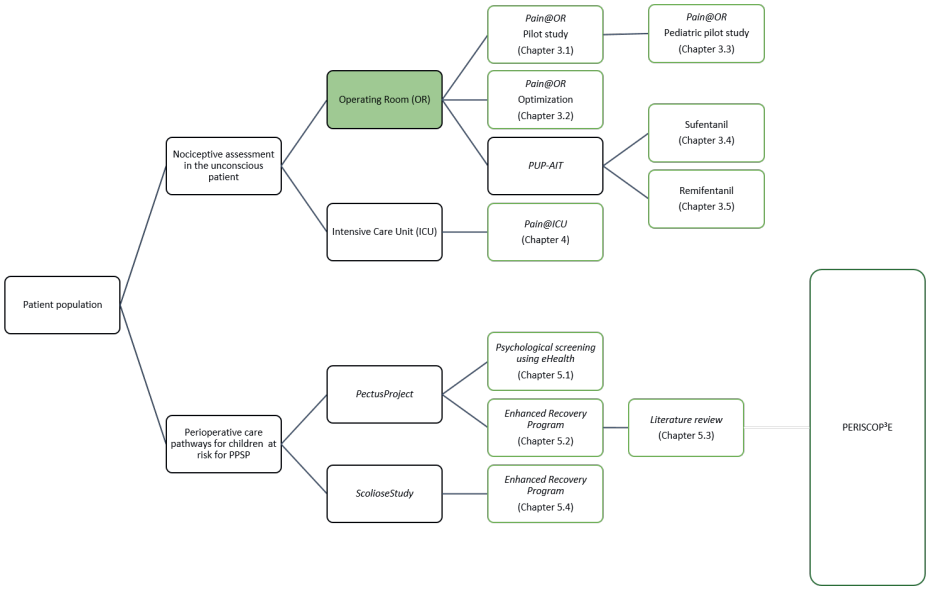
The PERISCOP^{3}E project bundles what science is still missing: biopsychosocial preventive care for surgical patients, using the available digital possibilities to be rolled out as widely as possible. This dissertation focused on generating a protocol for the first phase of PERISCOP^{3}E, in which both Kalkman and Althaus screening questionnaires, discussed earlier in the introduction, are being validated in an adult surgical patient group (see chapter 6). Moreover, well-being using the EQ-5D-5L instrument in a broad surgical population is being surveyed pre- and postoperatively. In addition, a cutoff score will be defined for participation in a "perioperative biopsychosocial enhanced vigilance program". After validation and cutoff determination, the design, implementation, and evaluation of such a PPSP vigilance program (in which patients at risk for PPSP are more closely monitored and treatment is started early when necessary) will be rolled out in the next years (phase 2, not in the scope of this thesis).

Research objectives

In conclusion, the strategic objectives of this research project are (1) the introduction of objective nociceptive assessment tools (reflex testing) in a real-life setting in adult unconscious patients during surgery or intensive care treatment and (2) the development, implementation, and re-evaluation of transmural perioperative care pathways for adolescents undergoing surgery at-risk for persistent pain. These two inquiries embrace the greater goal of persistent pain prevention and optimal procedure-related pain treatment using a biopsychosocial approach.

In extension, this holistic and more objective approach could prevent the development of central sensitization syndromes leading to chronification of pain and long-lasting pain-related morbidity. The findings of these focused strategies may be furthermore applied to ameliorate analgesic therapies during a hospital stay to decrease the suffering of patients, manage the development of opioid-induced hyperalgesia, and prevent the development of hyperalgesic states leading to chronic pain. Finally, the findings of this research project might also offer a platform to assess patient well-being by telemonitoring eHealth care as well as the design of a multifunctional database for patients, care providers and researchers.

Chapter 3. Pupillary dilation reflex measurement during general anesthesia



Overview of the research projects. Publications are shown in green and attached as separated chapters. OR: operating room, ICU: intensive care unit, PPSP: persistent postsurgical pain, PUP-AIT: PUPil dilation reflex Assessment for Intraoperative analgesic Titration. *Note: Telemonitoring studies were executed in the pre-covid period.*

This chapter focusses on nociceptive assessment in the unconscious patient during general anesthesia in the operation room (OR).

3.1 Pupillary dilation reflex and pupillary pain index evaluation during general anaesthesia: a pilot study.

Wildemeersch D, Baeten M, Peeters N, Saldien V, Vercauteren M, Hans G.

Published in Rom J Anaesth Intensive Care. 2018 Apr; 25(1): 19–23.
DOI: http://dx.doi.org/10.21454/rjaic.7518.251.wil

Abstract

Background

Pupillary response by pupillary dilatation reflex (PDR) is a robust reflex, even measurable during general anaesthesia. However, the ability of infrared pupillometry to detect PDR differences obtained by intraoperative opioid administration in anaesthesized patients remains largely unknown. We analyzed the performance of automated infrared pupillometry in detecting differences in pupillary dilatation reflex response by a inbuilt standardized nociceptive stimulation program in patients under general anesthesia with a standardized propofol/fentanyl scheme.

Methods

In this single center, interventional cohort study 38 patients (24–74 years) were enrolled. Patients were anesthetized with propofol until loss of consciousness. Two dynamic pupil measurements were performed in each patient (before opioid administration and after opioid steady state). Automated infrared pupillometry was used to determine PDR during nociceptive stimulations (10–60 mA) applied by a inbuilt pupillary pain index protocol (PPI) to the skin area innervated by the median nerve. Increasing stimulations by protocol are device specific and automatically performed until pupil dilation of > 13%. Pupil characteristics, blood pressure, heart rate values were collected.

Results

After opioid administration, patients needed a higher stimulation intensity (45.26 mA vs 30.79 mA, p = 0.00001). PPI score showed a reduction after analgesic treatment (5.21 vs 7.68, p = 0.000001), resulting in a 32.16% score reduction.

Conclusions

PDR via automated increased tetanic stimulation may reflect opioid effect under general anaesthesia. Further research is required to detect possible confounding factors such as medication interaction and optimization of individualized opioid dosage.

Keywords: analgesia, pain, monitoring

Introduction

Pain assessment in non-communicative patients is still challenging despite many novel innovative technologies. Under general anaesthesia, communication is impossible due to unconsciousness. Adequate measurement of nociception may allow the anaesthesiologist to individual titration of analgesics (mostly opioids), avoiding over- or underdosage. More and more anaesthesiologists attempt to minimize the dose of opioids, consequently reducing the well-known side effects. Correct nociceptive assessment and therefore appropriate individually based treatment, may be an ideal scenario. Appropriate pain assessment and evidence-based pain treatment may improve patient safety and outcome during hospital stay. Although current research addressing this complex issue provides some promising innovative techniques [1], no standardized objective pain monitoring protocols exist. Many professionals still use vital signs (heart rate, systolic blood pressure) or locomotor response as reliable indicators of nociception in the non-communicative patient under general anaesthesia [2].

Infrared pupillometry was introduced decades ago, but only recently used for nociceptive assessment. Concerns of unwanted device movement or subjective pupil diameter evaluation are no longer realistic with the introduction of an automated pupil tracking system [3]. Although recent research revealed a pupil dilation reflex (PDR) effect of antiemetics [4], and respiratory distress with hypoxia and/or hypercarbia [5], little is known about the influence by different opioids, age, or gender. Currently, portable video pupillometry is used for measuring pupil characteristics and the light-induced pupil reflex in response to noxious procedures [6–8].

However, if we want to evaluate the pupil response during noxious procedures (skin incision, pneumoperitoneum, etc.), monitoring of PDR elicited by standardized nociceptive stimulations in anesthesized patients needs to be further examined. Furthermore, there is a need for consensus to use and interpret different pupil assessment features as light-induced PDR, nociceptive stimulation induced PDR, constriction velocity, reaction latency or PPI score. We anticipated that a PDR evaluation, and in addition PPI score, by increasing tetanic stimulation may be related to analgesic treatment in anaesthesized patients.

Materials and methods

This single-center observational cohort study was performed in accordance with the ethical standards of ICH-GCP and the Declaration of Helsinki after study approval by the institutional review board and the Ethics Committee of the Antwerp University Hospital, Belgium (study identifier: 16/40/410). Registration at Clinicaltrials.gov (NCT02942316) was executed before study inclusion.

After written consent, patients planned for elective abdominal or gynaecological surgery with the American Society of Anesthesiologists physical status classification system (ASA) I or II were recruited for study inclusion from November 2016 until March 2017. History of ophthalmologic surgery, known pupil reflex disorders, cranial nerve lesions, expected difficult airway management, chronic opioid use (> 3 months) and preoperative use of topical interfering eye drops (atropine, phenylephrine) or antiemetics were defined as exclusion criteria.

Enrolled subjects underwent two consecutive pupil measurements under general anaesthesia. By convention the left eye was assessed after confirmation of pupil syndrome disorder absence. Patients were anaesthetized in a fully equipped operation room. No premedication was administered before surgery. On arrival in the operation theatre, standard monitoring and safe surgery checklist was executed. Venous catheter was inserted in a cubital vein. Non-invasive blood pressure was recorded every 5 minutes, and heart rate, ECG, oxygen saturation (SpO2), end-tidal-carbon dioxide concentration were recorded continuously.

Induction was established after preoxygenation by administration of a propofol bolus of 2 mg · kg−1 followed by continuous target controlled infusion (TCI) of propofol with effect-site concentration 5 µg · ml−1 (Marsh-Model; injectomat TIVA Agilia, Fresenius Kabi, Germany) [9, 10]. Manually assisted ventilation with 100% oxygen began as soon as the subjects became apneic. To facilitate orotracheal intubation rocuronium 0.6 mg · kg−1 was given when considered necessary by the attending anaesthesiologist. No deep neuromuscular block was used during surgery. Airway management was performed by laryngeal mask (LMA UniqueTM, LMA Deutschland GmbH, Bonn, Germany) placement or endotracheal intubation (Tracheal Tube MallinckrodtTM, CovidienTM, Tullamore, Ireland). First PDR measurement was performed when Richmond Agitation and Sedation Scale (RASS) ≤ −4 was achieved. If not, the rate of propofol was adjusted. Sedation depth by RASS classification was controlled by the attending anaesthesiologist, a resident in anaesthesiology and the principal investigator for PDR measurement approval. A second pupil assessment was executed after fentanyl 2 µg · kg−1 administration with a stabilization period of five minutes for airway management and opioid effect site equilibration [11, 12].

For PDR measurement, we used CE-approved NeuroLight AlgiScan® (IDMed, Marseille, France) pupillometer using infrared video recording allowing quantitative pupil size assessment during the steady state anaesthesia; i.e. no propofol adjustments were made during pupil analyses.

For nociceptive stimulation, two Ag-AgCl electrodes were placed at the skin area innervated by the median nerve. Optimal skin contact with low electrode impedance was defined on the touchscreen display. Constant current stimulations were generated during pupil measurement, increasing automatically the voltage according to the resistance. Voltage is limited to a maximum of 300 V. Therefore, at a current fixed at 60 mA, the maximum acceptable resistance is 5 KOhms. Patient movements during the stimulation were recorded.

The upper eyelid of the measured eye was opened during pupil assessment. A rubber cup placed to the orbit ensures optimal device position, pupil-camera distance and environmental darkness. There was never direct contact with the cornea. The contralateral eye was closed, reducing the effect of the consensual light response. Via the touch screen display the PPI-modus was selected for dynamic pupil measurement. This inbuilt measurement protocol generates an automatic electric stimulation pattern. Operating principle is the application of a standardized noxious stimulation (from 10 mA to 60 mA by incremental steps of 10 mA, with a duration of 1s, and pulse width of 200 µs) in increasing intensity, until pupillary dilation of more than 13% ([maximal diameter – minimal diameter]/maximal diameter × 100). When the defined criteria are reached, stimulation is automatically stopped and PPI score is determined (Table 1). The measurable pupil size (diameter) ranges between 0.1–10 mm. Furthermore, baseline (minimum) and maximum amplitude are recorded. Depending on necessary stimulation intensity, pupil measurement duration is between 2 and 16 seconds.

Maximum stimulation intensity (mA	Pupil reactivity	Generated PPI scor
10	Pupil dilation is greater than 13% during 10-mA stimulation	9
20	Pupil dilation is greater than 13% during 20-mA stimulation	8
30	Pupil dilation is greater than 13% during 30-mA stimulation	7
40	Pupil dilation is greater than 13% during 40-mA stimulation	6
50	Pupil dilation is greater than 13% during 50-mA stimulation	5
60	Pupil dilation is greater than 13% during 60-mA stimulation	4
60	Pupil dilation is greater than 13% during the second 60-mA stimulation	3
60 (5% < dilation < 13%)	Pupil dilation is greater than 13% during the third 60-mA stimulation	2
60 (dilation ≤ 5%)	Pupil dilation is greater than 13% during the last 60-mA stimulation	1
Note: if the pupil dilation is over 20% during stimulation, the PPI score is increased with one point		

Table 1. PPI Scoring algorithm

Statistical analysis

In this pilot study, no data were available to make assumptions for the sample size calculation.

Variables were reported as means ± standard deviation (SD). Pupil size variation was tested using non parametric analysis methods, as a normal distribution is unlikely in the study population. Mean stimulation intensity before and after opioid administration were compared using the Wilcoxon signed rank test in our paired data. Statistical analyses were performed with SPSS Statistics software, version 20.0 for Mac (IBM Corp., Armonk, NY, USA) and reviewed by a statistician member (E. Roelant, University Hospital Antwerp, Wilrijkstraat 10 – 2650 Edegem, Belgium) Statistical significance was considered with $p < 0.05$.

Results

Forty-one patients were enrolled for study inclusion; one patient dropped out due to an electrode impedance problem. Two subjects were excluded from statistical analysis because of outline baseline pupillary data (maximal stimulation intensity for primary measurement). Enrolled patients consisted of 27 women and 11 men, with a mean age of 46.53 ± 13.27 year, and mean BMI 26.01 ± 4.78 kg · m−2. No anti-emetic treatment was administrated prior to pupil analyses. All pupil measurements were taken in the absence of hypoxia (SpO2 awake: 98.34 ± 1.85%; SpO2 first PDR assessment: 99.11 ± 1.62%; SpO2 second PDR assessment: 99.20 ± 0.83%). Hypercarbia in the participants was excluded via end-tidal carbon dioxide monitoring with a target of ≤ 45 mmHg. Pupil characteristics are presented in Table 2.

Parameter	No opioid	After opioid	p value**
Baseline pupil diameter (mm)	3.57 ± 1.09	2.17 ± 0.38	< 0.0001
Stimulation intensity (mA)	30.79 ± 10.24	45.26 ± 14.66	0.000016
Pupil variation (mm)	1.09 ± 0.53	0.35 ± 0.21	< 0.0001
Pupil variation (%)	31.39 ± 14.81	15.97 ± 7.01	< 0.0001
PPI score*	7.68 ± 1.17	5.21 ± 2.16	0.000001

Data are expressed mean ± SD
* PPI = pupillary pain index; ** stat. sign. for $p < 0.05$

Table 2. Changes in pupil characteristics before and after opioid administration.

Baseline pupil diameter decreased by 39% by analgesic treatment. Pupil variation increased significantly after noxious stimulation without opioid, although the stimulation stops when 13% dilation is achieved. The necessary stimulation intensity increased significantly after opioid administration, correlating with a 32% reduction in PPI score. Fourteen patients needed a maximal stimulation intensity of 60 mA (37%) during PDR evaluation after fentanyl administration. Stimulations were well tolerated without significant variation in vital signs (Table 3).

	Before analgesia	After analgesia	p value*
Systolic blood pressure (mmHg)	121.55 ± 18.47	100.95 ± 18.75	0.000001
Heart rate (bpm)	70.66 ± 10.95	69.26 ± 12.25	0.094

Data are expressed mean ± SD
* stat. sign. for $p < 0.05$

Table 3. Variation in vital signs induced by opioid administration.

Discussion

This pilot study suggests that PDR measurement by infra-red pupillometry with an inbuilt standardized noxious stimulation protocol may be related to opioid administration in patients under general anaesthesia. An additional automatically generated PPI-score, in accordance with the standard pain assessment by a numeric rating scale (NRS) in communicative adults, reflects differences in PDR response after analgesic treatment. Larger pupil variation percentages before opioid administration indicates the fast mydriatic effect after tetanic stimulations via an automated inbuilt program.

Despite the ongoing debate of opioid free anaesthesia, mainly in patients at risk such as obstructive sleep apnoea syndrome or gastrointestinal surgery [13], no large trials were conducted for optimizing pain assessment in non-communicative patients during surgery. The lack of nociceptive evaluation in patients under general anaesthesia, impedes adequately treating pain and therefore under – or overdosing still occurs, further compromising the patient outcome. The stress response evoked by pain can have deleterious negative consequences. Increased circulating catecholamines can cause arteriolar vasoconstriction, impair tissue perfusion, and reduce tissue-oxygen partial pressure [14]. Furthermore, catabolic hypermetabolism resulting in hyperglycemia, lipolysis, and breakdown of muscle to provide protein substrate, impairs wound healing and increases the risk of wound infection [15–17]. Moreover, pain compromises postoperative comorbidities causing delay in early rehabilitation and prolongues the hospital stay. On the other hand, overdosing opioids are also associated with negative consequences such as opioid-induced hyperalgesia, ileus or nausea and vomiting.

Recently, De Jonckheere et al. presented some technological solutions for nociception monitoring [18]. The choice of assessment device relies, however, on the clinical context and general purpose.

Nociceptive assessment in non-communicative patients remains challenging for health care providers.

PDR is known as a robust reflex, parasympathetically mediated during general anesthesia [19]. Barvais et al. found that PDR upon a painful tetanic (100 Hz) stimulus was a better indicator for remifentanil titration than a haemodynamic response or BIS measurements during propofol TCI in healthy individuals [20]. Moreover, PDR evaluation recently showed promising results in awake and unconscious patients. Administration of classically used sedatives showed no depression of the PDR after activation of nociceptive A-delta and C-fibers [21]. It should be noted that during chronic opioid treatment, tolerance occurs in analgesic effect and respiratory depression effect, in contrast to the elicitation of miosis. This should be taken in account when interpreting PDR results.

Propofol, lidocaine and neuromuscular blocking agents do not affect pupil reactivity in contrast to modern used inhalation anaesthetics such as sevoflurane and desflurane [22, 23], and nociceptive stimulation still induces mydriasis under general anaesthesia. Up to now, all the mechanisms of blocking this pupil reflex are not fully understood. Furthermore, drugeffect measurements are still evaluated either as pupil variation from baseline or as an absolute effect by extreme accurate equipment [21]. Our results indicate that PRD measurements during standardized nociceptive stimulation of the skin may perceive the effects of endogenous opioid response in patients receiving propofol anaesthesia. To determine the effect of fentanyl we used a gradual increase in stimulation intensity in anaesthetized patients by protocol. An advantage of this automated schedule is that there is no need for unappropriated high stimulation. When the device detects a pupil variation of > 13%, nociceptive stimulation is interpreted and stopped. The use of automated pupillometry for nociceptive PRD evaluation in non-communicative adults may provide the caregiver the possibility to measure the reactivity of the autonomous system to nociceptive stimuli. Recently, Jakuscheit et al. used the PDR among others as nociceptive reflex and concluded this assessment as a reflection of the analgesia-nociception balance under general anaesthesia [24].

There are, however, some limitations to our pilot study such as the unequal gender distribution caused by including a majority of gynaecological patients. Evaluation of the heart rate, systolic blood pressure and the application of an anaesthesia depth device, as additional standard parameters for each nociceptive stimulation category would have been of particular value. To determine the effect of opioid administration, patients should obtain an equal anaesthesia depth prior to the first pupil measurement. Moreover, opioid administration with estimated effect site concentrations would define steady state analgesic plasma concentrations even more superior.

Conclusions

In conclusion, if caregivers would be able to improve opioid titration based on individual and more objective reflex parameters, adequate analgesic administration would be performed with less over – and underdosing. As a fast, straightforward and easy to use bedside device, PDR measurement in response to noxious stimulation may help the anaesthesiologist to evaluate the autonomous component of nociception in anaesthetized adults undergoing painful procedures. Whether this technique, including PPI scoring, may be helpful in recruiting perioperative opioids necessitates more clinical research.

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3.2 Pain assessment by pupil dilation reflex in response to noxious stimulation in anaesthetized adults.

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Abstract

Background

In response to noxious stimulation, pupillary dilation reflex (PDR) occurs even in anaesthetized patients. The aim of the study was to evaluate the ability of pupillometry with an automated increasing stimulus intensity to monitor intraoperative opioid administration.

Methods

Thirty-four patients undergoing elective surgery were enrolled. Induction by propofol anaesthesia was increased progressively until the sedation depth criteria (SeD) were attained. Subsequently, a first dynamic pupil measurement was performed by applying standardized nociceptive stimulation (SNS). A second PDR evaluation was performed when remifentanil reached a target effect-site concentration. Automated infrared pupillometry was used to determine PDR during nociceptive stimulations generating a unique pupillary pain index (PPI). Vital signs were measured.

Results

After opioid administration, anaesthetized patients required a higher stimulation intensity (57.43 mA vs 32.29 mA, $P < .0005$). Pupil variation in response to the nociceptive stimulations was significantly reduced after opioid administration (8 mm vs 28 mm, $P < .0005$). The PPI score decreased after analgesic treatment (8 vs 2, $P < .0005$), corresponding to a 30% decrease. The elicitation of PDR by nociceptive stimulation was performed without changes in vital signs before (HR 76 vs 74/min, $P = .09$; SBP 123 vs 113 mm Hg, $P = .001$) and after opioid administration (HR 63 vs 62/min, $P = .4$; SBP 98.66 vs 93.77 mm Hg, $P = .032$).

Conclusions

During propofol anaesthesia, pupillometry with the possibility of low-intensity standardized noxious stimulation via PPI protocol can be used for PDR assessment in response to remifentanil administration.

Keywords: analgesia, assessment, monitoring, reflex

Introduction

Despite the availability of numerous innovative technologies [1-2], analgesia assessment in anaesthetized patients is not integrated in routine perioperative patient care [3]. Patients are frequently unable to communicate as a result of sedative administration. For evaluation of a nociceptive/anti-nociceptive balance and subsequent optimal analgesic (mostly opioids) treatment, anaesthesiologists still use non-specific changes in heart rate (HR) or blood pressure (BP) in combination with the locomotor response as a surrogate for nociception[4]. It has been recently demonstrated that PDR can be elicited under general anaesthesia with an automated generated electrical stimulation protocol with increasing intensity [5,6]. These study results were consistent with findings from previous studies with a single (high) tetanic stimulation for PDR elicitation in non-communicative patients [7-9].

Given the development of pupilometers with an integrated automated pupil tracking system [10], PDR can be used during surgical procedures in the operation room for nociceptive state evaluation [11-13].

Recent research has revealed a PDR effect measured by single tetanic noxious stimulation, of anti-emetics [14] and respiratory distress with hypoxia and/or hypercarbia [15]. To date, little is known about PDR evaluation after multiple increasing standardized noxious stimulations starting at 10 mA generated by an inbuilt PPI protocol (PPI, pupillary pain index) as an alternative for high tetanic stimulation. Although significant research is devoted to nociceptive monitoring, less attention has been paid to different techniques for PDR elicitation.

The aim of this study was to evaluate the PPI stimulation protocol for PDR measurement before and after opioid administration in adult patients undergoing general anaesthesia.

Methods

Study design

This single-centre interventional cohort study was performed in accordance with the ethical standards of ICH-GCP and the Declaration of Helsinki after study approval by the institutional review board and ethics committee of Antwerp University Hospital, Belgium (study identifier: 16/40/410-2). Registration at Clinicaltrials.gov (NCT03140241) occurred before study inclusion.

After written consent, patients who planned for elective abdominal or gynaecological surgery with American Society of Anaesthesiologists physical status classification system (ASA) I and II were recruited for study inclusion from May 2017 until June 2017. Open surgery (laparotomy), body mass index >30 kg m−2, a history of ophthalmologic surgery, known pupil reflex disorders, Horner's or Adie's syndrome, previous eye trauma, cranial nerve lesions, expected difficult airway management, chronic opioid use (>3 months) and preoperative use of topical eye drops (atropine, phenylephrine), β antagonists or anti-emetics were defined as exclusion criteria. The patients did not receive premedication.

Definition of outcome parameters

The primary outcome was the difference in stimulation intensity necessary for pupil dilation of >13% before and after opioid (ie, remifentanil) administration, as defined by the inbuilt PPI stimulation protocol. Secondary outcome measurements were changes in vital signs before and after

standardized nociceptive stimulation. HR and BP were recorded before and immediately after stimulation.

Study protocol

The enrolled subjects underwent 2 consecutive, by convention left, pupil measurements under general anaesthesia. Pupil assessments were executed before surgery. Anaesthesia was induced with propofol (propolipid 1%) by target controlled infusion (TCI; Marsh-model; injectomat TIVA Agilia, Fresenius Kabi, Germany),16, 17 and the target effect-site concentration (Ce) was progressively increased until loss of consciousness (LOC). The sedation depth (SeD) ranged from 40 to 50 on the sedation depth brain monitor NeuroSense® (NeuroWave Systems Inc., Cleveland, OH). Thereafter, the first PDR measurement was performed. Consequently, the subjects received remifentanil by continuous infusion up to Ce 5 ng mL−1 using the pharmacokinetics of Minto.18 Manually assisted ventilation using a facemask with 100% oxygen was initiated as soon as the subjects became apnoeic. Then, 0.6 mg kg−1 rocuronium was administered to facilitate orotracheal intubation when considered necessary by the attending anaesthesiologist. No deep neuromuscular block was used during surgery. Airway management was performed by laryngeal mask (LMA Unique™; LMA Deutschland GmbH, Bonn, Germany) placement or endotracheal intubation (Tracheal Tube Mallinckrodt™, Covidien™, Tullamore, Ireland). A second pupil assessment was conducted after reaching a remifentanil plateau level of Ce 5 ng mL−1. Propofol adjustments were executed to maintain the defined SeD criteria during both pupil measurements. In the awake state and during the entire study period (Figure 1), SeD variables and HR were registered continuously, and the BP was recorded routinely every 2 minutes and after maximal stimulation intensity.

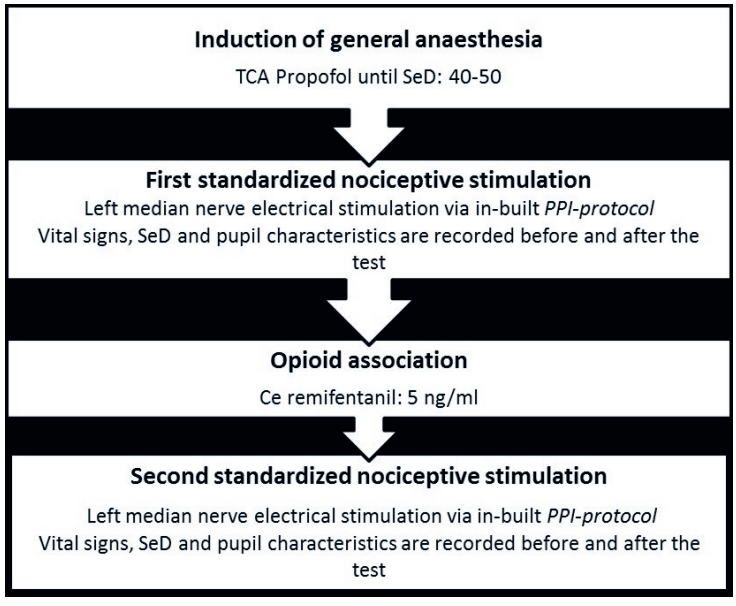

Fig 1. Summary of study timeline. TCA, target controlled analgesia; SeD, sedation depth; PPI, pupillary pain index; Ce, effect-site concentration

Standardized nociceptive stimulation and measurements of pupil characteristics

For PDR measurement, we used the CE-approved NeuroLight AlgiScan® (IDMed, Marseille, France) pupillometre using infrared video recording to allow quantitative pupil size assessment during steady-state anaesthesia. For nociceptive stimulation, 2 Ag-AgCl electrodes with low impedance were optimally placed at the skin area innervated by the median nerve. Constant current stimulations were generated during pupil measurement, and the voltage was automatically increased according to the resistance. The voltage is limited to a maximum of 300 V. Therefore, for a current fixed at 60 mA, the maximum acceptable resistance is 5 kΩ. The time to reach the medication plateau level and therefore pupil analyses were recorded.

The upper eyelid of the measured eye was opened during pupil assessment. A rubber cup was placed on the orbit ensured optimal device position, pupil-camera distance and environmental darkness. Direct contact with the cornea never occurred. The contralateral eye was closed, reducing the effect of the consensual light response.

Pupillary pain index protocol

Via the touch screen display, the PPI-modus was selected for dynamic pupil measurement. This inbuilt measurement protocol generates an automatic electrical stimulation pattern. The operating principle is the application of a standardized noxious stimulation (from 10 to 60 mA by incremental steps of 10 mA, with a duration of 1 second, and pulse width of 200 μs) starting at low stimulation intensity in increasing steps until a pupillary dilation of >13% is achieved ([maximal diameter − minimal diameter]/maximal diameter × 100). When the defined criteria are achieved, stimulation is automatically stopped, reducing unnecessary high stimulation. Then, the PPI score is determined (Table 1). The generated PPI score is calculated depending on the necessary stimulation intensity to provoke a pupil dilation of >13% (ie, inbuilt cut-off criteria) and pupil reflex amplitude. One point is added to the 9-level PPI score if the dilation of the pupil is >20% despite a halt of stimulation at 13%. The measurable pupil size (diameter) ranges between 0.1 and 10 mm. Furthermore, the baseline (minimum) and maximum amplitude are recorded. Depending on the necessary stimulation intensity, the pupil measurement duration is between 2 and 16 seconds.

Table 1. PPI Scoring algorithm

Maximum stimulation intensity (mA)	Pupil reactivity	Generated PPI score
10	Pupil dilation is greater than 13% during 10-mA stimulation	9
20	Pupil dilation is greater than 13% during 20-mA stimulation	8
30	Pupil dilation is greater than 13% during 30-mA stimulation	7
40	Pupil dilation is greater than 13% during 40-mA stimulation	6
50	Pupil dilation is greater than 13% during 50-mA stimulation	5
60	Pupil dilation is greater than 13% during 60-mA stimulation	4
60	Pupil dilation is greater than 13% during the second 60-mA stimulation	3
60 (5% < dilation < 13%)	Pupil dilation is greater than 13% during the third 60-mA stimulation	2
60 (dilation ≤ 5%)	Pupil dilation is greater than 13% during the last 60-mA stimulation	1

Note: if the pupil dilation is over 20% during stimulation, the PPI score is increased with one point

Statistical analysis

From an earlier pilot study, data were available to make assumptions for the sample size calculation, which included 34 subjects ($\alpha = .05$, $1-\beta = .9$, difference to detect = 10 mA).6 Data analyses were screened for quality by a statistical department member.

Pupil characteristics were based on median and quartiles. Heart rate and blood pressure variables were reported as means ± standard deviation (SD). Pupil size variation was tested using non-parametric analysis methods, as a normal distribution is unlikely in the study population. Mean stimulation intensity and sedation depth before and after opioid administration were compared using the unpaired Wilcoxon tests. These tests were also employed for comparisons of pupil diameter, HR, and SBP before and after nociceptive stimulation. Statistical analyses were performed with SPSS Statistics software, version 20.0 for Mac (IBM Corp., Armonk, NY, USA). Statistical significance was considered as $P < .05$.

Results

Thirty-four patients were enrolled in the study. Five subjects were found to require maximal stimulation intensity for the primary measurement (ie, 60 mA). Nevertheless, the PPI varied in this subgroup from 4 to 2. In the enrolled patients, the male/female ratio was 9/26, with a mean age of 45 ± 14 years and a mean BMI of 24.47 ± 3.53 kg m−2. The mean Ce of propofol was 7.34 ± 1.27 μg mL−1 to establish a mean overall sedation depth of 45.70 ± 2.76. Propofol adjustments were made if necessary to fulfil sedation depth criteria. All pupil measurements were performed in the absence of hypoxia or hypercarbia. No anti-emetic treatment or premedication (benzodiazepines) was administered prior to pupil analyses. The pupil characteristics are presented in Table 2. Differences in the baseline pupil measurements, stimulation intensity and PPI scores are presented in Figure 2. The BP and HR decreased from the awake state to the LOC (Table 3).

Table 2. Changes in pupil characteristics before and after opioid administration. PDRA, pupillary dilation reflex amplitude; PPI, pupillary pain index. Data are expressed as the overall median and interquartile range [IQR]. Loss of consciousness (LOC) and remifentanil Ce 5 ng mL^{-1} are reported for the first and second PDR assessment, respectively. Statistically significant for P < .05.

Parameter	LOC	Remifentanil Ce 5 ng mL^{-1}	*P*-value[a]
Baseline pupil diameter (mm)	4.00 [IQR 3.30-4.50]	1.90 [IQR 1.70-2.00]	<.0005
Stimulation intensity (mA)	30.00 [IQR 20.00-40.00]	60.00 [IQR 60.00-60.00]	<.0005
PDRA (mm)	1.11 [IQR 0.91-1.47]	0.16 [IQR 0.11-0.23]	<.0005
Pupil variation (%)	28 [IQR 21-39]	8 [IQR 6-12]	<.0005
PPI score	8 [IQR 7-9]	2 [IQR 1-2]	<.0005

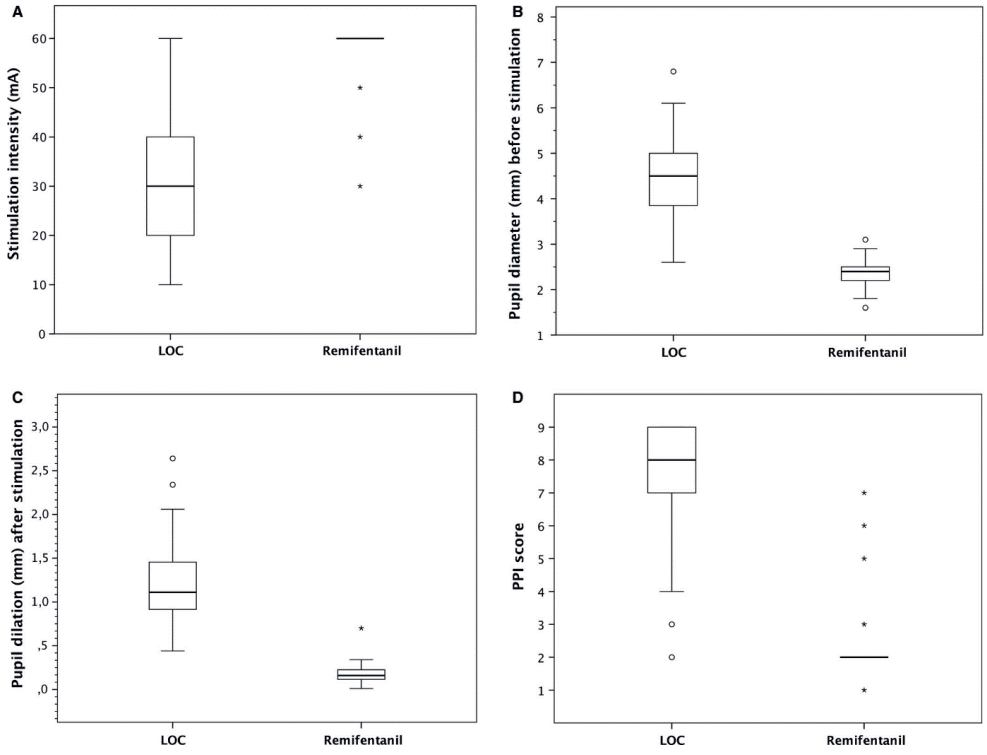

Fig 2. (A), Boxplots of necessary stimulation intensity to elicit PDR via a PPI stimulation protocol. The thick horizontal line indicates the median, the limits of the box indicate the 25th (Q1) and 75th (Q3) percentiles, and the whiskers denote the extreme values (Q1 − 1.5*[IQR]; Q3 + 1.5*[IQR]). (B), Boxplots of baseline pupil diameter in millimeters (mm) before stimulation. (C), Boxplots of pupil dilation in millimeters (mm) evoked by the standardized noxious stimulation. (D), Boxplots of the pupillary pain index (PPI) score based on stimulation intensity and pupil variation.

Table 3. Variation in vital signs during the study protocol. SBP, Systolic blood pressure; DBD, diastolic blood pressure; HR, heart rate; SeD, sedation depth. Data are expressed as the mean ± SD. Loss of consciousness (LOC) and remifentanil Ce 5 ng mL−1 are reported for the first and second PDR assessment, respectively.

	SBP (mm Hg)	DBP (mm Hg)	HR (/min)	SeD
Awake	142 ± 29	76 ± 13	77 ± 12	92 ± 2
LOC				
Before PDR	123 ± 25	69 ± 14	76 ± 12	46 ± 3
After PDR	113 ± 19	64 ± 13	74 ± 11	
Remifentanil				
Before PDR	99 ± 19	52 ± 13	63 ± 12	45 ± 4
After PDR	94 ± 12	49 ± 8	62 ± 11	

In the absence of noxious stimulation, the pupil size (baseline diameter) decreased from the LOC to the point that remifentanil Ce 5 ng mL−1 was achieved. The sedation level (SeD) was comparable for both pupil assessments. The pupil dilation response to the built-in noxious stimulation PPI protocol decreased from LOC to remifentanil Ce 5 ng mL−1, ie, stimulation intensity increased significantly after opioid administration. At the second PDR evaluation, the pupil variation (amplitude response after SNS) was remarkably reduced without frequent pupil "overshooting" (dilation of >13%). After opioid administration, maximal stimulation was necessary in 30 subjects to obtain a pupillary dilation of at least 13%. The PPI score, which was automatically coupled by the pupillometre to stimulation intensity, decreased by a mean of 5 points from the LOC to remifentanil Ce 5 ng mL−1.

Discussion

This study suggests that pupillometry with a built-in standardized PPI protocol for increasing stimulation intensity is a good alternative for single tetanic noxious stimulation PDR evaluation and therefore useful for analgesia level assessment in patients under general anaesthesia with propofol. The use of lower stimulation intensities in this pre-scheduled PPI protocol may provide the anaesthesiologist with sufficient information about PDR without causing unnecessary changes in HR or BP.

In awake subjects, PDR occurs after sympathetic pathway stimulation with a dilatation response as a result of radial muscle contraction. Under general anaesthesia, the robust PDR is parasympathetically mediated. In the anaesthetized patient, sympathetic activity is depressed by the administration of sedative drugs, enhancing the parasympathetic influence towards the Edinger–Westphal (E.W.)

nucleus. E.W. neurons are pacemaker cells with intrinsic firing characteristics to the sphincter pupillae muscle fibres. General anaesthesia, therefore, results in miosis. When applying a nociceptive stimulation sufficient to activate nociceptors via Aδ- or C fibres in an anaesthetized individual, pupil dilation occurs through E.W. neuron inhibition and consequently passive sphincter relaxation [19-20].

Propofol, lidocaine and neuromuscular blocking agents do not affect pupil reactivity in contrast to modern inhalation anaesthetics, such as sevoflurane and suprane, and nociceptive stimulation still induces mydriasis under general anaesthesia [21-22]. Opioids mediate pupil diameter under general anaesthesia by E.W. nucleus disinhibition, resulting in miosis, and depress PDR in a dose-dependent manner [23]. To date, the mechanisms of blocking this pupil reflex are not completely understood.

Larson et al. [11] demonstrated the superiority of pupillometry for assessing nociception above vital signs during isoflurane and propofol anaesthesia. More recent research from Barvais and colleagues confirms those findings in volunteers during propofol anaesthesia. PDR upon a single painful tetanic stimulation was a better indicator for remifentanil titration than a haemodynamic response or BIS measurements during propofol TCI in healthy individuals [23].

In our study methodology, we used propofol TCI and remifentanil via continuous infusion, which is the most common technique for total intravenous anaesthesia (TIVA).

Sedation depth monitoring equipment is being used more frequently for individual titration of anaesthesia depth. Previous research demonstrated that the bispectral index was a better indicator for sedation titration than haemodynamic parameters, and many anaesthesiologists are familiar with this technology [24]. Despite what has been suggested in the past, sedation depth monitors are not as sensitive for nociceptive responses elicited by noxious stimulation and can therefore not help anaesthesiologists in assessing perioperative analgesia levels. The occurrence of perioperative movement suggests a lack of analgesia to many anaesthesiologists. However, an insufficient sedation level may contribute to this event. Furthermore, the presence of movement as a reaction to an SNS generated by the PPI protocol may indicate a patients' need for increased opioid administration. Guglielminotti and colleagues concluded that a PDR evoked by SNS is accurate in the prediction of movement during a painful (surgical) stimulation [9].

Our results indicate that PRD measurements during standardized nociceptive stimulation of the skin generated via a PPI protocol may demonstrate the effects of the endogenous opioid response in patients receiving propofol anaesthesia. To determine the effect of remifentanil, we used a gradual increase in stimulation intensity in anaesthetized patients per protocol. An advantage of this automated schedule is that there was no need for inappropriately high stimulation. When the device detects a pupil variation of >13%, the nociceptive stimulation is interpreted and stopped. The use of automated pupillometry for nociceptive PRD evaluation in non-communicative adults may provide the caregiver the possibility to measure the reactivity of the autonomic system to nociceptive stimuli. PDR elicited by an SNS is at least as accurate as the estimated remifentanil Ce to predict movement, as evaluated upon cervix dilation by Guglielminotti [9]. Recently, Jakuscheit et al. [25] used PDR as a nociceptive reflex and concluded that this assessment is a reflection of the analgesia-nociception balance under general anaesthesia. Appropriate pain assessment and evidence-based pain treatment may not only reduce over- or under-dosing of opioids but may also even improve patient safety and outcome during hospital stays. Although current research addressing this complex issue provides

some promising innovative techniques, no standardized objective pain monitoring protocols exist [2]. Furthermore, there is a need for consensus to use and interpret different pupil assessment features, such as light-induced PDR [15,26], nociceptive stimulation-induced PDR [8, 27], pupillary unrest [28], constriction velocity and reaction latency [29] or PPI score [5].

There are some limitations to this study. First, the unequal gender distribution caused by the inclusion of gynaecological patients may bias study results. Weak gender effects on pupillary light reflex have been suggested [30-31]. To date, no gender difference in PDR under general anaesthesia has been demonstrated. Second, no conclusions can be made regarding the assessment of the nociception level given that only 2 dosages of remifentanil are allowed. Moreover, the majority of the subjects had a PPI score of 2, suggesting the possibility of opioid dose reduction.

To date, whether a titratable analgesia level is assessable using PPI remains unknown. Additional research is needed to further clarify the sensitivity of the PPI protocol used and the discriminating value of a pupil dilation cut-off of 13%. Third, the design of this proof of concept study does not include individual opioid management protocols. Ideally, adequately treating pain in patients under general anaesthesia is performed by multiple reproducible, objective analgesia assessments. In addition, it is essential to monitor patients during surgery to determine the adequacy of the therapeutic intervention (ie, opioid administration) based on individually derived PDR indices. Moreover, this study only validates the remifentanil Ce protocol and does not measure the adequacy of surgical analgesia. However, up to now there are no studies concerning analgesia level assessment via PDR-PPI measurement during surgery evaluating opioid dosing and patient-related outcome measures. Our findings must, therefore, be evaluated in larger comparative descriptive studies or randomized controlled trials.

In conclusion, if anaesthesiologists could improve opioid titration based on individual and more objective reflex parameters, adequate analgesic administration would be executed with less over- and under-dosing. As a fast, straightforward, reliable and easy-to-use bedside device, PDR measurement in response to standardized nociceptive stimulation may help the anaesthesiologist to evaluate the autonomous component of nociception in anaesthetized adults undergoing painful procedures. Moreover, PDR could be of additional value in patients for whom anaesthesiologists' cannot use classic pharmacokinetic algorithms based on the patient's age or body mass index.

Whether this technique, including PPI scoring, may be helpful in reducing perioperative opioids and whether it positively impacts the length of stay and the development of chronic pain after surgery requires additional clinical research.

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3.3 A feasibility study of the Pupillary Pain Index measurement in Anesthetized Children.

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Abstract

What we already know

a) Pain assessment in anesthetized children is challenging and currently used methods are not specific.

b) Pupillometry has already shown to be interesting and the pupillary pain index (PPI) in anesthetized adults shows promising results. What new information this study ads. c) PPI can be a useful tool for non-invasive nociceptive assessments, in anesthetized, pediatric patients.

Background

Inadequate treatment of pain has numerous negative consequences. However, treatment with opioids can also be detrimental, with potential harmful effects after overdosing. Intraoperative hemodynamic parameters used today are non-specific nociceptive surrogate markers and insufficient to provide an objective nociceptive assessment. Furthermore, those variables have a wide variety depending on age.

Aim

This study aims to evaluate whether pupillary pain index (PPI), via pupillary dilation reflex (PDR), can be used as a feasible nociceptive monitoring tool in the pediatric surgical population. Furthermore, pupil characteristics in two age classes (A = 28 days to 23 months, B = 24 months to 11 years) are identified.

Methods

Twenty pediatric patients scheduled for elective surgery under general anesthesia at the Antwerp University Hospital (UZA, Edegem, Belgium) were included. PDR was determined by an automatic stimulation pattern whereby intensity was increased (1s stimulation, 10-60mA, steps of 10mA). Pupil measurements were executed at two standardized times during a steady state sevoflurane T0 and T1, respectively without and with opioids. Vital signs were registered during measurement.

Results

PPI score decreased after opioid administration (group A: 2 vs 1, $P<0.05$; group B: 2 vs 1 $P<0.05$). Vital signs did not change significantly during noxious stimulation. In both groups the PDR amplitude and pupil variation decreased when opioids were administered (amplitude A: 0.24mm vs 0.06mm, B: 0.24mm vs 0.07mm; variation A: 12.1% vs 2.9%; B: 10.3% vs 2.5%, respectively). At T1, miosis was only observed in group B (group A: 1.87mm vs 1.84mm, $P=0.7$; group B: 2.27mm vs 2.51mm, $P<0.05$).

Keywords: Pupillary pain index; Pupillometry; Children; Nociception; Opioids; Perioperative

Background

Pain is a complex concept, as it combines multiple features of psychology, while it also encompasses behavioral aspects and physiology. Nociception is the sensory nervous system's process of encoding noxious stimuli. Monitoring nociception remains a challenge in patients. Non-specific parameters such as elevated heart rate (HR), systolic blood pressure (SBP) or movement, used as surrogate nociceptive indicators, have already shown to be inaccurate to assess this nociceptive- anti-nociceptive balance [1-4].

Opioids are mainly used for perioperative analgesia despite our knowledge of its consequences, such as more opioid dependency, constipation, urine retention and respiratory depression, even in children [5]. This re-enforces the need for adequate pain management and prevention of excess use of opioids, avoiding under-or overdosage contributing to discomfort.

Moreover, nociceptive neural activation augments a stress response. Minimizing this response has obvious beneficial effects on outcome, namely decreased morbidity and mortality in surgical patients [6]. In addition, excessive nociceptive activity could initiate chronic (postoperative) pain [7]. To adequately manage anti-nociceptive therapies, optimal monitoring tools should ideally be available. Therefore, there is a need for more objective nociceptive evaluation in order to accommodate patient-specific analgesia by using adequate titration of opioids.

Pupil size is determined by the opposing action of smooth muscles in the iris innervated by the sympathetic and parasympathetic divisions of the autonomic nervous system [8]. During general anesthesia, sedative drugs are depressing the sympathetic activity whereby the parasympathetic system gains influence through the Edinger-Westphal (EW) nucleus, resulting in miosis. In awake subjects, pupillary reflex dilation (PRD) occurs after sympathetic pathway stimulation with a dilatation response. In anaesthetized subjects, a nociceptive stimulus will inhibit the EW nucleus leading to a passive sphincter relaxation, thus PRD [9]. Opioids block the inhibitory influence on the EW nucleus whereby miosis is induced. Further, they depress PRD in a dose-dependent fashion [9].

Pupillometers are widely available to allow accurate quantification of the pupil diameters [9,10]. PRD is a physiological response to noxious stimuli. We can describe PRD as (1) the maximal increase in the pupil diameter after noxious stimulation, the amplitude (PRDA) or as (2) a percentage of initial pupil diameters, the variation (PRDV). Studies in both children and adults have shown that it is a particularly sensitive noxious stimulation measurement, which is moreover well correlated with opioid concentrations [1-3,11]. However, without a standard pupillary measurement technique, there can be no meaningful comparison of PRD for nociception. Hence, the pupillary pain index (PPI) was created. PRD measurements derived from titrated noxious stimulation will allow to determine a score from 1 (high electrical stimulus, no PRD) to 9 (low electrical stimulus, high PRD). In adults, PPI have been shown to be a reliable indicator [12,13]. To date, no data regarding the accurateness of PPI in the pediatric population is available. Therefore, this study investigates pupil reactivity, after standardized noxious stimulation in anesthetized children before and after opioid administration.

The primary objective of the study was to determine the electrical intensity of the PPI protocol necessary to have a pupil dilation of >13% with and without opioids, as defined by the in-built stimulation protocol. In other words, to determine the PPI score with and without opioids in different age classes.

Secondary objectives were to differentiate the obtained information from commonly used variables for nociception: HR, SBP and movement of a limb (e.g. withdrawal or extension of arm). An additional secondary objective was to identify age-specific pupil characteristics.

Methods

This prospective, observational, and open study was approved by the local ethics committee of the Antwerp University Hospital, Belgium (study identifier: 17/46/519) and registered at Clinicaltrials.gov (NCT03449732). After obtaining informed written consent of parents and children, 20 subjects of two age classes (A= 28 days-23 months, B= 24 months-11 years) were included, with physical status I-II of the American Society of Anesthesiologists (ASA). All patients were scheduled for elective surgery with general anesthesia.

Exclusion criteria were; history of eye disease or current eye disease, current treatment with drug interacting with the autonomic or central nervous system, expected difficult airway and preoperative opioid use.

Anesthesia Protocol

Patients received no premedication. Standard monitoring was used throughout the pupil measurements, including heart rate (HR), pulse oximetry, electrocardiogram (ECG) monitoring, non-invasive blood pressure (NIBP) and gas analysis (sevoflurane, CO2 and O2). Anesthetic induction was performed either intravenously (propofol) or by inhalation (8% sevoflurane in 100% oxygen), as chosen by the attending anesthesiologist. If not yet present, an IV line was placed before tracheal intubation.

After tracheal intubation, mechanical ventilation was initiated and adapted to maintain end-tidal (ET) carbon dioxide (CO2) between 35 and 40 mmHg. A steady-state end-tidal concentration of sevoflurane minimum alveolar concentration (MAC) of 1.5 was obtained during pupil measurements.

Pupillometric measurements

Pupil measurements were assessed through Algiscan (IDMed, Marseille, France), a non-invasive portable infrared pupillometer. The upper eyelid was opened and the rubber cup of the infrared camera was placed on the orbit, so it surrounded the eye, excluding the contralateral light reflex. The same eye was used for every measurement, the contralateral eye remained closed. Two electrodes with low impedance were placed on the skin area innervated by the median nerve. This pupillometer has an inbuilt standardized algorithm of automated increase in stimulus intensity, with the end of the stimulation being determined by a threshold of pupillary dilation. The protocol was created to provide a uniform nociceptive stimulus, the pupillary pain index (PPI). It consists of measuring the changes in pupillary dilation in response to an automatic increase of noxious stimulus, which is the intensity of electrical stimulation through the electrodes. The protocol starts at 10mA and raises to 60mA by incremental steps of 10mA. If a pupillary dilation of >13% compared to baseline pupil size is met, electrical stimulation automatically stops, reducing unnecessary noxious stimulation. A PPI score is generated based on the maximum intensity value to provoke a pupil dilation of >13% and pupil reflex amplitude. The score ranges from 1, PRD <5% for 60mA stimulation, to 9, PRD of >13% for 10mA stimulation. In addition, the baseline (minimum) and maximum amplitude were recorded. Total duration of PRD using PPI is maximum 30 seconds including eye opening and placement of the pupillometer. Stimulation of a complete PPI protocol lasts maximum 8 seconds, followed by an standard post-stimulation observation period of 15 seconds and eyelid closing.

Data analysis including HR, systolic blood pressure (SBP), patient movements and pupil measurements was performed in two different ways. First, at baseline steady-state without opioids (T0), one before and one after PPI measurement. Second, one after injection of fentanyl 2µg/kg (T1), also one measurement before and after PPI. Measurement was at least 3 minutes after the opioid injection to obtain a pharmacological effect. A study design flowchart is presented in figure 1.

Figure 1: Flowchart of the study design. Twenty children, planned for elective surgery, were included. During measurement, a steady-state sevoflurane MAC of 1.5 was achieved and vital signs were monitored. Pupil measurements were taken at two standardized times, without (T0) and with opioids (T1). PRD, pupillary reflex dilation.

Statistical analysis

In this pilot study, no previously published data were available to make assumptions for the sample size calculation. Pupil characteristics, HR and SBP variables are given as mean ± standard deviation (SD). Non-parametric analyzation methods were used for pupil size variation. Mean stimulation, pupil diameter, HR, SBP and movement pre- and post-stimulus were compared using the unpaired Wilcoxon signed rank test. Statistical analyses were performed with SPSS Statistics software, version 26.0 for Windows (IBM Corp., Armonk, NY, USA). P-values less than 0.05 were considered as statistically significant.

Results

Data were collected in 20 children, 10 from each age class. Table 1 shows the demographics of the participants, including the anesthetic induction method and the use of muscle relaxants. Most subjects were male since the study took place predominantly in urological procedures.

	Group A (n=10)	Group B (n=10)
Male / Female	09-Jan	09-Jan
Age (months)	15 ± 3	(57 ± 34)
Age (years)	(1 ± 0)	4 ± 3
Length (cm)	78 ± 5	100 ± 19
Weight (kg)	11 ± 2	20 ± 10
BMI (kg/m2)	17 ± 1	17 ± 3
ASA		
1	7	6
2	3	4
Induction		
sevoflurane	9	7
intravenous	1	3
Muscle relaxant	9	9

Table 1: Demographics of the participants

After the administration of opioids, there was a significant decrease in PPI scores and reduction of the pupil dilation amplitude (PRDA) and variation (PRDV).

In group A no difference in pupil baseline diameter was found (p=0.731), whereas in group B there was a difference in baseline diameter of the pupil before and after fentanyl use (p = 0.026).

The electrical intensity necessary to dilate the pupil >13% was maximum (60mA) in group A for all participants. In group B less electrical stimulation was needed in one patient to obtain a dilation of >13%. A summary of these findings is displayed in table 2.

Data are presented as mean ± SD. T0 describes time at baseline without opioids, whereas T1 describes time after injection of fentanyl. Data are presented as mean ± SD. There were no significant differences in HR or SBP before and after pupil measurements, with or without opioid. Hemodynamic variables are shown in table 3. None of the patients moved, curare were administered in 90% (n=18) of the cases.

Group A	**T0**	**T1**	**P NPAR**
Baseline (mm)	1.87 ± 2.50	1.84 ± 0.32	0.731
Stimulation intensity (mA)	60 ± 0	60 ± 0	1
PDRA (mm)	0.24 ± 0.14	0.06 ± 0.04	0.007
Variation (%)	12.1 ± 6.62	2.9 ± 2.42	0.007
PPI	2.3 ± 1.05	1.1 ± 0.32	0.01
Group B	**T0**	**T1**	**P NPAR**
Baseline (mm)	2.27 ± 0.46	2.51 ± 0.68	0.026
Stimulation intensity (mA)	58 ± 6.32	60 ± 0	0.317
PDRA (mm)	0.24 ± 0.11	0.07 ± 0.06	0.005
Variation (%)	10.3 ± 5.19	2.50 ± 2.17	0.005
PPI	2.4 ± 1.65	1.1 ± 0.32	0.007

Table 2: Changes in pupil characteristics before and after fentanyl administration for both groups

Group A	**Pre**	**Post**	**P**	**P wilcoxon**
HRT0	142.8 ± 12.59	146.80 ± 14.91	0.231	0.074
HRT1	141.70 ± 16.23	141.70 ± 15.23	0.231	0.863
SBPT0	84.4 ± 4.20	83.20 ± 4.96	0.316	0.396
SBPT1	80.5 ± 10.10	78.70 ± 8.22	0.254	0.095
Group B	**Pre**	**Post**	**P**	**P wilcoxon**
HRT0	114.60 ± 17.73	116.2 ± 16.36	0.283	0.258
HRT1	111.80 ± 16.01	112.8 ± 15.88	0.231	0.473
SBPT0	85.10 ± 8.63	80.4 ± 7.56	0.283	0.03
SBPT1	77.00 ± 6.99	78.40 ± 7.41	0.333	0.257

Table 3: Vital signs before and after fentanyl administration for both groups. HRT0 (heart rate at T0), HRT1 (heart rate at T1), SBPT0 (systolic blood pressure at T0), SBPT1 (systolic blood pressure at T1). Pre and post describe the vital signs at, before, and after stimulation. Data are presented as mean ± SD.

Discussion

Our study demonstrates that opioids have a markable influence on the PRD and PPI scores in anesthetized children, with a significant result in both age classes. This suggests that PPI may be useful as an objective parameter of nociception. In our study, miosis after opioid administration only occurred in children older than 2 years. One explanation is that the dose of fentanyl is too little to elicit miosis in children younger than 2. As demonstrated in a study of Barvais et al., basal pupil size in adults decreased from a target effect compartment concentration of remifentanil upward of 2 ng/ml, (but not at a concentration of 1 ng/ml) [3]. On the contrary, Larson et al. describes a stable resting pupil size in adults at isoflurane end-tidal concentrations of 0.8%. Even at incrementing doses of alfentanil, they did not observe increasing miosis [2]. A recent study of Sabourdin et al. also found these unexpected results [14].

Another explanation could be that at this depth of anesthesia, high concentrations of sevoflurane blunts the sympathetic tone of the pupil so that the maximum miotic state of the pupil is already met before administrating opioids in children younger than 2 years.

In our work, almost everyone could be maximally electrically stimulated with a stimulation of 60mA before developing a pupil dilatation of >13%. This is in line with earlier research of Bourgeois et al. They observed a markedly higher MACpup of sevoflurane (MAC to inhibit the PRD in 50% of the subjects in response to skin incision) in prepubertal children (2-12 years). PRD remained because a MAC of 1.5 is still lower than the MAC of 1.9 necessary to abolish PDR in MACpup [4].

Emery et al. investigated the use of PRD in children aged 10 months to 5 years during combined general/caudal epidural anesthesia. They observed a significantly greater maximum pupillary dilation in response to tetanic stimulation in children over 2 years of age (1.3 ± 0.8 mm SD) compared with children less than two years of age (0.6 ± 0.3 mm SD) [15]. In our study we could not confirm these findings, given the fact that we did not observe a significant difference of PRDA or PRDV between both age classes. They related these data to an incomplete optic nerve myelination and maturation of the cells of the lateral geniculate body until approximately the age of 2 years. [15] In our data, we did detect a difference in basal diameters between children younger or older than 2 years old, independent of opioid use. Indeed, this can be linked to the maturation of distinct neural pathways. Our findings of the basal diameter in children >2 years old can be well correlated to those in other studies. [1,2,14]

Our findings are consistent with earlier research which shows that commonly used variables for analgesia as HR, SBP and movement are less sensitive than PRD. As confirmed in adults [3,16], as well as in children. [1,17] These surrogates depend on many more factors than analgesia alone, such as volume status, age and depth of anesthesia. Further, it is interesting that PPI can be used without eliciting hemodynamic changes or inappropriate high noxious stimulation.

By using PPI, we can measure the reactivity of the autonomous system to noxious stimuli on a scale from 1 to 9. Recently, Sabourdin et al. concluded that PPI indeed reflects the level of analgesia in children older than 2 years [14]. Other research of Vinclair et al. has demonstrated that the PPI score could accurately predict the nociceptive response in sedated critically ill adults [12]. Additionally, it is proven that the PPI score is reduced after remifentanil administration [13]. Our results of reduced PPI scores after fentanyl are in line with these earlier findings. A preliminary study even showed a correlation between the PPI score and an observational pain scale [18]. Indeed, pupil measurements

have been shown to correlate with pain intensity [17] Further investigations are necessary to examine the clinical implications of our findings.

Undeniably, pupillometry does have certain shortcomings. It only provides discontinuous information in contrast to other systems. Additionally, no information is provided regarding the patient's ascending and descending pain pathways. This pilot study has several limitations. First, unequal gender distribution is present in the study population. This can be explained by the fact that most of the included children were scheduled to undergo a urological surgical procedure. Second, different induction methods were used.

However, theoretically, propofol would have little effect at time of measurement considering the half-life of propofol. Further, no significant difference of basal pupil size was found regarding the induction method and earlier studies have been used successfully in patients receiving sevoflurane and propofol [16]. The third limitation is the lack of accurate measurement of depth of hypnosis because MAC brain does not equal MAC lungs. However, we waited until a steady state was reached. Fourth, opioid administration with estimated effect site concentrations would define analgesic plasma concentrations in a better way. Finally, there is little specificity of PPI to different noxious stimulations or clinical situations.

Conclusion

In conclusion, this pilot study shows a significant reduction in PPI scores following fentanyl administration in anesthetized children. It suggests that this technique may have a value for objective nociceptive assessment in the pediatric surgical population. More clinical research is necessary to confirm this hypothesis and to assess the clinical implications.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Antwerp University Hospital, Belgium (study identifier: 17/46/519) and registered at Clinicaltrials.gov (NCT03449732). We obtained an informed consent of all participants before inclusion.

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Availability of data and materials

The dataset analyzed in the current study are available from the corresponding author on reasonable request.

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3.4. Pupillary dilation reflex and pain index evaluation during general anesthesia using sufentanil: a double blind RCT.

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Abstract

In a single center double blind randomized controlled trial we evaluated if pupillometry controlled use of sufentanil is better than free choice administration of sufentanil by anesthesiologists. Sixty-one patients undergoing elective surgery were enrolled. The intervention group had a higher opioid use (20.1 mcg vs 14.8 mcg, p = 0.017) and longer recovery time (52 min vs 40 min, p = 0.025). There was no significant difference with pain killer usage and health state index at day one post-operative. This study showed no need for PRD assessment in response to sufentanil administration during daycare procedures.

Keywords: pupillometry, pain index, anesthesia, sufentanil, analgesia

Introduction

Pain assessment in non-communicative patients is still challenging despite many novel innovative technologies. Under general anesthesia, communication is impossible due to unconsciousness. Adequate measurement of nociception may allow the anesthesiologist to individual titration of analgesics (mostly opioids), avoiding over- or underdosage. More and more anesthesiologists attempt to minimize the dose of opioids, consequently reducing the well-known side effects. Correct nociceptive assessment and therefore appropriate individually based treatment, may be an ideal scenario. Although current research addressing this complex issue provides some promising innovative techniques, no standard objective pain monitoring protocol exists [1, 2]. Infrared pupillometry exists for decades [3]. Although nowadays there are only a few studies about portable video pupillometry in anesthetized patients. However, if we want to evaluate the pupil response during noxious procedures (skin incision, pneumoperitoneum, etc.), monitoring of pupillary reflex dilation (PRD) elicited by standardized nociceptive stimulations in anesthetized patients needs to be further examined. Furthermore, there is a need for consensus to use and interpret different pupil assessment features as light-induced PRD, nociceptive stimulation induced PRD, constriction velocity, reaction latency or pupillary pain index (PPI) score.

We anticipated that a PRD evaluation, and in addition PPI score, by increasing tetanic stimulation may be related to analgesic treatment in anesthetized patients. A pilot study was performed including 41 patients. The baseline pupil diameter decreased significantly (39%) after analgesic treatment. Also, there was a significant descent (32%) of the PPI score [4]. Algiscan© generated empirically the PPI score chart. Power analysis showed a need of N = 28 to measure a stimulation intensity difference between T0 and T1 measurement of 10 mA (α: 0.05, power 0.9). The power for a difference of PPI score, to detect a difference of 2 points, was N = 16 (α: 0.05, power 0.9).

The primary outcome parameter was the postoperative pain intensity. Queried as pain intensity by numeric rating scale (NRS) and the amount of pain killer usage. Our hypothesis was that patients with a good titrated sufentanil administration peroperative should have less pain and less need of pain medication. Secondary outcome parameters were PRD characteristic such as stimulation intensity (Int), baseline pupil diameter, pupil reflex dilation amplitude (PRDA) and PPI score. Total opioid usage during surgery and recovery time was registered. Additionally, nausea and vomiting, length of stay at the post anesthesia care unit (PACU) and health state index using the EQ5D5L questionnaire.

Up to now, two articles describe pupillometry when using sufentanil were published [5, 6]. The article of Berthoud found a lower use of sufentanil in the intervention group, but no decrease of cumulative morphine use postoperative nor less chronic pain at 3 months [5]. The study of Bartholmes outlined also a decrease of sufentanil use. Also they had a decrease of noradrenaline use and postoperative pain after 24h [6]. They both used another way to determine to lower, keep steady or increase the infusion rate.

Materials and Methods

Study design and data collection

This was a single center double blind randomized controlled trial at the University Hospital of Antwerp, Belgium. The study was performed in accordance with the ethical standards of ICG-GCP and the Declaration of Helsinki after study approval by the institutional review board and the Ethics Committee (EC17/28/319) of the University Hospital of Antwerp. Registration at clinicaltrials.gov

(NCT03248908) was executed before study inclusion. A power analysis was done beforehand. With N= 28 of each group was estimated to receive statistic significant results. An enrollment of 60 patients was carried out to have a margin of error in each group. We did not do any interim analyses. There were no stopping guidelines. After written consent, patients planned for elective abdominal or gynecological surgery were recruited for study inclusion from October 2017 until August 2021. Inclusion criteria were elective abdominal of gynecological surgery, no locoregional anesthetics, age > 18 years and ASA I, II or III. Exclusion criteria were medical history of eye surgery, known bilateral eye disease, known nervus opticus or nervus oculomotorius deficit, active pheochromocytoma, active psychiatric disease, opioid usage > 7 days preoperative and active oncologic treatment with chemotherapy. Also use of medication that interfere with the pupillary measurements such as use of high dose α-1 or β-blocker (no intake on the day of surgery), use of benzodiazepines on the day of surgery, topical use of atropine or phenylephrine, use of scopolamine or dopamine antagonists were excluded. During anesthesia it was forbidden to give dehydrobenzperidol (DHBP), alizapride, fentanyl and atropine as examined in two studies beforehand [7, 8]. Because of the high risk of post-operative nausea or vomiting of some patients, we tolerated the administration of DHBP or alizapride after the last PPI measurement. Enrolled subjects were divided into four groups. Group 1 was the sufentanil flowchart group and group 2 was the sufentanil control group. In analogy with this project, a study using remifentanil is expected. It was a double blind randomized controlled trial, so by the site www.randomization.com, a randomization was made. The subjects underwent consecutive pupil measurements under general anesthesia. By convention, the left eye was assessed after confirmation of pupil syndrome disorder absence. Patients were anesthetized in a fully equipped operation room. No premedication was administered before surgery. On arrival in the operation theatre, standard monitoring and safe surgery checklist were executed. A venous catheter was inserted in a cubital vein. Non-invasive blood pressure was recorded every 5 minutes. Heart rate (HR), ECG, oxygen saturation (SpO2) and end-tidal-carbon dioxide concentration were recorded continuously. Also, a bispectral index monitoring (BIS) (NeuroSENSE Monitor©, NeuroWave Systems Inc) [10] recorded continuously.

Before induction were demographic data collected. Length and weight were registered. Ideal body (IBW) weight was calculated by length (cm) – 100 for men / 105 for women. If actual body weight was lower dan IBW, then actual body weight was used. When actual body weight was higher than IBW, then corrected body weight (CBW) was used. CBW was calculated by IBW + 0.4 x (weight –

IBW). Further ASA-classification, SpO2 before administration of oxygen, blood pressure, HR and BIS awake were collected. Also, the use of any antihypertensive drug, including β-blocker was checked.

Induction was established, after preoxygenation, by administration of a propofol continuous target-controlled infusion (Marsh-Model: injectomat TIVA Agilia, Fresenius Kabi, Germany) [9] up to the value of BIS was between 40 and 60. The effect site concentration of propofol (CE-Prop) was noted. When necessary, lidocaine and dexamethasone were allowed to give, as there is no known interference with pupil measurement [7, 8]. Manually assisted ventilation with 100% oxygen began as soon as the patients became apneic. The observer performed the first, T0, measurement at the moment the patient had a BIS value between 40 and 60. For note, before the first dosage of an opioid or curare. After the first measurement the anesthesiologist gave the opioid as noted by the right group following the randomization. When necessary, the curare was also administered after the first measurement.

After a waiting time of 6 minutes, which is the effect site equilibration time of sufentanil [10], the T1 was performed. Whereafter every 10 minutes a new measurement was conducted. The last measurement happened at start closure the wound or when there was no wound at the end of surgery. At each measurement we collected also the blood pressure, HR, movement and BIS. For PRD measurement, we used CE-approved NeuroLight Algiscan® (IDMed, Marseille, France) pupillometer using infrared video recording allowing quantitative pupil size assessment during the steady state anesthesia. For nociceptive stimulation, two Ag-AgCl electrodes were placed at the skin area innervated by the median nerve. Optimal skin contact with low electrode impedance was defined on the touchscreen display. Constant current stimulations were generated during pupil measurement, increasing automatically the voltage according to the resistance. Voltage is limited to a maximum of 300 V. Therefore, at a current fixed at 60 mA, the maximum acceptable resistance is 5 kOhm. The upper eyelid of the measured eye was opened during pupil assessment. A rubber cup placed to the orbit ensured optimal device position, pupil-camera distance and environmental darkness. There was never direct contact with the cornea. The contralateral eye was closed, reducing the effect of the consensual light response. Via the touch screen display the PPI-modus was selected for dynamic pupil measurement. This inbuilt measurement protocol generated an automatic electric stimulation pattern. Operating principle is the application of a standardized noxious stimulation (from 10 mA to 60 mA by incremental steps of 10 mA, with a duration of 1s, and pulse width of 200 µs) in increasing intensity, until pupillary dilation of more than 13% ([maximal diameter – minimal diameter] / maximal diameter x 100). When the defined criteria were reached stimulation is automatically stopped and PPI score was determined (table 1), when the pupil variation (VAR) was >20% a plus 1 was added to the score. The measurable pupil size (diameter) ranged between 0.1 and 10 mm. Furthermore, baseline (minimum), PRD, VAR, Int and PPI score were recorded. Depending on necessary stimulation intensity, pupil measurement duration is between 2 and 16 seconds.

Up to now, there is no guideline to decide which PPI score is “good”. Therefore, decision on expert opinion stated that 1 or 2 is sufficient. Three or more was too much. As mentioned above, there were 2 sufentanil group. The intervention group had the target to reach a score of 1 or 2. This was done by a start bolus of 0.2 mcg/kg CBW of sufentanil. If the measured score was 3 or more then another bolus of 0.1 mcg/kg CBW was given. At the sufentanil control group had the anesthesiologist a free choice of the amount of sufentanil to give. At the end of the surgery the observer noted time of stop CE-Prop, stop surgery time, temperature, neuromuscular transmission monitoring by train-of-

four (TOF) test (TOF-watch®, Draeger), SpO2 and BIS. Also the time of extubation was noted. At the anesthesiologist was asked if acetaminophen, NSAID, tramadol, morphine or local wound infiltration was given. Also if antiemeticum dexamethasone or ondansetron was given. In need we tolerated the gift of DHBP or alizapride, but only after the last measurement to prevent measurement influence.

The anesthesiologist had to fill in a blind form with the study group, the opioid that was given and the total dose of the opioid. The form went in a closed envelop and only went open after all the measurements. By the PACU staff a second form was filled in. At this file we collected time of arrival and departure of the recovery. The Aldrete score at arrival and departure. The need of anti-emeticum, vomiting and/or nausea was noted. The need of supplemental oxygen and so needed the oxygen flow was noted. Also, pain was questioned and if necessary which and how much rescue pain killer was given, followed by pain reassessment.

At home, the patients were asked to fill in an online questionary during five days. The use of pain killers was asked and calculated by the Medication Quantification Scale. Numeric Rating Scale (NRS) of pain with 0 is no pain and 10 is maximal pain, NRS activity with 0 is no activity and 10 is very active and NRS sleep with 0 equals “did not sleep” and 10 means “did sleep very well” were asked using an online evaluation dairy. The questions “Did you had nausea in the last 24 hours?” and “Did you throw up last 24 hours?” were also asked. Also, the EQ-5D-5L questionary was used, the calculation was by the United Kingdom score as there is no Belgian score. At least patients were asked to place a dot on the EQ VAS-score about their feeling of health whereby 0 equals the worst health imaginable and 100 is the best health imaginable. This questionary was already used in previous studies in our centrum [11].

One of the authors took care of the informed consent of the patient. The same author did also all the peroperative measurements. He was blinded of the used product (remifentanil or sufentanil) and dosage because the anesthesiologist had to give one syringe with opioid and one syringe with NaCl 0.9%. Both of the products are translucent. The syringes were also hidden for the observer, so it was not possible to make an estimation of the used amount of opioid. Also, the participants, because they were under anesthesia, were blinded. The staff of the recovery ward was blinded because the anesthesiologist did not tell them in which group the patient was allocated.

Statistical analysis

Results were expressed as mean and interquartile range for continuous variables, as median and interquartile range for ordinal variables and as numbers and percentages for categorical variables. Comparison between continuous variables was done with first a test of normality. As significant value of Kolmogorov-Smirnov and Shapiro-Wilk test for both groups was > 0.05 then there was a normal distribution and independent samples T-test was used with significance two-sided $p < 0.05$ to be significant. When there was no normal distribution, Mann-Whitney U test was used and exact significance 2-tailed $p < 0.05$ was used to describe a significant difference. For ordinal variables the Mann-Whitney U test was used as described above. For categorical variables the chi-square test was used with the Pearson asymptomatic significance 2-tailed $p < 0.05$ to be significant. In the study were also repeated measures for which paired samples test was used with significance two-sided $p < 0.05$ to be significant. At the paired samples tests were the percentual difference and standard deviation noted. Statistical analysis was performed using IBM SPSS Statistics version 28.0.0.0.

Initially, we wanted to analyze the use of pain medication, pain score and health state index at day 5. Unfortunately, because of a big drop out of not filled in online questionnaires we decided to only statistic analyze post-operative day 1. Because the most of the patients, also in the intervention group, did not reach the wanted PPI score of 1 or 2. We did a subgroup analyze between the patients with a score of 1 or 2 and the patients with a score of ≥ 3.

Results

Demographic data

In total 62 patients participated to the PUP-AIT study. By randomization 31 patients enrolled in the "sufentanil flowchart group" or intervention group, 31 enrolled in the "sufentanil free use" group or control group. From the sufentanil flowchart group had one patient no confirmation of the right group and was not analyzed (consort flow diagram table 2).

Baseline demographic data are presented in table 3. Patients had no significant difference in age, sex, discipline, CBW, SpO2 start, HR start, use of antihypertensive drugs and CE-Prop. Although there were only 16.7% and 6.5% males included due to the amount of gynecologic patients with 76.7% and 83.9% respectively. The systolic blood pressure was significant lower in the "sufentanil flowchart" group compared with the "sufentanil control" group. The BIS was calculated as (BIS right + Bis lift) divided by two and called BIS mean (BISm). There was no significant difference in BISm.

The baseline measurement at T0 was after induction with propofol, but before administration of sufentanil or curare. Results of the T0 measurement are presented in table 4. There was no significant difference in baseline pupil diameter, PRDA, VAR, Int or PPI. Respectively, the mean baseline was 4.11 and 4.21 mm, the mean PRDA was 1.58 and 0.94 mm. So the variation was 23.9% and 22.8% at a median intensity of 35 and 30 mA. Both median PPI were 8. There was also no statistical significance in SBP, HR or BISm. The BISm reached 63.3% and 71% the target value of 40 – 60, which was not a statistical significant difference.

Peroperative measurements

The first peroperative measurement was conducted 6 minutes after administration of sufentanil and called T1 measurement. Results are presented in table 5. Between the two groups there was no significant difference between baseline pupil diameter, PRDA, VAR, Int or PPI. At T1 there was also a significant difference in systolic blood pressure with respectively 94 mmHg and 102 mmHg ($p = 0.02$). HR and BIS did not show a significant difference.

If we compared baseline reduction of the PPI score T0 versus T1 for both groups, there was a significant reduction of 50.9% and 51.0% with both $p < 0.001$. The comparison T0 versus T1 of PPI gave for the flowchart group a significant reduction of 14.5% ($p = 0.034$). The PPI reduction for the control group was 9.7% ($p = 0.263$) and was therefore not significant. The wanted PPI-score of 1 or 2 was reached in 5 cases (16.7%) of the flowchart group and 5 cases (16.1%) of the control group ($p = 0.955$).

The second peroperative measurement was conducted 10 minutes after T1 and called T2 measurement. Results are presented in table 6. Also in T2 there was no significant difference between baseline pupil diameter, PRDA, VAR, Int or PPI. The PPI reduction between T0 and T2 became also significant in the free use group. The systolic blood pressure did not show a significant difference this measurement. Also HR and BIS were not significant. In the control group, there was a

baseline PPI reduction of 25% significance 0.020. At the T2 measurement reached 8 (28.6%) of 28 cases and 9 (29.0%) of 31 cases the wanted PPI score of 1 or 2 (p = 0.969). Two data of the of the flowchart group were not filled in and are missing.

The last measurement was at the beginning of closing the operative wound(s). This measurement called end-measurement. Results are presented in table 7. Also at this measurement there was no significant difference at baseline, PRDA, VAR, Int or PPI. Also the SBP, HR and BIS did not show any significant difference. In 9 of the 29 cases (31%) the end PPI was 1 or 2 in the flowchart group, at the free use group this was 8 of 31 cases (26%) (p = 0.653). One data of the flowchart group was not filled in and is missing.

Table 8 compares the two groups intra operatively. Time between start and stop propofol had a median time of 36 and 37 minutes with p 0.499. The time between stop propofol and extubation was median 12 and 13:30 minutes (p = 0.927). Two data of the flowchart group were missing. Wake up conditions were not significant different for temperature, SpO2 or BIS. The TOF-count was 4 at all curarized patients. At one patient in the flowchart group it was only 55%, but at that patient the woke up times were not noted. Peroperative all but one patient of the free use group received acetaminophen. That patient had an allergy to acetaminophen. Respectively 87 and 81% received an NSAID (p = 0.731). 20 and 10% received tramadol (p = 0.301). None of the patients received morphine. 30 and 36% received local wound infiltration (p = 0.786). Dexamethasone was respectively given to 63 and 68% of the patients (p 0.791). Ondansetron to 13 and 23% (p = 0.508). DHBP or alizapride was given in 13% of both groups, only after the last measurement. As mentioned before, this is a deviation from the study protocol, but because there are no further pupillary measurement it does not have influence. In the intervention group, the mean dose of sufentanil was 20.1 mcg, in the control group was the mean dose 14.8 mcg, which is a significant difference (p = 0.017).

Postoperative outcome

The median time at recovery was respective 52 and 40 minutes (p 0.025), a significant difference in favor of the control group (see table 9). Aldrete at arrival was in both groups 8. At departure there were in the first group 2 cases with score less than 10, in the second group there was one score of 9. None of the patients in both group suffered from PONV and none need an antiemeticum. 16% intervention group versus 20% control group needed supplemental oxygen (p = 0.741). Respectively 2 and 3 cases needed extra opioids, namely dipidolor, at recovery.

Follow-up

At day 1 the medication use was comparable between the two groups. Results are presented in table 10. After the results the number of answers are shown. The median NRS was 2 for the flowchart group and 1 for the control group (p = 0.249). The level of activity median of both groups was 5 (p = 0.804). The level of sleep quality median was respectively 7 and 6 (p = 0.429). 23% of the intervention group had nausea while none of the control group (p = 0.223). 15% of the intervention group threw up, whilst none of the control group (p = 0.48). The Health State Index of the flowchart group was 0.656, the control group 0.702 (p = 0.464). The EQVAS score at D1 was respectively 56 and 70 (p = 0.152).

In range vs out of range

We compared also the difference in the intervention and the control group between a PPI score of 1 or 2 and a PPI score of ≥ 3. See results in table 11. When we compared the amount of sufentanil

used, there was no statistical significance to reach a score of 1 or 2 or higher in the two groups. Also the time of the operation, measured by the duration of propofol infusion, did not show any significance. When we looked further to the postoperative period, there was also no statistical significance in health state index and EQ-VAS score.

Discussion

Our primary outcome parameter was postoperative pain intensity. Patients in the study group had a NRS median of 2, the control group had a NRS median of 1. There was no significant statistical difference and no clinical relevance. According to our opinion, it is good to have low pain scores. At our center we try to have a pain score less than 3. The pain medication used in both groups was also comparable. Unfortunately there was already a drop with patients not or partially filled in the online questionary at day 1.

We noticed the use of sufentanil was significant lower in the control group. We can explain this due to the higher dosage of sufentanil use by the flowchart group in comparison with what we do daily at the hospital. But with the pilot study we noticed there was need of more use of sufentanil. The wake up time was comparable between the two groups with respectively 12 and 13 minutes. So the higher amount of sufentanil use does not cause longer wake up times. The relative long wake up times are probably due to the continuous propofol administration.

The PDR characteristics were comparable in both groups. In the flow chart group was already a significant reduction of PPI at the T1 measurement, the significant reduction of PPI was only at the T2 measurement in the control group. With the use of sufentanil only 16% in both groups had a PPI score of 1 or 2 at the T1 measurement, 28% and 29% of the subjects had a score of 1 or 2 at the T2 measurement. Probably due to the higher amount of sufentanil the effect was faster.

The recovery ward times with respectively 52 and 40 minutes was significant lower in the control group. The minimum recovery ward care takes 30 minutes at our center. So although the priority care is a comfortable patient, the use of time and resources cannot be neglected. None of the patients suffered from PONV.

D1 postoperative was the health state index and the EQ-VAS score comparable in the two groups with a favor for the control group. There was nausea and vomiting noticed in the flow chart group, but not in the control group. This may be due to the higher amount of opioids administered. At least we made a in group comparison between the patients that reached the target and the patients that did not reach a score of 1 or 2. Probably there is too low power to make the results significant. Interpretation show us that administered amount of sufentanil in both intervention and control group are equal with comparable surgical times. The day 1 health state index and EQ-VAS score seems likeworthy in the intervention group, but tends to be worse in the control group for patients with PPI-score 1 or 2.

We have some hypothesis why sufentanil in combination with PPI measurement does not show benefits. First, because of administration of sufentanil, the pupil narrows, so with the same pupil dilation there is a bigger VAR and a higher PPI-score. Secondly, there is probably not a full occupancy of the opioid receptors.

There was no report of a serious adverse event during the whole study follow up period.

One of the limitations was the investigation of only day care patients. We had permission to include gynecologic and abdominal elective surgery patients. So the most patients are female and the most operations are rather short. More evidence is needed for operations of more than two hours or major operations like thoracic surgery. Another limitation of our trial is the big drop out of the online questionary. Unfortunately it made it more difficult to reach statistic difference. Participation was always voluntary. Before the start of covid patients where not used to fill in online questionary's. To our knowledge, our study is the first one that used pupillometry in combination with bolus sufentanil. There are two known studies with continuous sufentanil in cardiac surgery which showed a less consummation of sufentanil in their intervention group [5, 6]. In these two studies are also a reasonably amount of patients with a score of ≥ 3. Only the study of Bartholmes showed a decrease of morphine use in the first 24 hours. Our dosage of sufentanil is considerably lower in gynecologic and abdominal surgery as is expected in comparison with cardiac surgery. To our opinion both groups were comparable. We included patients from October 2017 until August 2021. The longtime of inclusion was due to another study running in our center and because of Covid 19.

Conclusion

This study examined the usefulness of pupillometry in combination with sufentanil. There was no significant improvement of health state index at day 1 post-operative. The control group had a NRS score 1 at day 1 post-operative while the intervention group had a score of NRS score 2.

Whereby there was less sufentanil use in the control group in comparison to the intervention group. There was also a significant shorter stay at the recovery ward for the control group. In our opinion there is no reason to believe that it comes due to a different type of surgery, duration of surgery or patient type. The lesser use of sufentanil has a consequence of faster recovery time. There was no difference in post-operative outcome, health state or pain score of the patients.

In most patients, intervention and control group, we did not reach the purposed pain score of 1 or 2. We cannot link it to a difference of sufentanil usage. Nor the outcome is worse in patients who did not reach the wanted score.

Our first conclusion is that there was no significant improvement of health or pain at day 1 post operative. The second conclusion is that our model of PPI score in combination with sufentanil does not guarantee a score of 1 or 2.

In our study we cannot recommend the additionally usage of pupillometry in combination with sufentanil during abdominal or gynecological day care elective surgery. To our knowledge, no other published study use pupillometry in combination with bolus sufentanil. Further investigation is needed to decide the good PPI score with eventually a change in the flowchart model, also the needed amount of sufentanil to administer needs to be investigated further. When the measurements are more stable, a new research is needed for the postoperative outcome.

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Appendix

Table 1

Pupillometry Pain Index score

Maximum Intensity (mA)	PPI score	Pupil reactivity patient
10	9	Dilatation ≥ 13% stimulating 10 mA
20	8	Dilatation ≥ 13% stimulating 20 mA
30	7	Dilatation ≥ 13% stimulating 30 mA
40	6	Dilatation ≥ 13% stimulating 40 mA
50	5	Dilatation ≥ 13% stimulating 50 mA
60	4	Dilatation ≥ 13% stimulating 60 mA
60	3	Dilatation ≥ 13% during 2nd stimulation 60 mA
60 (5% < pupil dilatation < 13%)	2	Dilatation ≥ 13% during 3rd stimulation 60 mA
60 (pupil dilatation ≤ 5%)	1	Dilatation ≥ 13% during 4th stimulation 60 mA

PPI: Pupillometry Pain Index.

Note: when pupil dilatation was more than 20% than the resulting score was PPI score + 1.

Table 2

Consort Flow Diagram

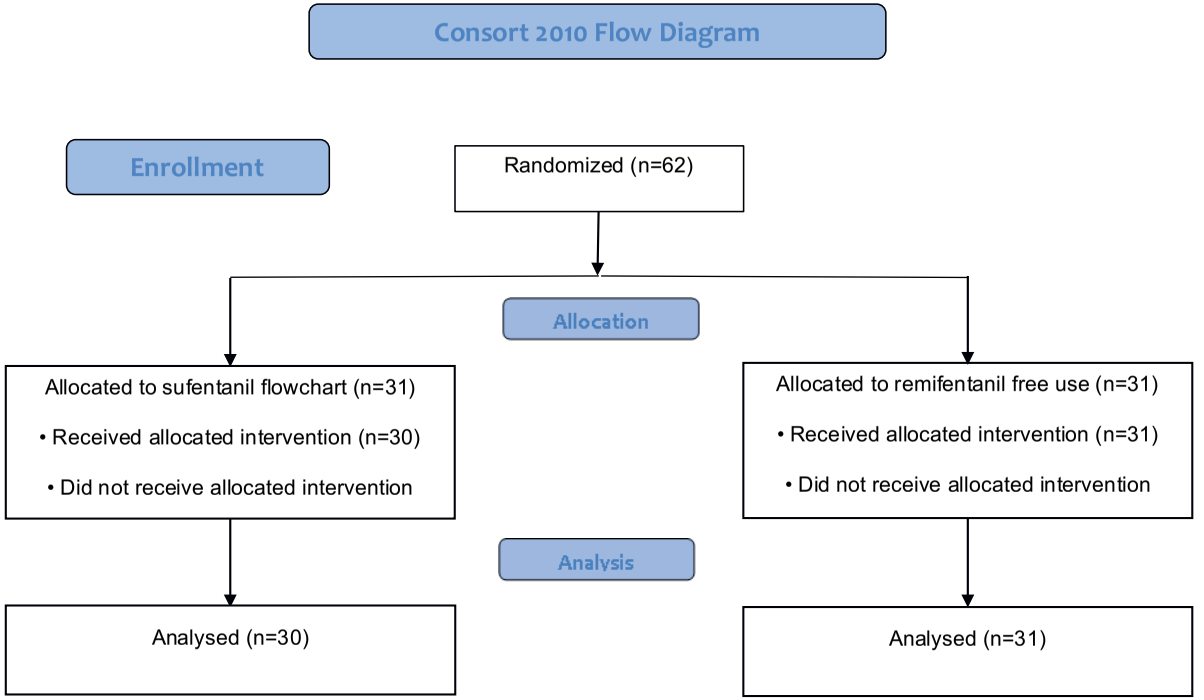

Table 3

Demographic data

TOTAL	Sufentanil flow chart	Sufentanil free use	p-value
N = 61	N = 30	N = 31	
Age (years)	40 (35,5 - 43,9)	44 (38,6 - 50,2)	0,188
Male	5 (16,7%)	2 (6,5%)	0,211
Discipline	76,7% gynecology, 23,3% abdominal	83,9% gynecology, 16,1% abdominal	0,479
CBW (kg)	64,8 (62,00 - 67,54)	63,6 (59,58 - 67,58)	0,622
SpO2 start (%)	98,6 (98,04 - 99,09)	98,8 (98,40 - 99,21)	0,659
SBP start (mmHg)	127 (120,9 - 133,8)	139 (131,8 - 145,8)	**0,014**
HR start (bpm)	72 (66,5 - 77,3)	75 (69,6 - 79,6)	0,462
Antihypertensiva use	1 (3,3%)	4 (12,9%)	0,173
Pre neurowave (%)	91,1 (87,83 - 94,30)	92,1 (91,38 - 92,82)	0,291
CE-Prop start	7,4 (6,88 - 7,84)	7,2 (6,67 - 7,72)	0,683

CBW male = (weight - 100) + (0,4 x (weight - 100)) ; female = (weight - 105) + (0,4 x (weight - 105))

SBP: systolic blood pressure, HR: heart rate, CE-Prop: effect site concentration propofol

Table 4

T0 measurement

TOTAL	Sufentanil flow chart	Sufentanil free use	p-value
N = 61	N = 30	N = 31	
T0 Baseline (mm)	4,11 (3,802 - 4,418)	4,21 (3,870 - 4,556)	0,65
T0 PRDA (mm)	1,58 (0,274 - 2,885)	0,94 (0,786 - 1,095)	0,794
T0 Var (%)	23,9 (19,66 - 28,07)	22,8 (18,81 - 26,80)	0,71
T0 Int (mA) (median)	35 (31,7 - 41,6)	30 (33,5 - 44,0)	0,828
T0 PPI (median)	8 (6,6 - 8,2)	8 (5,7 - 7,8)	0,576
T0 SBP (mmHg)	114 (106,7 - 121,0)	119 (113,1 - 124,6)	0,269
T0 HR (bpm)	71 (66,2 - 77,3)	69 (63,0 - 74,2)	0,264
T0 Neurowave	44,2 (40,20 - 48,10)	46,7 (42,51 - 50,94)	0,367
T0_neurowave (between 40 - 60)	19 (63,3%)	22 (71,0%)	0,525

PRDA: pupil reflex dilation amplitude, VAR: variation, Int: intensity, PPI: pupillary pain index

SBP: systolic blood pressure, HR: heart rate

Table 5

T1 measurement

TOTAL	Sufentanil flow chart	Sufentanil free use	p-value
N = 61	N = 30	N = 31	
T1 baseline (mm)	2,02 (1,874 - 2,166)	2,07 (1,954 - 2,175)	0,934
T1 PRDA (mm)	0,33 (0,291 - 0,376)	0,34 (0,307 - 0,377)	0,758
T1 VAR (%)	16,2 (14,39 - 18,07)	16,2 14,58 - 17,75)	0,952
T1 Int (mA)	40 (32,5 - 43,5)	40 (35,5 - 44,5)	0,692
T1 PPI (median)	7 (5,3 - 7,0)	7 (5,2 - 6,9)	0,887
T1 SBP (mmHg)	94 (90,8 - 98,2)	102 (96,9 - 108,0)	0,020
T1 HR (bpm)	63 (58,1 - 67,9)	63 (59,3 - 62,9)	0,966
T1 Neurowave	42,8 (37,72 - 47,81)	41,0 (36,2 - 45,7)	0,494
T0-T1 baseline reduction	50,9% (2,09 ± 0,911) **p < 0,001**	51,0% (2,15 ± 0,966) **p < 0,001**	
T0-T1 PPI	14,5% (1,267 ± 3,118) **p = 0,034**	9,7% (0,65 ± 3,147) p = 0,263	

T1 PPI 1 or 2 vs ≥ 3 (p = 0,955)		
PPI 1 or 2	5 (16,7%)	5 (16,1%)
PPI ≥ 3	25 (83,3%)	26 (83,9%)

PRDA: pupil reflex dilation amplitude, VAR: variation, Int: intensity, PPI: pupillary pain index
SBP: systolic blood pressure, HR: heart rate

Table 6

T2 measurement

TOTAL	Sufentanil flow chart	Sufentanil free use	p-value
N = 59	N = 28	N = 31	
T2 baseline (mm)	2,19 (2,005 - 2,374)	2,21 (2,067 - 2,361)	0,447
T2 PRDA (mm)	0,41 (0,254 - 0,567)	0,35 (0,270 - 0,434)	0,991
T2 VAR (%)	17,4 (11,35 - 23,50)	16,3 (12,28 - 20,24)	0,76
T2 Int (mA)	55 (44,1 - 53,8)	50 (42,0 - 51,0)	0,441
T2 PPI (median)	5 (3,9 - 5,8)	6 (4,1 - 6,0)	0,678
T2 SBP (mmHg)	98 (92,7 - 103,7)	104,1 (97,5 - 110,8)	0,139
T2 HR (bpm)	63 (58,4 - 66,9)	62 (58,5 - 66,0)	0,896
T2 Neurowave	39,3 (34,08 - 44,55)	40,5 (35,01 - 45,95)	0,754
T0-T2 PPI	35,4% (0,557) **p < 0,001**	25,0% (0,685) **p = 0,020**	

T2 PPI 1/2 vs ≥ 3 (p = 0,969)		
PPI 1 or 2	8 (28,6%)	9 (29,0%)
PPI ≥ 3	20 (71,4%)	22 (71,0%)

PRDA: pupil reflex dilation amplitude, VAR: variation, Int: intensity, PPI: pupillary pain index
SBP: systolic blood pressure, HR: heart rate

Table 7

Tend measurement

TOTAL	Sufentanil flow chart	Sufentanil free use	p-value
N = 60	N = 29	N = 31	
Tend baseline	2,05 (1,942 - 2,162)	2,02 (1,904 - 2,132)	0,666
Tend PRDA	0,30 (0,248 - 0,353)	0,33 (0,264 - 0,390)	0,915
Tend VAR	14,1 (11,93 - 16,35)	15,8 (12,59 - 19,09)	0,898
Tend Int (mA)	60 (43,9 - 55,4)	50 (43,4 - 52,7)	0,430
Tend PPI (median)	5 (3,6 - 5,5)	5 (4,0 - 5,7)	0,510

Tend SBP	100 (94,2 - 105,4)	104 (96,9 - 110,2)	0,387
Tend HR	63 (57,5 - 68,3)	61 (57,7 - 65,3)	0,658
Tend Neurowave	43,9 (40,12 - 47,71)	43,2 (39,0- - 47,40)	0,806

Tend PPI 1/2 vs ≥ 3 (p = 0,969)		
PPI 1 or 2	9 (31,0%)	8 (25,8%
PPI ≥ 3	20 (69,0%)	23 (74,2%)

PRDA: pupil reflex dilation amplitude, VAR: variation, Int: intensity, PPI: pupillary pain index

SBP: systolic blood pressure, HR: heart rate

Table 8

Intra operatively

TOTAL	Sufentanil flow chart	Sufentanil free use	p-value
N = 61	N = 29	N = 31	
T start to stop propofol (min)	36:00 (32:47 - 53:56)	37:00 (37:28 - 55:25)	0,499
T stop propofol to wake-up (min)	12:00 (11:30 - 15:42)	13:30 (11:51-15:36)	0,927
temp °C	36,0 (35,86 - 36,20)	36,0 (35,83 - 36,15)	0,734
SpO2 %	98 (97,5 - 98,9)	99 (98,5 - 99,1)	0,245
Neurowave	47,9 (45,28 - 50,52)	45,16 (41,97 - 48,36)	0,199

	N = 30	N = 31	
Paracetamol %	30 (100%)	30 (97%)	>0,999
NSAID %	26 (87%)	25 (81%)	0,731
Contramal %	6 (20%)	3 (10%)	0,301
Morfine %	0 (0%)	0 (0%)	>0,999
Wound infiltration %	9 (30%)	11 (36%)	0,786
Dexamethasone %	19 (63%)	21 (68%)	0,791
Ondansetron %	4 (13%)	7 (23%)	0,508
DHBP / alizapride post last measurement	4 (13%)	4 (13%)	>0,999

	N = 30	N = 31	
dosis sufentanil (µcg)	20,1 (16,38 - 23,81)	14,8 (12,93 - 16,58)	**0,017**

Table 9

Post anesthesia care unit

TOTAL	Sufentanil flow chart	Sufentanil free use	p-value
Time recovery (min)	52:00 (46:08 - 58:17) (N= 23)	40:00 (38:13 - 50:10) (N= 25)	**0,025**
Aldrete arrival	8 (6,6 - 8,3) (N= 24)	8 (7,7 - 8,7) (N= 29)	0,147
Aldrete departure	1 score 8, 1 score 9, 21 score 10 (N= 23)	1 score 9, 26 score 10 (N= 27)	NA
PONV	0 (0%) (N= 25)	0 (0%) (N= 30)	0,999
Supplemental oxygen	4 (16%) (N= 25)	6 (20%) (N= 30)	0,741
Pain killer	2 (12%) (N= 25)	3 (10%) (N= 30)	> 0,999

Table 10

Questionnary

TOTAL	Sufentanil flow chart	Sufentanil free use	p-value
N = 61			
Medtracking D1	15,25 (12,334 - 18,162) (N = 25)	14,43 (12,273 - 16,592) (N = 28)	0,758
NRS pain D1 (median)	2 (1,4 - 4,1) (N = 13)	1 (0,2 - 3,9) (N = 11)	0,249
NRS activity D1 (median)	5 (4,6 - 7,3) (N = 13)	5 (4,4 - 7,1) (N = 11)	0,804
NRS sleep D1 (median)	7 (5,7 - 8,1) (N = 13)	6 (3,8 - 8,0) (N = 11)	0,429
Nausea D1 (%)	23% (N = 13)	0% (N = 11)	0,223
Vomiting D1	15% (N = 13)	0% (N = 12)	0,48
Health State Index D1	0,656 (0,5133 - 0,7996) (N = 16)	0,702(0,5814 - 0,8233) (N = 23)	0,464
EQVAS score D1	56 (46,6 - 70,6) (N = 16)	70 (56,9 - 78,8) (N = 23)	0,247

3.5. Pupillary reflex dilation and pain index evaluation during general anesthesia using remifentanil: a double blind RCT.

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Abstract

In a single center double blind randomized controlled trial we evaluated if pupillometry controlled use of remifentanil is better than free choice administration of remifentanil by anesthesiologists. Fifty-five patients undergoing elective surgery were enrolled. After induction, a first pupillary reflex dilation (PRD) measurement was performed using pupillometry. A second identical evaluation was performed six minutes after remifentanil administration and adapted every 10 minutes. Corrected for body weight and operation time both groups had an administration of 0.21 mcg kg-1 min-1 remifentanil. There was no dose reduction of remifentanil. There was no significant difference in pain killer usage and health state index at postoperative day one. This study showed no additional value for PRD assessment in response to remifentanil administration during daycare procedures.

Key Words

Pupillometry
Pain index
Anesthesia
Sufentanil
Analgesia

Introduction

Pain assessment in non-communicative patients is still challenging despite many novel innovative technologies. Communication under general anesthesia is impossible due to unconsciousness. Adequate measurement of nociception may allow the anesthesiologist to individual titration of analgesics (mostly opioids), avoiding over- or underdosage. More and more anesthesiologists attempt to minimize the dose of opioids, consequently reducing the well-known side effects. Correct nociceptive assessment and therefore appropriate individually based treatment, may be an ideal scenario. Although current research addressing this complex issue provides some promising innovative techniques, no standard objective pain monitoring protocol exists [1, 2].

Infrared pupillometry exists for decades [3]. Although nowadays there are only a few studies about portable video pupillometry in anesthetized patients. However, if we want to evaluate the pupil response during noxious procedures (skin incision, pneumoperitoneum, etc.), monitoring of pupillary reflex dilation (PRD) elicited by standardized nociceptive stimulations in anesthetized patients' needs to be further examined. Furthermore, there is a need for consensus to use and interpret different pupil assessment features as light-induced PRD, nociceptive stimulation induced PRD, constriction velocity, reaction latency or pupillary pain index (PPI) score.

We anticipated that a PRD evaluation, and in addition PPI score, by increasing tetanic stimulation may be related to analgesic treatment in anesthetized patients. A pilot study was performed including 38 patients. The baseline pupil diameter decreased significantly (39%) after analgesic treatment. Also, there was a significant descent (32%) of the PPI score [4]. Algiscan© generated empirically the PPI score chart. Power analysis showed a need of N = 28 to measure a stimulation intensity difference between T0 and T1 measurement of 10 mA (α: 0.05, power 0.9). The power for a difference of PPI score, to detect a difference of 2 points, was N = 16 (α: 0.05, power 0.9).

The primary outcome parameter was the postoperative pain intensity. Queried as pain intensity by numeric rating scale (NRS) and the amount of pain killer usage. Our hypothesis was that patients with a good titrated remifentanil administration peroperative should have less pain and less need of pain medication. Secondary outcome parameters were PRD characteristics such as stimulation intensity (Int), baseline pupil diameter, pupil reflex dilation amplitude (PRDA) and PPI score. Total opioid usage during surgery and recovery time were registered. Additionally, nausea and vomiting, length of stay at the post anesthesia care unit (PACU) and health state index using the EQ5D5L questionnaire.

Up to now, little study is published about using pupillometry to titrate remifentanil dosage. Sabourdin and colleagues illustrated a significant decrease in the pupillometry group (3.8 vs 7.9 mcg kg-1 min-1, $p < 0.001$) [5]. Therewith, the postoperative morphine consumption and pain after 3 months was also significant decreased. Kim and colleagues showed a nonsignificant dose reduction in the PPI group versus control group (0.079 vs 0.108 mcg kg-1 min- 1 $p = 0.115$) [6]. Furthermore, Choi did a study with children in which there was a significant remifentanil reduction of 25% (0.117 mcg kg-1 min-1 vs 0.156 mcg kg-1 min-1 $p = 0.02$) [7].

Materials and Methods

Study design and data collection

This was a single center double blind randomized controlled trial at the University Hospital of Antwerp, Belgium. The study was performed in accordance with the ethical standards of ICG-GCP and the Declaration of Helsinki after study approval by the institutional review board and the Ethics Committee (EC17/28/319) of the University Hospital of Antwerp. Registration at clinicaltrials.gov (NCT03248908) was executed before study inclusion. A power analysis was done beforehand. With N = 28 of each group was estimated to receive statistic significant results. An enrollment of 60 patients was carried out to have a margin of error in each group. We did not do any interim analyses. There were no stopping guidelines.

After written consent, patients planned for elective abdominal or gynecological surgery were recruited for study inclusion from October 2017 until August 2021. Inclusion criteria were elective abdominal of gynecological surgery, no locoregional anesthetics, age > 18 years and ASA I, II or III. Exclusion criteria were medical history of eye surgery, known bilateral eye disease, known nervus opticus or nervus oculomotorius deficit, active pheochromocytoma, active psychiatric disease, opioid usage > 7 days preoperative and active oncologic treatment with chemotherapy. Also use of medication that interfere with the pupillary measurements such as use of high dose α-1 or β-blocker (no intake on the day of surgery), use of benzodiazepines on the day of surgery, topical use of atropine or phenylephrine, use of scopolamine or dopamine antagonists were excluded. During anesthesia it was forbidden to give dehydrobenzperidol (DHBP), alizapride, fentanyl and atropine as examined in two studies beforehand [8, 9]. Because of the high risk of postoperative nausea or vomiting of some patients, we tolerated the administration of DHBP or alizapride after the last PPI measurement.

Enrolled subjects were divided into two groups. Group 1 is the remifentanil flowchart group, group 2 is the remifentanil control group. In analogy with this project, a study using sufentanil is expected. It was a double blind randomized controlled trial, so by the site www.randomization.com a randomization was made.

The subjects underwent consecutive pupil measurements under general anesthesia. By convention the left eye was assessed after confirmation of pupil syndrome disorder absence. Patients were anesthetized in a fully equipped operation room. No premedication was administered before surgery. On arrival in the operation theatre, standard monitoring and safe surgery checklist were executed. Venous catheter was inserted in a cubital vein. Non-invasive blood pressure was recorded every 5 minutes. Heart rate (HR), ECG, oxygen saturation (SpO2) and end-tidal-carbon dioxide concentration were recorded continuously. Also a bispectral index monitoring (BIS) (NeuroSENSE Monitor©, NeuroWave Systems Inc) [10] recorded continuously.

Before induction were demographic data collected. Length and weight were registered. Ideal body (IBW) weight was calculated by length (cm) – 100 for men / 105 for women. If actual body weight was lower dan IBW, then actual body weight was used. When actual body weight was higher than IBW, then corrected body weight (CBW) was used. CBW was calculated by IBW + 0.4 x (weight – IBW). Further ASA-classification, SpO2 before administration of oxygen, blood pressure, HR and BIS awake were collected. The use of any antihypertensive drug, including β-blocker was checked. Induction was established, after preoxygenation, by administration of a propofol continuous target controlled infusion (Marsh-Model: injectomat TIVA Agilia, Fresenius Kabi, Germany) [11] up to the value of BIS was between 40 and 60. The effect site concentration of propofol (CE-Prop) was noted. When necessary, lidocaine and dexamethasone were allowed to give, as there is no known interference with pupil measurement [8, 9]. Manually assisted ventilation with 100% oxygen began as soon as the patients became apneic.

The observer performed the first, T0, measurement at the moment the patient had a BIS value between 40 and 60. For note, before the first dosage of an opioid or curare. After the first measurement the anesthesiologist gave the opioid as noted by the right group follow the randomization. When necessary, curare was also administered after the first measurement.

After a waiting time of 6 minutes, the T1 measurement was performed. Whereafter every 10 minutes a new measurement was conducted. The last measurement happened at start closure the wound or when there was no wound at the end of surgery. At each measurement we collected also the blood pressure, HR, movement and BIS. For PRD measurement, we used CE-approved NeuroLight Algiscan® (IDMed, Marseille, France) pupillometer using infrared video recording allowing quantitative pupil size assessment during the steady state anesthesia. For nociceptive stimulation, two Ag-AgCl electrodes were placed at the skin area innervated by the median nerve. Optimal skin contact with low electrode impedance was defined on the touchscreen display. Constant current stimulations were generated during pupil measurement, increasing automatically the voltage according to the resistance. Voltage is limited to a maximum of 300 V. Therefore, at a current fixed at 60 mA, the maximum acceptable resistance is 5 kOhm.

The upper eyelid of the measured eye was opened during pupil assessment. A rubber cup placed to the orbit ensured optimal device position, pupil-camera distance and environmental darkness. There was never direct contact with the cornea. The contralateral eye was closed, reducing the effect of the consensual light response. Via the touch screen display the PPI-modus was selected for dynamic pupil measurement. This inbuilt measurement protocol generated an automatic electric stimulation

pattern. Operating principle is the application of a standardized noxious stimulation (from 10 mA to 60 mA by incremental steps of 10 mA, with a duration of 1s, and pulse width of 200 µs) in increasing intensity, until pupillary dilation of more than 13% ([maximal diameter – minimal diameter] / maximal diameter x 100). When the defined criteria was reached stimulation automatically stopped and PPI score was determined (table 1). When the pupil variation (VAR) was >20%, a +1 was added to the score. The measurable pupil size (diameter) ranged between 0.1 and 10 mm. Furthermore, baseline (minimum), PRD, VAR, Int and PPI score were recorded. Depending on necessary stimulation intensity, pupil measurement duration is between 2 and 16 seconds.

Up to now, there is no guideline to decide which PPI score is "good". Therefore, decision on expert opinion stated that 1 or 2 is sufficient. Three or more was too much. As mentioned above, there were 2 remifentanil groups. The intervention group followed the Minto model and started at 5.0 ng/ml using CBW [12]. When the next measurement was 1 or 2, than the concentration was lowered by 0.2 ng/ml. When the next measurement was 3 or more, than the concentration was raised by 0.2 ng.ml. At the remifentanil control group had the anesthesiologist a free choice of the amount of remifentanil to give.

At the end of the surgery the observer noted time of stop CE-Prop, stop surgery time, temperature, neuromuscular transmission monitoring by train-of-four (TOF) test (TOFwatch ®,Draeger), SpO2 and BIS. Also the time of extubation was noted. At the anesthesiologist was asked if acetaminophen, NSAID, tramadol, morphine or local wound infiltration was given. Also if anti-emeticum dexamethasone or ondansetron was given. In need we tolerated the gift of DHBP or alizapride, but only after the last measurement to prevent measurement influence.

The anesthesiologist had to fill in a blind form with the study group and the total dose of remifentanil. The form went in a closed envelop and only went open after all the measurements.

By the PACU staff a second form was filled in. At this file we collected time of arrival and departure of the recovery. The Aldrete score at arrival and departure. The need of antiemeticum, vomiting and/or nausea was noted. The need of supplemental oxygen and so needed the oxygen flow was noted. Also pain was questioned and if necessary which and how much rescue pain killer was given, followed by pain reassessment.

At home the patients were asked to fill in an online questionary during five days. The use of pain killers was asked and calculated by the Medication Quantification Scale. Numeric Rating Scale (NRS) of pain with 0 is no pain and 10 is maximal pain, NRS activity with 0 is no activity and 10 is very active and NRS sleep with 0 equals "did not sleep" and 10 means "did sleep very well" were asked using an online evaluation dairy. The questions "Did you have nausea in the last 24 hours?" and "Did you throw up last 24 hours?" were also asked. Also the EQ-5D-5L questionary was used, the calculation was by the United Kingdom score as there is no Belgian score. At least patients were asked to place a dot on the EQ VAS-score about their feeling of health whereby 0 equals the worst health imaginable and 100 is the best health imaginable. These questionary was already used in previous studies in our centrum [13].

One of the authors took care of the informed consent of the patient. The same author did also all the peroperative measurements. The syringe was hidden for the observer, so it was not possible to make an estimation of the used amount of opioid. Also the participants, because they were under anesthesia, were blinded. The staff of the recovery ward was blinded, because the anesthesiologist did not tell them in which group the patient was allocated.

Statistical analysis

Results were expressed as mean and interquartile range for continuous variables, as median and interquartile range for ordinal variables and as numbers and percentages for categorical variables. Comparison between continuous variables was done with first a test of normality. As significant value of Kolmogorov-Smirnov and Shapiro-Wilk test for both groups was > 0.05 then there was a normal distribution and independent samples T-test was used with significance two-sided $p < 0.05$ to be significant. When there was no normal distribution, Mann-Whitney U test was used and exact significance 2-tailed $p < 0.05$ was used to describe a significant difference. For ordinal variables the Mann-Whitney U test was used as described above. For categorical variables the chi-square test was used with the Pearson asymptomatic significance 2-tailed $p < 0.05$ to be significant. In the study were also repeated measures for which paired samples test was used with significance two-sided $p < 0.05$ to be significant. At the paired samples tests were the percentual difference and standard deviation noted. Statistical analysis was performed using IBM SPSS Statistics version 28.0.0.0.

Initially, we wanted to analyze the use of pain medication, pain score and health state index at day 5. Unfortunately, because of a big drop out of not filled in online questionnaires we decided to only statistic analyze postoperative day 1.

Results

Demographic data

In total 59 patients participated to the PUP-AIT study. By randomization 30 patients enrolled in the “remifentanil flowchart group” or intervention group, 29 enrolled in the “remifentanil free use” group or control group (table 2). From both groups were two patients not analyzed because of a deviation from the study protocol. So 28 patients were analyzed for the intervention group and 27 for the control group.

Baseline demographic data are presented in table 3. Patients had no significant difference in age, sex, discipline, CBW, SpO, HR, use of antihypertensive drugs and CE-Prop. There were in both groups only 14% males included due to the amount of gynecologic patients with 78% in both groups. The neurowave was calculated as (BIS right + BIS lift) divided by two and called BIS mean (BISm). There was no significant difference in BISm.

The baseline measurement at T0 was after induction with propofol, but before administration of sufentanil or curare. Results of the T0 measurement are presented in table 4. There was no significant difference in baseline pupil diameter, PRDA, VAR, Int or PPI. Respectively, the mean baseline was 4.1 and 3.9 mm, the mean PRDA was 1.0 and 1.1 mm. The variation was 26% and 28% at a median intensity of 30 mA in both groups. Both median PPI were 8. There was also no statistical significance in SBP, HR or BISm. The BISm reached in 89 and 93% the target value of 40 – 60, which was not a statistical significant difference.

Peroperative measurements

The first peroperative measurement was conducted 6 minutes after start administration of remifentanil and called T1 measurement. Results are presented in table 4.

Between the two groups there was no significant difference between baseline pupil diameter, PRDA, VAR, Int or PPI. At T1 there was also a significant difference in systolic blood pressure with respectively 94 mmHg and 102 mmHg (p = 0.02). HR and BISm did not show a significant difference.

If we compared baseline reduction of the PPI score T0 versus T1 for both groups, there was a significant reduction of 46.8% and 49.8% with both p < 0.001. The comparison T0 versus T1 of PPI gave for the flowchart group a significant reduction of 62.4% (p < 0.001). The control group had also a significant PPI reduction of 74.8% (p = 0.001). The wanted PPI-score of 1 or 2 was reached in 20 cases (71.4%) of the flowchart group and 25 cases (92.6%) of the control group (p = 0.078).

The last measurement was at the beginning of closing the operative wound(s). This measurement called end-measurement. Results are presented in table 4. Also at this measurement there was no significant difference at baseline, PRDA, VAR, Int or PPI. Also the SBP, HR and BISm did not show any significant difference. In 26 of the 28 cases (92.9%) the end PPI was 1 or 2 in the flowchart group, at the free use group this was 25 of 31 cases (92.6%) (p = 0.970).

Table 5 compares the two groups intra operatively. Time between start and stop propofol had a median of 27 and 36 minutes with p 0.228, respectively. The time between stop propofol and extubation was median 12 and 10 minutes (p = 0.812). For wake up conditions there was no significance in temperature, SpO2 or neurowave. The TOF-count was 4 at all neuromuscular blocked patients. At one patient in the flowchart group it was < 80% with wake-up time 9 minutes. Three patients of the control group had TOF < 80% with wakeup times of 15, 17 and 18 minutes. There was no significant difference of intra-venous pain medication. 14% versus 44.4% received wound infiltration (p = 0.014) which differenced significant. Dexamethasone was respectively given to 43 and 59% of the patients (p 0.224). Ondansetron to 7 and 33% (p = 0.015), which was significantly more in the control group. DHBP or alizapride was given in 11 and 4%, only after the last measurement. As mentioned before, this was a deviation from the study protocol, but because there are no further pupillary measurement it did not have influence. In the intervention group, the mean dose of remifentanil was 422 mcg, in the control group was the mean dose 595 mcg without significant difference (p = 0.351). When we corrected the dose to CBW and length of propofol infusion, we had 0.21 mcg kg-1 min-1 for both groups (p = 0.926).

Postoperative outcome

The median time at recovery was respectively 40 and 47,5 minutes, with p = 0.966. See table 5, the missing results are noted. Aldrete at arrival was in both groups 8. At departure only one patient of the flow chart group had Aldrete 9, all the other patients of both groups had Aldrete 10. Only one patient suffered from postoperative nausea or vomiting, it was a patient of the control group. Respectively 1 and 3 patients needed supplemental oxygen (p = 0.246). 39 and 44% of the patients received a supplemental pain killer (p = 0.728).

Follow-up

At day 1 the medication use was comparable between the two groups. Results are presented in table 6. After the results the number of answers are shown. The median NRS was 3 for the flowchart group and 3 for the control group (p = 0.758). The level of activity median of both groups was 4 (p = 0.492). The level of subjective sleep quality median was respectively 5 and 7 (p = 0.297). One patient of the intervention group had nausea while none of the control group (p = 0.382). No vomiting was noted. The Health State Index of the flowchart group was 0.76, the control group 0.68 (p = 0.108). The EQVAS score at D1 was respectively 65 and 63 (p = 0.793).

Discussion

Our primary outcome parameter was postoperative pain intensity. Patients in both groups had a NRS of 3 without statistical significance. According to our opinion, it is good to have low pain scores in the study. The in-hospital goal for discharge is NRS 3 or less. The pain medication use in both groups was also comparable. Unfortunately there was already a drop out of patients not or partially filled in the online questionary at day 1.

The mean use of remifentanil was, corrected for weight and length of surgery, the same in both groups. The expected more adequate titration of remifentanil was not demonstrated in this study group. May be, the correction of 0.2 ng/ml after each measurement was too small.

The PDR characteristics were comparable in both groups. Already after 6 minutes 71 and 92% of the patients had a PPI score of 1 or 2. At the end had 92% of the patients the right PPI score. This can be due to the fast onset of remifentanil. In this study protocol, starting dose was 5.0 ng/ml, it could be good to start with. To our opinion it showed that pupillometry can be used to measure the effect of remifentanil.

The recovery ward times in minutes were respectively 40 (min 25 - max 99) and 47,5 (min 15 – max 110). Probably due to the use of remifentanil had 39 and 44% of the patients need for supplemental postoperative analgesics. Analyses of both groups demonstrated, there was a significant difference between the patients with or without extra pain medication, namely median time 40 versus 60 minutes ($p < 0.001$). At day one postoperative, the health state index and the EQ-VAS score were comparable in the two groups with a favor for the control group (p = 0.793). Only one patient of the flow chart group had nausea, none of the control group. Because there was only a small difference of opioid administration in the two groups, Not surprisingly, no statistical difference was shown.

There was no report of a serious adverse event during the whole study follow-up period.

One of the limitations was the investigation of only daycare patients. This trial included gynecologic and abdominal patients, resulting in a mainly female study population. The most operations were rather short. More evidence is needed for pupillometry application during major surgery like thoracic surgery.

Another limitation of our trial is the big drop out of the online questionary. Unfortunately, it made it more difficult to reach statistic difference. Participation was always voluntary. Before the start of

COVID-19 pandemic patients were not used to filling out online questionaries. To our opinion both groups were comparable. We included patients from October 2017 until August 2021. The long inclusion time was due to another study running in our center and because of the Covid 19 pandemic period.

Conclusion

This study examined the usefulness of pupillometry in combination with remifentanil. There was no significant improvement of health state index at day 1 post-operative. The control group had a NRS score 1 at day 1 post-operative while the intervention group had a score of NRS score 2.

Unexpectedly, the corrected dosage of remifentanil was more or less the same in both groups. So there was no dose reduction of remifentanil, hence there was no diminishing of side effects. Probably, the dose of remifentanil could have lowered more quickly. In most patients, intervention and control group, the purposed pain score below 3 was reached. PPI can be useful to quantify the effect of remifentanil. Notwithstanding, no health reward could be demonstrated in this study group.

Our first conclusion is that there was no significant improvement of health or pain at day 1 post-operative. The second conclusion is that our model of PPI score in combination with remifentanil did not give a lower dosage of remifentanil.

In this study, no additionally value of pupillometry usage in combination with remifentanil during abdominal or gynecological day care elective surgery was shown. To our knowledge, three other published studies used pupillometry in combination with remifentanil, which showed a lower dosage. Further investigation is needed to evaluate PPI score cutoff criteria and determine additional value of intraoperative pupillometry use. There are no sources of funding. There are no potential conflicts of interest.

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Appendix

Table 1

Pupillometry Pain Index score

Maximum Intensity (mA)	PPI score	Pupil reactivity patient
10	9	Dilatation ≥ 13% stimulating 10 mA
20	8	Dilatation ≥ 13% stimulating 20 mA
30	7	Dilatation ≥ 13% stimulating 30 mA
40	6	Dilatation ≥ 13% stimulating 40 mA
50	5	Dilatation ≥ 13% stimulating 50 mA
60	4	Dilatation ≥ 13% stimulating 60 mA
60	3	Dilatation ≥ 13% during 2nd stimulation 60 mA
60 (5% < pupil dilatation < 13%)	2	Dilatation ≥ 13% during 3rd stimulation 60 mA
60 (pupil dilatation ≤ 5%)	1	Dilatation ≥ 13% during 4th stimulation 60 mA

PPI: Pupillometry Pain Index.
Note: when pupil dilatation was more than 20% than the resulting score was PPI score + 1.

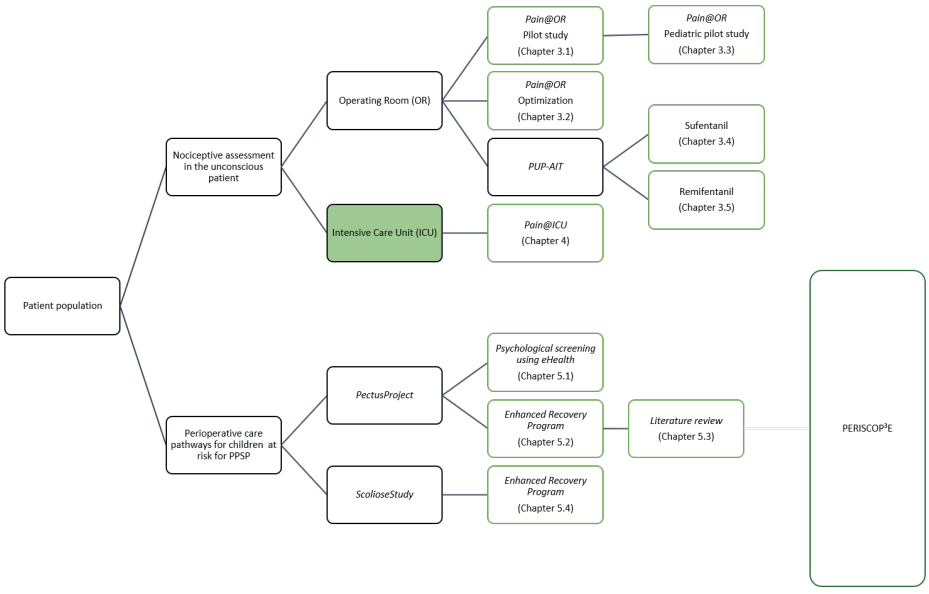
Table 2

Demographic data baseline

TOTAL	Remifentanil flowchart	Remifentanil free use	p-value
N= 55	28	27	
Age (years)	45 (39,1 - 50,0)	40 (34,5 - 44,6)	0.172
Male	4 (14,3%)	4 (14,8%)	0.956
Discipline	78,6% gynaecologic	77,8% gynaecologic	0.943
Corrected body weight (kg)	65,3 (61,94 - 68,71)	64,7 (61,49 - 67,84)	0.773
SpO2 start (%)	98,5 (97,95 - 99,05)	96,4 (92,58 - 100)	0.856
Systolic blood pressure (mmHg)	133 (125,1 - 141,4)	133 (125,3 - 140,3)	0.931
Heart rate (bpm)	72 (66,33 - 76,81)	79 (72,61 - 85,17)	0.072
Antihypertensiva use	4 (14,3%)	2 (7,4%)	0.413
Pre BIS monitoring (%)	92 (90,9 - 92,5)	92 (91,2 - 93,0)	0.240
Effect site concentration propofol induction	6,9 (6,56 - 7,23)	7,5 (70,02 - 8,02)	0.107

CBW: male = (weight - 100) + (0,4 x (weight - 100)) ; female = (weight - 105) + (0,4 x (weight - 105))

Chapter 4. Pupillary dilation reflex and nociceptive flexion reflex measurements in critically ill.



Overview of the research projects. Publications are shown in green, and attached as separated chapters. OR: operating room, ICU: intensive care unit, PPSP: persistent postsurgical pain, PUP-AIT: PUPil dilation reflex Assessment for Intraoperative analgesic Titration. *Note: Telemonitoring studies were executed in the pre-covid period.*

This chapter focusses on pain assessment in critically ill ICU admitted adults, introducing the pupil dilation reflex and nociceptive flexion reflex.

4.1 Objective nociceptive assessment in ventilated ICU patients: a feasibility study using pupillometry and the nociceptive flexion reflex.

Wildemeersch D, Gios J, Jorens Ph, Hans G.

Published in JoVE (Journal of Visualized Experiments) 137 (2018): e57972.
DOI: 10.3791/57972

Abstract

The concept of objective nociceptive assessment and optimal pain management have gained increasing attention. Despite the known negative short- and long-term consequences of unresolved pain or excessive analgosedation, adequate nociceptive monitoring remains challenging in non-communicative, critically ill adults. In the intensive care unit (ICU), routine nociceptive evaluation is carried out by the attending nurse using the Behavior Pain Scale (BPS) in mechanically ventilated patients. This assessment is limited by medication use (e.g., neuromuscular blocking agents) and the inherent subjective character of nociceptive evaluation by third parties.

Here, we describe the use of two nociceptive reflex testing devices as tools for objective pain evaluation: the pupillary dilation reflex (PDR) and nociception flexion reflex (NFR). These measurement tools are non-invasive and well tolerated, providing clinicians and researchers with objective information regarding two different nociceptive processing pathways: (1) the ascending component of the somatosensory system and (2) the pain-related autonomic reactivity. The use of PDR and NFR measurements are currently limited to specialized pain clinics and research institutions because of impressions that these are technically demanding or time-consuming procedures, or even because of a lack of knowledge regarding their existence.

By focusing on the two abovementioned nociceptive reflex assessments, this study evaluated their feasibility as a physiological pain measurement method in daily practice. Pursuing novel technologies for evaluating the analgesia level in unconscious patients may further improve individual pharmacological treatment and patient related outcome measures. Therefore, future research must include large well-designed clinical trials in a real-life environment.

Introduction

Many critically ill patients in the Intensive Care Unit (ICU) are prone to experience pain during daily care or during diagnostic or therapeutic procedures. Substandard nociceptive evaluation and consequent suboptimal pain management may increase stress and anxiety [1]. Persistent pain not only increases circulating catecholamines, compromises tissue perfusion and reduces oxygen delivery [2] but also activates catabolic hypermetabolism, thus contributing to hyperglycemia, lipolysis and muscle loss. All of these elements impair the healing process and increase the risk of infections [3-6].

As stated by the International Association for the Study of Pain (IASP), clinicians must use pain assessment tools that are valid for all patients, and self-reports remain the golden standard for pain evaluation. However, there are many situations in which patients are unable to communicate, especially because of critical illness or when they are mechanically ventilated (MV). The increased interest in ICU patient-related outcome measures has amplified the need for structured and reliable techniques for nociceptive assessment when a patient is unable to report pain and discomfort. Attempts to address this need have been hampered by the lack of specific, reproducible and feasible monitoring tools. In recent years, considerable effort has been directed toward providing physicians with more objective nociceptive parameters. However, many studies executed in the ICU have focused on the use of vital signs as possible surrogates for pain assessment and underlie not to use blood pressure or heart rate as a specific parameter for pain [7-8].

As reported in previous research, untreated pain significantly compromises patient outcomes and should therefore always be assessed independently of vital signs, and assessments should not be influenced by a patient's inability to communicate [7-12]. This approach of objective nociceptive assessment has gained considerable support due to the known negative consequences of pain. Especially in ICU patients, physiological and psychological effects can be substantial and long-lasting and may significantly decrease health-related quality of life [13-14].

Currently, no objective pain monitoring protocol exists that can readily be applied to a large group of critically ill patients. The implementation of objective assessment tools in ICU patients could optimize pain management and thus prevent the development of central sensitization syndromes. Moreover, opioid-induced hyperalgesia (OIH), chronification of pain, and long-lasting pain-related morbidity may decrease. Finally, the application of nociceptive reflex evaluation tools may provide a unique translational platform on which new pharmacological analgesic compounds can be tested.

The aim of the proposed methodology is to provide an overview of the technical requirements and provide a precise description of the protocols used to assess nociceptive reflexes in non-communicative ICU patients. Overall, we aim to provide a comprehensive guide for the use of objective pain measurement tools in the ICU and in other circumstances in which sedated or unconscious patients need to be assessed.

Methods

Critically ill unconscious adults admitted to the ICU were screened for study inclusion from October 2016 until December 2017. All were mechanically ventilated and received a strict analgosedation protocol containing propofol/remifentanil or propofol/sufentanil, which are the two most commonly used schemes in our hospital. A history of ophthalmologic surgery, known pupil reflex disorders,

Horner or Adie's syndrome, previous eye trauma, cranial nerve lesions or acute intracranial hypertension caused by traumatic brain injury, tumor compression or bleeding, fulminant stroke, known (poly)neuropathy related to diabetes or other neurological conditions known to influence reflex activity, intra- or extracorporeal treatment (pacemaker, intra-aortic balloon pump, extracorporeal life support), chronic opioid use (> 3 months), age < 18 years, and the use of topical interfering eye drops (atropine, phenylephrine), α2 adrenergic agonists [15], the use of other analgosedation protocols than described by the inclusion criteria or neuromuscular blocking agents were defined as exclusion criteria.

The demographic variables and medical data of the enrolled subjects, including the Simplified Acute Physiology Score II (SAPS II)[16], were extracted from the digital patient data management system (e.g., Metavision).

Pain Assessment

ICU patients were screened for study inclusion, which required a medical history and admission diagnosis to assess the inclusion and exclusion criteria mentioned above. Physiological reflexes were assessed in the ICU environment under real-life conditions: no specific modifications were made regarding temperature or noise control. Reflex assessment was executed during daytime working hours at the individual patient room of approximately 20 °C. All generated data (reflex characteristics) can be stored by each of the two devices when this function is enabled on the touch screen display.

Measurement of the Pupil Dilation Reflex

A pupillometry device was used for pupil dilation reflex (PDR) assessment using infrared video recording for quantitative pupil size evaluation. For the application of standardized nociceptive stimulation, two low-impedance Ag-AgCl electrodes were placed on the skin area innervated by the median nerve on the left arm after skin preparation (Figure 1). The current was fixed at 60 milliampères (mA) with a maximum acceptable resistance of 5 kOhms, defining a voltage limitation of 300 volts (V).

Figure 1. Electrode placement for PDR evaluation.

PDR assessment was performed using an inbuilt pupillary pain index (PPI) measurement protocol that generates an automatic electric stimulation pattern for dynamic pupil reflex evaluation. Standardized noxious stimulation was applied with increasing intensity (from 10 mA to 60 mA with incremental steps of 10 mA, a duration of 1 s, and a pulse width of 200 µs) until pupillary dilation greater than 13% ([maximal diameter – minimal diameter]/maximal diameter * 100) or maximal stimulation at 60 mA was achieved. When the defined criteria were reached, stimulation was automatically interrupted, and a PPI score was displayed (Table 1). Baseline pupil size (before standardized noxious stimulation), pupil reflex amplitude (PRA), stimulation intensity and the PPI score were recorded. The duration of PDR measurement was between 2 and 16 seconds depending on the number of required stimulations.

Table 1. PPI protocol

Maximum stimulation intensity (mA)	Pupil reactivity	Generated PPI score
10	Pupil dilation is greater than 13% during 10-mA stimulation	9
20	Pupil dilation is greater than 13% during 20-mA stimulation	8
30	Pupil dilation is greater than 13% during 30-mA stimulation	7
40	Pupil dilation is greater than 13% during 40-mA stimulation	6
50	Pupil dilation is greater than 13% during 50-mA stimulation	5
60	Pupil dilation is greater than 13% during 60-mA stimulation	4
60	Pupil dilation is greater than 13% during the second 60-mA stimulation	3
60 (5% < dilation < 13%)	Pupil dilation is greater than 13% during the third 60-mA stimulation	2
60 (dilation ≤ 5%)	Pupil dilation is greater than 13% during the last 60-mA stimulation	1

Note: if the pupil dilation is over 20% during stimulation, the PPI score is increased with one point

Several studies have suggested the use of pupillometry in non-communicative ICU adults. Paulus et al. demonstrated that PDR evaluation may predict analgesia requirements during endotracheal aspiration [17]. Moreover, this method may be able to reveal different levels of analgesia and could have discriminatory properties regarding different types of noxious procedures [18-19]. Recently, scientific interest has been directed toward the use of specific protocols for PDR assessment because of their low stimulation currents. The PPI protocol suggested in our approach has been previously investigated in anesthetized adults, revealing a significant correlation between PDR and opioid administration [20]. Furthermore, Sabourdin et al. [21] demonstrated that PDR can be used to guide individual intraoperative remifentanil administration and therefore reduce intraoperative opioid consumption and postoperative rescue analgesia requirements.

Measurement of the Nociceptive Flexion Reflex

To assess the role of primary afferent fibers in the transmission of nociceptive signals from peripheral nociceptors to the sympathetic chain, the nociceptive flexion reflex (NFR) was evaluated. Reflex elicitation is mediated after A-delta fibers are activated by a complex interaction between neurons located in the dorsal horn of the spinal cord [22]. Rhudy and colleagues described the RIII reflex, a late response of the NFR with high-threshold nociceptive characteristics measured electromyographically (EMG) over the biceps femoris muscle after nociceptor activation [23].

Increasing electrical stimulations are performed via cutaneous Ag-AgCl electrodes at the lateral malleolus, triggering the solely sensory sural nerve. The reflex response is evaluated in time and amplitude through EMG recording (Figure 2; Reprinted with permission of PH Dr med. Jan Baars, Managing Director, Dolosys GmbH.).

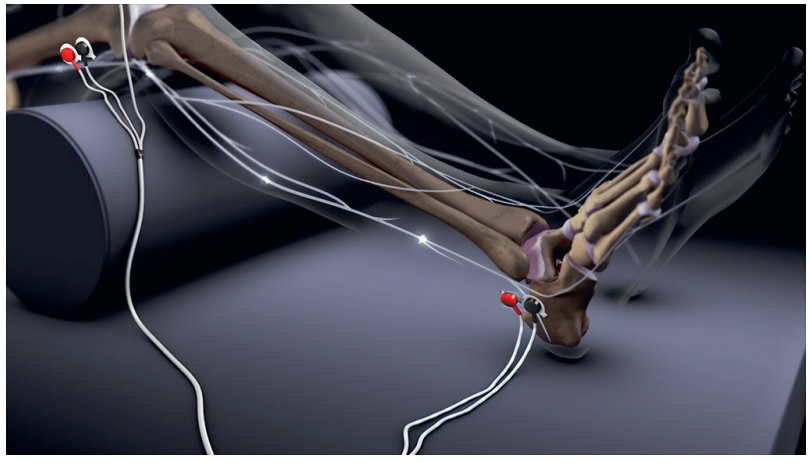


Figure 2. Electrode placement for NFR assessment.

Following Willer et al., using the described reflex registration setup, the required stimulation intensity to elicit the NFR (threshold tracking) can be used as an objective nociceptive assessment correlating with subjective pain scores [24-28]. Subsequently, numerous studies have been conducted to identify reflex characteristics (mainly reflex threshold and amplitude) and their correlation with pain intensity sensation in conscious adults. These studies revealed that the reflex threshold and response amplitude is closely related to pain intensity [27,29-30]. Furthermore, standardized NFR scoring criteria, such as the reflex peak and the mean reflex EMG activity, can be used as reliable criteria for defining this NFR [23,31-32]. According to recent research, the defined reflex characteristics contributing to the NFR, despite their empirically derived origin, showed good test-retest reliabilities [33,34]. The duration of NFR recording, taking into account the (variable) step size range (0.5 mA – 2 mA), interstimulus interval of 8 seconds with an interval randomization of 20% to avoid possible habituation and reflex range between 90 – 180 ms after stimulation [35], was between 5 and 15 minutes depending on the necessary stimulation intensity to elicit the NFR and therefore the number of required stimulations (maximum of 100 mA).

Study protocol

This single-center cohort study was performed in accordance with the ethical standards of ICH-GCP and the Declaration of Helsinki after it was approved by the institutional review board and ethics committee of the Antwerp University Hospital, Belgium (study identifier: 16/33/334). The study was registered at Clinicaltrials.gov (NCT02916004) before its initiation.

All included patients were sedated in accordance with the standard hospital sedation protocol before study enrollment. The patients were titrated to a Richmond Agitation-Sedation Scale (RASS) set by the ICU physician. Patients were sedated to a RASS - 4 prior to study inclusion. All patients were routinely titrated to a Behavior Pain Scale (BPS) of 3 by the ICU analgosedation protocol.

Note: Determining therapeutic measures solely on the basis of the excitability of the recorded pain reflexes is not recommended. When interpreting the measurements, possible effects on the efferent branch of the reflex arc must be considered. Patients who are sedated or anesthetized have a higher pain reflex threshold than non-sedated patients. For reflex assessment, higher currents may be required. Monitoring of physiological parameters (heart rate, blood pressure, breathing rate) is recommended.

Safety Precautions

Verify potential confounders for noise control (other devices, alternating mattress).
Verify if the ambient temperature is in the normal range.

Positioning of the Subject

Position the patient in the bed to maintain angles of 120° of flexion of the hip and 130-160° at the knee.
Place the palmar side of the wrist upwards.
Ensure that the non-measured eye is closed during reflex recording.

Preparation of the Skin for Electrode Application. Note: This will reduce electrode impedance.

Clip or shave hair at the application sites.
Check the application sites, they must be clean and dry. If necessary, remove any body lotion by cleaning the skin with soap and water and rub the skin gently with a dry wash cloth or gauze.
Abrade the application sites with available abrasive material. Use the skin preparation paper over a large area rather than only a single swipe.
Apply each electrode immediately after skin preparation.

Placement of the Electrodes for Pupil Dilation Reflex (PDR) Assessment

Note: Please see the Figures for an overview of electrodes application.
Use Ag-AgCl electrodes with highly conductive wet gel to ensure an optimal signal during reflex recording.
Maintain an inter-electrode distance of 30 mm (center-to-center).
Place two stimulation electrodes for PDR recording, at the wrist on the skin area innervated by the median nerve, keeping the palmar side of the wrist facing upwards.

Placement of the Electrodes for Nociceptive Flexion Reflex (NFR) Assessment

Note: Please see the Figures for an overview of electrodes application. Magnetic and electrical fields may appear as background noise or other artefacts in the measurement trace. Maximal acceptable noise level using the followings protocol is set from values higher than 10 µV. High noise level is defined when the maximum amplitude in the area before the stimulation ('noise area', i.e., -130 ms up to -10 ms before stimulation) exceeds this adjustable threshold ('maximum acceptable noise level'). Noise values are not used to calculate the threshold and the stimulation is repeated with the current intensity until an EMG signal with no noise is determined. To limit the occurrence of artefacts, verify the device has been updated to the latest version. Artefacts can be reduced by optimal electrode placement and skin preparation.

Use two stimulation electrodes at the ankle and place the electrodes distal to the lateral malleolus, stimulating the sural nerve area.
Use two registration electrodes for EMG recording at the biceps femoris muscle. Place the electrodes four finger breadths above the popliteal fossa, posterior to the iliotibial band on the ipsilateral leg.
Use one reference electrode, placed at the quadriceps tendon.

Safety Check

Identify the materials: battery status (PDR tool), accessibility of a plug connection nearby (NFR evaluation monitor), lead wires and connections to the labeled device sockets.
Identify the patient: patient number, medical history, current medications, behavior pain scale, and sedation depth.

Pupillary Dilation Reflex Assessment: Getting Started

Attach the lead wire to the stimulation electrodes at the wrist. Verify that the black-labeled part is attached to the most distal electrode. Perform an impedance control indicated by the colored symbols, if necessary repeat the preparation procedure.
Turn the infrared camera on.
Select the measurement protocol: 'pupillary pain index' (PPI) through menu selection on the touch screen display.
Clean the camera and eye cab with water and disinfect them.

Pupillary Dilation Reflex Assessment: Installation

Open the eyelid and place the camera in an optimal position. Let the rubber eyecup rest on the orbit, enclosing the whole eye. Verify whether pupil detection has been set correctly and adjust the camera if necessary. The operator may have to raise the eyelid more. Center the pupil in the middle of the screen and verify the position by pursuing a pupil completely colored green.
Close the contralateral eye, decreasing the consensual light response.
Wait for a least 5 seconds to start the measurement, ensuring a stabilization period necessary for pupil accommodation (dark measurement environment).

Pupillary Dilation Reflex Assessment: Measurement

Start the test by pushing the trigger button. Hold the button until the pupil assessment is complete (a few seconds). Ensure that the entire measurement cycle is executed by 2 audible signals (first at the

start, second when the test is finished). Do not move the camera during measurement; a countdown is shown on the screen when stimulation intensity is increasing automatically from 10 mA up to maximum 60 mA.

Identify the results automatically displayed after 15 seconds on the screen

- Baseline pupil size (mm) before noxious stimulation (yellow horizontal line).
- Maximal pupil size (mm) after noxious stimulation (white horizontal line).
- Different levels of noxious stimulations by colored bands and values.
- Maximal pupil variation (% and mm).
- PPI score

Save the measurement results by pressing the icon after pupil assessment.

Nociception Flexion Reflex Assessment: Getting Started

Attach the lead wires for stimulation, recording and reference. Verify whether the black-labeled parts are attached to the most distal electrodes; white is for reference value recording at the knee.

Turn the device on when connected to a power supply. Identify the USB flash drive if data storage is desired.

Nociceptive Flexion Reflex Assessment: Installation

Press the settings button to go to the configuration menu to verify the stimulation settings and the threshold determination procedure for reflex measurement in unconscious sedated patients. Verify Measurement technique is on threshold tracking. Verify the Stimulus type is determined as RIII reflex. Select off when asked for NRS input. Choose Peak Z Score as Evaluation criterion. Use >100 number of stimuli. Initiate stimulation at 1 mA intensity, with minimum and maximum step size of 0.5 mA. Verify the Interstimulus interval is defined as 8 s with a reflex range of 90 – 180 ms.

Nociceptive Flexion Reflex Assessment: Measurement

Start the measurement, i.e., automatic reflex threshold tracking.
Reduce impedances when 'High noise level' appears by repeating the skin preparation protocol.
Identify reflex features.

- Identify the currents applied to the patient and number of stimulations.
- Identify the raw EMG displayed 200 ms before to 300 ms after stimulation via the EMG electrode on the thigh.
- Identify the reflex range and the reflex threshold value. The parameter is shown numerically (value in mA).

Results

We used both reflex assessments in a total of 40 critically ill ventilated subjects (38% females) at the ICU department using the previously described protocol. Patients with various indications for analgo-sedation were included: 58% for primary respiratory insufficiency, 23% due to multiple organ failure, 10% of the patients had a septic shock, and 9% were defined as being sedated for other reasons (e.g., cardiogenic reasons). All measurements were performed by the same investigator. Sedative agent dosing was never adjusted during the assessment. The pupil characteristics and EMG responses are shown in Table 2.

Table 2. Pupil characteristics and EMG responses after nociceptive reflex assessment. 'Error' measurements are defined as high impedance or noise problems during measurements

Analgesia Protocol	Overall	Remifentanil	Sufentanil	No opioid
Number of subjects	40	32	5	3
PDR elicitable	100%	100%	100%	100%
PDR stimulation intensity (mean ± SD, mA)	49.75 ± 12.91	49.69 ± 2.31	54.00 ± 6.00	43.33 ± 6.67
PDR PPI score (mean ± SD)	4.55 ± 0.39	5.09 ± 0.50	4.00 ± 1.73	6.33 ± 0.88
NFR elicitable	72%	69%	60%	0%
NFR measurement error (no reflex assessed)	15%	19%	20%	-
NFR threshold (mean ± SD)	44.93 ± 4.93	39.93 ± 4.65	48.22 ± 16.84	53.33 ± 8.37

Vital signs remained unchanged during measurements, even with high (> 60 mA) nociceptive stimulation. Therefore, no nociceptive reflex assessment had to be terminated early due to an increase in blood pressure, heart rate or change in ventilatory parameters. Identification of the PDR was possible in all subjects using the described protocol. Nevertheless, the NFR was identified in only 72% of the patients. Moreover, NFR threshold tracking was not possible in 13% of the patients despite optimal measurement conditions, suggesting a deep analgosedation level. However, excessive nociceptive stimulation (i.e., stimulation currents above 100 mA) was not used.

Discussion

This paper describes the application of two nociceptive reflex devices for objective (patient-independent) pain assessment in adult ICU patients. Moreover, the evaluation of the PDR and the NFR characteristics are described.

Pain and delirium are common in hospitalized patients, often in combination, and may adversely affect outcome parameters. In the ICU, opioids are frequently administered, sometimes in combination with other sedative agents, to protect patients against stressful stimuli such as nursing care or various diagnostic or therapeutic procedures and to improve mechanical ventilation therapy, or they may be necessary due to critical illness. However, extensive evidence indicates that (unnecessary) prolonged administration of analgosedation to ICU patients negatively affects morbidity and mortality. Furthermore, the implementation of reliable evidence-based analgosedation protocols could further improve patient outcomes [36-38].

The described reflex evaluation techniques can be considered quality indicators in healthcare and are closely associated with the use of opioids; further implementation could result in shorter ICU stays and improved short- and long-term outcomes. Furthermore, measuring nociceptive reflex thresholds through nociceptive assessments could result in targeted and patient-specific opioid administration. Therefore, evaluation and validation of the available objective pain assessment tools in critically-ill patients are urgently needed. Infrared pupillometry for PDR assessment has shown promising results [39-40]. Consistent with previous studies, this study demonstrated that pupillometry in unconscious patients in a very technological environment is feasible, fast and straightforward [41-42]. Moreover, using the derived PPI score, the clinician is provided with an indication of the level of analgesia. Our study has clearly demonstrated that NFR can be routinely evaluated in ICU patients. However, it

raises some significant points. First, NFR assessment may not be measurable due to persistent high electrode impedance despite maximal skin preparation. Secondly, we identified patients in whom NFR was not present, even with the maximal stimulation intensity. Despite the fact that NFR measurement is more challenging to perform, NFR threshold evaluation has shown promising results in patients under propofol-remifentanil sedation [43].

Improving reflex assessment skills, the authors advise the performer to take some key steps into account. It is imperative to pursue a low electrode impedance for generating high quality output. As such, cleaning the skin with isopropyl alcohol should be limited to patients in whom electrode adhesion may be problematic (lotion-covered skin) since it may dehydrate the skin and therefore increase impedance. Abrading the skin at the electrode application site with intended material will optimize measurement variables. However, care should be taken not to injure the skin of the patient. Before reflex assessment, the user can easily perform an impedance control in a similar way for both devices, looking to the colored electrode symbol on the main screen. A green symbol indicates an optimal electrode impedance, a yellow symbol implies a 'good' impedance. When the symbol is red colored, the impedance is too high for measurement and the skin preparation procedure should be repeated. In addition, the use of (very) small stimulation electrodes is recommended (i.e., 45 mm × 30 mm) to avoid electrode overlap which may lead to incorrect reflex recording. Finally, explore the device settings before starting reflex measurement as default settings or stimulation characteristics can change between different patient populations. The issue of obvious concern is that of high unnecessary currents application in mainly awake, conscious patients.

Despite the growing interest in physiological pain assessment in unconscious patients [2, 16-18], there are some limitations that need to be acknowledged for both devices. Most notably, the pupillometer uses an inbuilt measurement model called 'pupillary pain index' containing stepwise increasing tetanic stimulations. The measurement protocol is stopped when the pupil dilates more than 13% from its baseline size, a fixed cut-off criteria. By using this inbuilt limit, the occurrence of tachycardia and hypertension in response to nociceptive stimulations is assumed. Although pupillometry stimulation models are more frequently used, data confirming this hypothesis is lacking. Furthermore, the true challenge of this model lies in the practical implementation of these tests in routine clinical practice. Although more objective and patient-independent nociceptive reflex measurements may offer new perspectives for analgesic management, preparation and measurements require approximately 15 minutes (especially for NFR assessment), which remains challenging in a fast-paced work environment. Moreover, no normative data are currently available for 'normal reflex ranges' in critically ill patients. Optimizing the skills and expertise of health care workers with respect to the use of these highly innovative tools may generate extraordinary results that can further classify analgesia levels, improve pain detection, prevent chronic pain disorders and enable (re)evaluation of pain management. Moreover, opportunities for economic valorization may arise, and the use of objective pain assessment tools may offer a unique translational platform for the testing of new pharmacological, analgesic compounds.

Measurements of more objective nociceptive reflexes, such as the PDR and NFR, may help clinicians evaluate patients' specific analgesic needs, especially in those who are not able to report pain levels themselves. Whether these two assessment tools can be applied on a wide scale in daily practice remains to be determined. The ability of both innovative devices to predict nociceptive status and

their ability to guide clinicians in optimizing analgesic treatment in non-communicative critically ill patients warrants further investigation.

Acknowledgments

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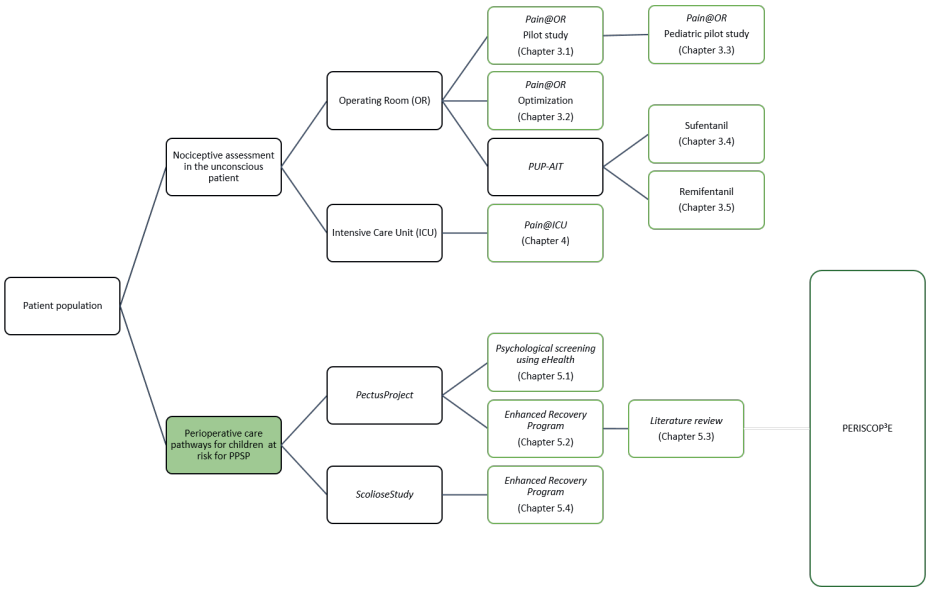
Chapter 5. An holistic Enhanced Recovery Program (ERP) for adolescents undergoing elective surgery including psychosocial screening and long-term follow up.



Overview of the research projects. Publications are shown in green, and attached as separated chapters. OR: operating room, ICU: intensive care unit, PPSP: persistent postsurgical pain, PUP-AIT: PUPil dilation reflex Assessment for Intraoperative analgesic Titration. *Note: Telemonitoring studies were executed in the pre-covid period.*

This chapter focusses on short –and long-term pain assessment in adolescents undergoing specific elective surgery, at risk for pain chronification.

5.1 Preliminary Evaluation of a Web-Based Psychological Screening Tool in Adolescents Undergoing Minimally Invasive Pectus Surgery: Single-Center Observational Cohort Study.

Wildemeersch D, Bernaerts L, D'Hondt M, Hans G.

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DOI: 10.2196/mental.9806

Abstract

Background

Preoperative anxiety and depression are predominant risk factors for increased postoperative pain. Thoracic wall deformities in adolescents often cause low self-esteem, which contributes to psychological concerns. Several studies have suggested a relationship between preoperative mental health support and enhanced recovery after surgery.

Objectives

This study investigated the validity of screening questionnaires concerning psychological trait and state characteristics via a patient-specific online platform.

Methods

Patients scheduled for elective pectus surgery between June 2017 and August 2017 were invited to participate in clinical interviews and online self-report questionnaires. All patients were recruited in the Anesthesiology Department, Antwerp University Hospital, Belgium. This single-center observational cohort study was performed in accordance with the ethical standards of the International Council for Harmonisation–Good Clinical Practice guidelines and the Declaration of Helsinki after obtaining study approval by the Institutional Review Board and Ethics Committee of the Antwerp University Hospital, Belgium (study identifier: 17/08/082). An online preoperative psychological inventory was performed using the Rosenberg Self-Esteem Scale, Hospital Anxiety and Depression Scale, and State-Trait Anxiety Inventory. Postoperatively, pain intensity and interference were assessed using the Multidimensional Pain Inventory, Coping With Pain Questionnaire, and numeric pain rating scale assessment. Patient satisfaction of the Web-based platform was evaluated.

Results

A total of 21 adolescent patients used our Web-based psychological perioperative screening platform. Patients rated the mobile phone app, usability, and accessibility of the digital platform as good or excellent in 85% (17 out of 20 respondent participants) 89% (17/19), and 95% (20/) of the cases, respectively. A total of 89% (17/) of the patients rated the effort of generating answers to the online questionnaires as low. The results from the completed questionnaires indicated a strong negative correlation between self-esteem and the anxiety trait (R=–0.72, P<.001) and overall anxiety characteristics (R=–0.49, P=.04). There was a positive correlation between depressive and anxiety characteristics and the anxiety trait (R=0.52, P=.03 and R=0.6, P=.02, respectively) measured by the online self-report questionnaires. Moreover, preoperative anxiety was positively correlated with postoperative pain interference (R=0.58, P=.02). Finally, there was a negative correlation between self-esteem and pain interference (R=–0.62, P=.01).

Conclusions

Perioperative screening of psychological symptoms and trait characteristics with specific treatment, if necessary, could further improve postoperative pain and overall health status. Research on eHealth technology, even for psychological patient care, is rapidly increasing.

Trial Registration: ClinicalTrials.gov NCT03100669; https://clinicaltrials.gov/ct2/show/NCT03100669 (Archived by WebCite at http://www.webcitation.org/6zPvHDhU5)

Introduction

Pectus excavatum and carinatum occur in 1 of 400 to 1000 children, with a 4:1 male-to-female predominance [1]. Many patients experience aesthetic challenges and even a compromised self-esteem during the vulnerable phase of puberty. Surgery is more often planned for aesthetic reasons than a necessary correction due to compression of underlying organs. Although minimally invasive repair of pectus (MIRP) has become common practice because of surgical stress response reduction, less blood loss, and a smaller incision, it still remains associated with severe postoperative pain. Moreover, the intensity of postoperative pain following MIRP has been shown to be the overriding factor in a patient's perception of the quality of the postoperative period. The fact that many adolescents experience moderate to severe pain for the first time and develop a new dependence on their parents further contributes to their decreased well-being after the surgical procedure. Many investigators have shown that preoperative psychosocial factors such as anxiety further increase postsurgical pain [2-4].

Recently, several authors assessed quality of life and self-esteem following surgical pectus repair [5-7]. Not surprisingly, adolescents with a chest wall deformity have lower self-esteem and higher anxiety or even depressive characteristics than healthy controls. Moreover, children and parents experience surgery as a stressful period and often feel underprepared for the operation, postoperative pain, and recovery. Many of them reported an interest in perioperative psychosocial screening. Previous research by Rabbitts et al [8] showed that health care providers agree that families would benefit from enhanced coping skills. Therefore, investigators have proposed a flexible screening tool to examine anxiety and dysfunctional coping strategies in children undergoing major surgery [8].

Little research has been conducted on the influence of preoperative psychological questionnaires on postoperative pain via eHealth services. With such services, patients and their relatives can complete questionnaires when and where they want, making participation less demanding. Even more, caregivers can introduce mental health screening before surgery as part of the surgical care.

The primary aim of the study was to develop and implement a Web-based patient platform for preoperative psychological yellow flag screening and early identification of risk factors for subacute or persistent postoperative pain. In addition, the applied screening battery was evaluated for usefulness in adolescents undergoing elective pectus surgery and feasibility for online questionnaire completion.

Psychological variables and their relationship with postoperative outcome parameters such as persistent, subacute pain were assessed. Finally, self-esteem was evaluated being an important indirect factor contributing to persistent pain via the development of anxiety, depression, or maladaptive coping strategies.

Methods

Recruitment

A total of 22 patients were scheduled for elective pectus surgery during summer holidays (June to August 2017) and were invited for clinical interviews and to complete online self-report questionnaires. All patients were recruited in the Anesthesiology Department, Antwerp University Hospital, Belgium (Figure 1). This single-center observational cohort study was performed in accordance with the ethical standards of International Council for Harmonisation–Good Clinical

Practice and the Declaration of Helsinki after obtaining study approval by the Institutional Review Board and Ethics Committee of the Antwerp University Hospital, Belgium (study identifier: 17/08/082). Patients with a history of psychiatric disease, chronic opioid use (more than 3 months), or revision surgery were excluded. No single patient reported clinically relevant preoperative pain symptoms.

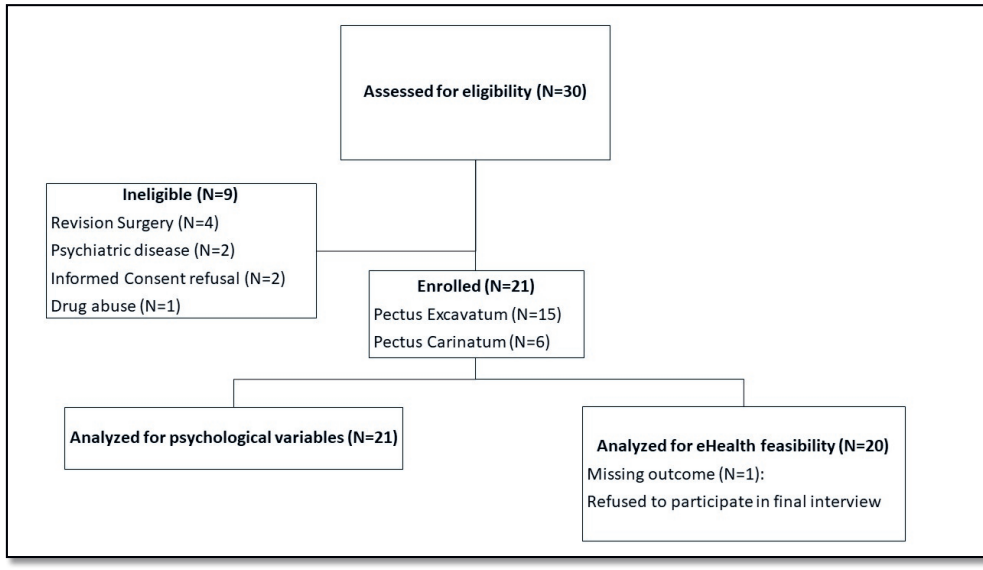

Fig. 1. Flow diagram of patient screening and study inclusion during the summer holidays of 2017.

Analyses of variance revealed no significant differences between pectus excavatum and pectus carinatum patients with respect to age or body mass index. The Haller index for defining the severity of the deformity in pectus excavatum patients based on computed tomography varied from 3.00 to 7.00 (mean 3.59 [SD 1.47]; median 3.00 [95% CI 2.24-4.95]); nevertheless, it was measured in 1 of 2 pectus excavatum patients. The mean age of the subjects was 14.82 (SD 1.30) years, and the majority of the participants (20/21,95%) were men; 90% (19/21) were not the only child in the family, and 52% (11/21) had a high education level (general secondary education—high school). Figure 2 shows a flowchart of the study.

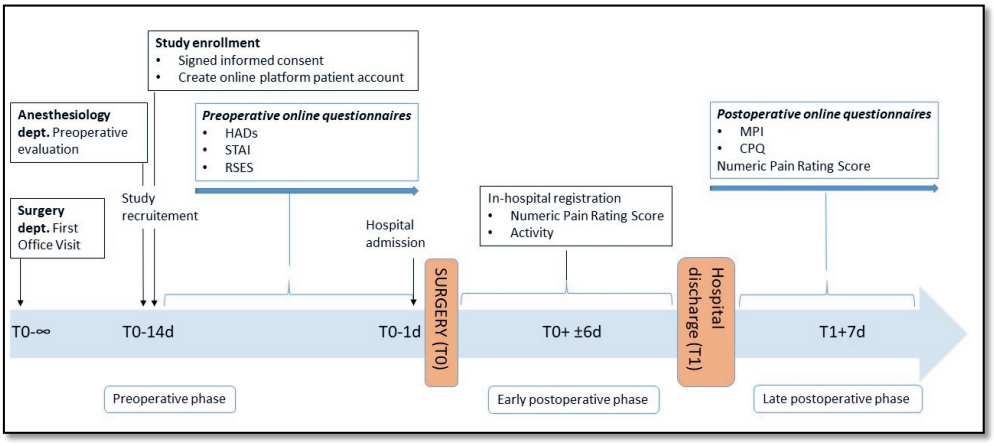

Fig. 2. Studyprotocol design. T0: day of surgery; T1: day of hospital discharge. HADs: Hospital Anxiety and Depression Scale; STAI: State-Trait Anxiety Inventory; RSES: Rosenberg Self-Esteem Scale; MPI: Multidimensional Pain Inventory; CPQ: Coping Pain Questionnaire.

Web-Based Platform

To provide patients with an individualized approach, we developed an electronic medical record coupled with a set of questionnaires. The Antwerp Personalized Pain Initiative app (Appi@Home, see Figures 3 and 4) supports an innovative approach by offering an online platform. Patients are provided with a unique code that allows them to fill out the preselected questionnaires. In addition, the patient becomes an active participant in the global preventive and further therapeutic approach, if necessary.

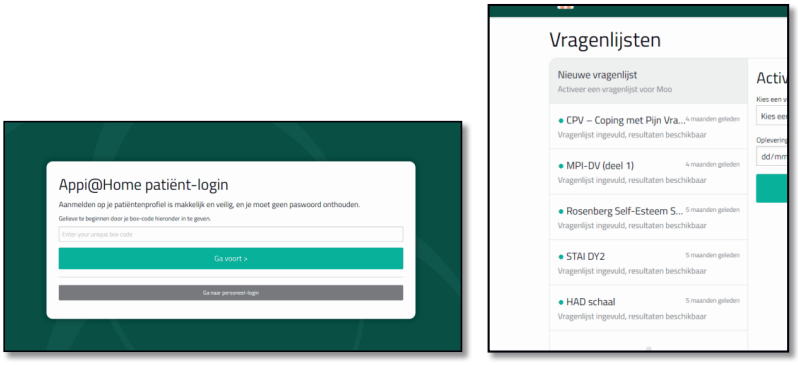

Fig. 3-4. Screenshots from the designed Web-based platform 'Antwerp Personalized Pain Initiative', Appi@home.

Preoperative Psychological Assessments

State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) Form Y is an instrument used to assess state and trait anxiety. State anxiety is defined as fear, nervousness, and discomfort temporarily induced by situations perceived as dangerous or threatening in which the autonomic nervous system is activated. State anxiety can vary in intensity and change over time. Trait anxiety involves rather stable individual differences in the predisposition to experiencing fear, stress, and discomfort. People with high trait anxiety characteristics will experience certain situations as more threatening or dangerous than people with low trait anxiety. In this study, the Dutch version (STAI-version-DY-2) was used. This 20-item scale is designed to assess pervasive feelings of trait anxiety. Items are rated by respondents on a 4-point Likert-type scale. Higher scores indicate higher levels of anxiety, and norm tables are available for different groups. The STAI-version-DY-2 has demonstrated acceptable internal consistency (alpha>.85) and 1-month test/retest reliability (r>.70) in adolescents, healthy adults, and military samples [9]. Van Der Ploeg et al [10] developed a Dutch translation [11].

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) has been developed to detect states of depression and anxiety in a hospital setting. It assesses core components of anxiety and depression without involving physical complaints. The questionnaire has 2 subscales, anxiety and fear, and both subscales consist of 7 items. Higher scores indicate more emotional complaints. Cutoff scores are available for quantification. For each subscale, a score of 8 or greater is associated with possible anxiety or depression. A score of 11 or greater is associated with probable anxiety or depression. The questionnaire was developed as a screening tool and can exclude but not assess emotional disorders [12,13]. The basic psychometric properties of the HADS as a self-rating instrument should be considered quite good in terms of factor structure, intercorrelation, homogeneity, and internal consistency [14]. Spinhoven et al [15] validated a Dutch version that was used in this study.

Rosenberg Self-Esteem Scale

The Rosenberg Self-Esteem Scale (RSES) is a self-report measure for self-esteem containing 10 items that was constructed for the investigation of a person's feelings about themselves in terms of self-confidence and intrinsic value. Self-esteem is an important measure for screening problems of social adaptation and predicting mental health problems. Items are rated by respondents on a 4-point Likert-type scale [16]. We used 2 scoring procedures for optimal interpretation of our results. The total score ranges from 0 to 30 according to the first procedure and from 10 to 40 according to the second procedure. The higher the total scores, the higher the level of self-esteem. Franck et al [17] developed a Dutch translation and evaluated the psychometric properties. The results showed high internal consistency and high congruent validity. Their findings support the usefulness of the Dutch RSES as a measure of self-esteem [17].

Postoperative Psychological Assessments

Multidimensional Pain Inventory

Kerns et al [18] applied cognitive behavioral concepts on chronic pain and developed the (West Haven Yale) Multidimensional Pain Inventory (MPI). This questionnaire assesses different pain-relevant aspects. The subjective characteristic of pain and the consequences on different aspects of the patient's life are the main objectives of the questionnaire [18]. Lousberg et al [19] developed a Dutch version of the questionnaire (MPI-DVL). The MPI-DVL consists of 61 items, ordered in 3 parts.

The first part, used by the authors to assess the psychosocial aspects of pain, consists of 5 subscales: pain severity, interference, life control, affective distress, and social support. Items are rated by respondents on a 7-point Likert-type scale. The authors evaluated the psychometric properties of the Dutch version, and their results showed good reliability and validity [19]. In this study, the first 2 subscales (pain severity and interference) are used for data analyses.

Coping With Pain Questionnaire

The Coping Strategy Questionnaire (CSQ) is an instrument developed to assess the coping strategies people use when experiencing pain. Research has shown that people develop their own coping style resulting from past experiences with pain and a general coping style for difficult situations. This instrument contains 44 items designed to evaluate 8 strategies for coping with pain (reinterpreting pain sensations, using coping self-statements, ignoring sensations, diverting attention, praying/hoping, catastrophizing, increasing behavioral activities, and exhibiting pain behaviors). The perceived effectiveness of the coping efforts was assessed with 2 items: control over pain and the ability to decrease pain [20]. Spinhoven et al [21] developed the Dutch version of the CSQ, the Coping With Pain Questionnaire (CPQ), which is slightly different. The CPQ contains 44 items in 8 subscales (diverting attention, reinterpreting pain sensations, using coping self-statements, ignoring pain sensations, praying/hoping, catastrophizing, increased behavioral activities, and perceived control over pain). The respondent answers questions on a visual analog scale (VAS) for the CPQ instead of a 7-point Likert-type scale (for the CSQ). The respondents indicate how often they use a specific coping behavior by putting a line on a 10-cm-long line with end points defined as “I never do that” and “I always do that.” The psychometric properties of the instrument are good [21]. CPQ active and passive coping indices were calculated according to the method described by Soares and Grossi [22] and Nicholas et al [23]. The scores of 5 subscales (diverting attention, reinterpreting pain sensations, coping self-statements, ignoring pain sensations, and increasing behavioral activities), which reflect active coping, were calculated to determine an active coping index. Two scales (catastrophizing, praying/hoping) that refer to passive coping were used to create a passive coping index. The subscale that assessed perceived control over pain was the self-efficacy index [22,23].

Numerical Rating Scale

The numerical rating scale (NRS) is an 11-point scale used for pain assessment. Self-report by a patient is considered the gold standard for pain intensity measurement. Caregivers familiar with communicating with patients in pain asked the patient how much pain they had suffered from in the previous 24-hour period. All patients were educated in pain rating, where 0 represents “no pain” and 10 represents “the worst pain possible,” using whole numbers. The mean score after the first 5 postoperative days was calculated [24]. Patients continued the pain intensity registration through the platform until completion of the postoperative questionnaires, 7 days after hospital discharge.

Daily Activity and Patient Mobility

Patients were assessed according to their mobility and daily activity by the attending physiotherapist. Every patient was given a daily score based on the exercise executed as part of the rehabilitation process after surgery during hospitalization. Scores ranged from 1 (exercise in the supine position), 2 (sitting), 3 (standing), to 4 (walking).

Statistical Analysis

A paired sample t test was used to assess differences in RSES bifactor questionnaire scoring after data normality assessment with the Shapiro-Wilk test. Associations between questionnaire scores

were determined with a Spearman correlation coefficient. Statistical analyses were performed with SPSS Statistics software (IBM Corp). Statistical significance was considered when P<.05.

Patient demographics and questionnaire results

The demographic patient characteristics are presented in Table 1. Eighteen adolescents completed the preoperative questionnaires, and 16 fully completed the postoperative questionnaires (Table 2). Furthermore, from the raw CPQ data, coping subscales were calculated to score the pectus patients on 3 coping categories (active coping strategy, passive coping strategy, and self-efficacy).

Table 1. Sociodemographic characteristics (N=21). PE: pectus excavatum, PC: pectus carinatum, BMI: body mass index.

Characteristic	Result
Type of deformity, n, PE[a]: PC[a]	15:6
Gender, n, male: female	20:1
Age, years, mean (SD)	14.81 (1.33)
Height, cm, mean (SD)	173.67 (8.88)
BMI[a], kg/m², mean (SD)	18.44 (2.03)

Table 2. Anxiety and depression characteristics, self-esteem rating, multidimensional pain questionnaire results, and coping with pain evaluation via eHealth technology. [a]HADS: Hospital Anxiety and Depression Scale, [b]STAI: State-Trait Anxiety Inventory, [c]RSES: Rosenberg Self-Esteem Scale, [d]MPI: Multidimensional Pain Inventory, [e]CPQ: Coping With Pain Questionnaire.

Questionnaire		Score mean (SD)
HADS[a] fear		6.11 (3.27)
HADS depression		3.50 (2.81)
STAI[b]		37.94 (6.88)
RSES[c]		21.56 (3.55)
MPI[d]		
	Pain severity	1.88 (0.78)
	Pain interference	3.20 (0.69)
CPQ[e] (raw data)		
	Diverting attention	3.88 (2.05)
	Reinterpreting pain sensation	23.29 (12.30)
	Catastrophizing	9.59 (8.42)
	Ignoring pain sensation	25.18 (12.69)
	Praying/hoping	23.47 (14.64)
	Coping self-statements	38.94 (12.12)
	Increasing behavioral activities	21.71 (9.84)
	Perceived pain control	11.59 (4.65)
CPQ subscale		
	Active coping score (raw data)	23.52 (7.41)
	Passive coping score (raw data)	16.53 (9.22)
	Self-efficacy score (raw data)	11.59 (4.65)

Detailed questionnaire result

Hospital Anxiety and Depression Scale

The HADS fear subscale indicated the presence of an anxiety disorder. The overall mean score was 6.11 (SD 3.27). The mean score ranged from 0 to 7, which indicated the absence of anxiety states prior to surgery. Thirteen patients scored between the range of 0 to 7 (no anxiety), 3 patients scored between the range of 8 to 10 (possible anxiety), and 2 patients scored in the range of 11 or higher (probable anxiety).

The HADS depression subscale indicated the presence of a depressive disorder. The overall mean score was 3.50 (SD 2.81). This mean score ranged from 0 to 7, which indicated the absence of depressive states prior to surgery. Sixteen patients scored between the range of 0 to 7 (no depression), and 2 patients scored between the range of 8 to 10 (possible depression).

State-Trait Anxiety Inventory

The DY-2 version of the STAI measured trait anxiety. The overall mean score of the study sample was 37.94 (SD 6.88). Compared with available data on controls (normal group of male military recruits approximately 18 years old), the overall mean score was in decile 6 indicating a mean level of anxiety.

Rosenberg Self-Esteem Scale

The RSES is a measure of global self-esteem. The mean score of the overall patient sample was 21.56 (SD 3.55) and was above the theoretical midpoint of 15. No single patient scored beneath this cutoff. The results can be compared with the data from the study by Schmitt and Allik [25], in which self-esteem levels were compared across 53 nations. The mean scores of this study sample were above the Belgian mean level of 19.66 (SD 5.28). The results of this study sample were higher than the average level of global self-esteem.

Multidimensional Pain Inventory

The MPI measured different pain-relevant aspects. The mean score of the study sample was compared with available normative data (mean and standard deviation) of the International Association for the Study of Pain Primary Site: Thoracic Region [18]. The overall mean pain severity score was 1.88 (SD 0.78), which was lower than the mean score of the normative sample (5.01 [SD 0.82]). The overall mean pain interference score was 3.20 (SD 0.69), which was lower than the mean score of the normative sample (5.01 [SD 0.80]).

Coping With Pain Questionnaire

The CPQ assessed different pain coping strategies. The mean raw subscale scores were compared with those of a normal group of patients with chronic low back pain or neck pain. The decile scores are written in parentheses below. The overall mean diverting attention score was 23.29 (SD 12.30) (decile 5). The overall mean reinterpreting pain sensation score was 8.47 (SD 6.99) (decile 2). The overall mean catastrophizing score was 9.59 (SD 8.42) (decile 2). The overall mean ignoring pain sensation score was 25.18 (SD 12.69) (decile 4). The overall mean praying/hoping score was 23.47 (SD 14.64) (decile 6). The overall mean coping self-statements score was 38.94 (SD 12.12) (decile 6). The overall mean increasing behavioral activities score was 21.71 (SD 9.84) (decile 3). The overall mean perceived pain control score was 11.59 (SD 4.65) (decile 7). Note that these scores represent the pain coping ability of the study sample. The mean postoperative pain (day 1 to day 5) was low

(mean NRS 1.89, mean MPI pain severity 1.88), reflecting the need to develop strategies to cope with pain.

Postoperative Pain

As shown in Table 3, all included patients received a postoperative evaluation score involving pain assessment (NRS) during hospital admission and a reassessment before postoperative questionnaire completion.

Table 3. Pain rating scores up to 5 days after surgery and highest mean pain score before postoperative questionnaire completion (first week after hospital discharge).

Numerical rating scale for pain assessment	**Score mean (SD)**
Postoperative day 1	1.36 (1.43)
Postoperative day 2	2.10 (2.00)
Postoperative day 3	1.91 (1.38)
Postoperative day 4	2.71 (1.79)
Postoperative day 5	2.09 (1.15)
Mean score first 5 postoperative days	1.89 (0.82)
Highest mean score before questionnaire completion	3.13 (1.83)

eHealth Technology

The primary variable was a patient's global assessment of the feasibility for the mobile phone app, internet platform, and accessibility of the questionnaires (using a 4-point categorical scale where 1=poor, 2=fair, 3=good, and 4=excellent). Twenty patients rated the eHealth implementation at the final interview after questionnaire completion.

Secondary end points included the time burden for questionnaire completion (using a 5-point categorical scale, where 1=low burden, 2=rather low, 3=average, 4=rather high, and 5=high) and response burden after a single reminder of the importance of questionnaire completion.

Patients rated the mobile phone app, individual online platform usability, and accessibility as good or excellent in 85% (17/20), 89% (17/19), and 95% (20/21) of responses, respectively. No individual scored the usability or accessibility as poor. Regarding the time burden assessment, 67% (12/18) indicated a (rather) low effort for questionnaire completion, and 22% (4/18) mentioned an average effort was required. Overall, 76% (16/21) of the patients were able to complete the online questionnaires within the imposed deadline.

Correlations

Preoperative Psychological Screening Tool

Assessing the usefulness of the online implemented questionnaires, correlations have been calculated. The results (see Table 4) showed a strong negative correlation between self-esteem (RSES) and anxiety characteristics (HADS anxiety) and between self-esteem and anxiety trait scores (STAI). Furthermore, there was a positive correlation between STAI and anxiety characteristics and depression symptoms (HADS anxiety and depression).

Table 4. Correlation between the preoperative psychological dimensions.

Psychological variables	Self-esteem		Depressive characteristics		Anxiety characteristics		Anxiety trait	
	R	*P* value	*R*	*P* value	*R*	*P* value	*R*	*P* value
Self-esteem	1.00		-0.15	.56	–0.49	.04	–0.72	<.001
Depressive characteristics			1		0.31	.21	0.52	.03
Anxiety characteristics					1.00		0.55	.02
Anxiety trait							1.00	

Pain Measurement, Inpatient Versus Outpatient Evaluation

The study findings showed a low positive correlation between the mean pain scores for the first 5 days after surgery and the pain severity scores measured with the postoperative questionnaire after hospital discharge (R=0.35, P=.18), although the differences were not significant. No correlation was found between daily activity scores and pain severity and pain interference.

Preoperative Psychological Screening Tools and Postoperative Outcome Measures (Pain and Coping Characteristics)

Finally, the results demonstrated a negative but non-significant correlation between self-esteem and pain interference (R=–0.62, P=.14) (Table 5). There was a positive correlation between present anxiety characteristics and passive coping behavior (R=0.55, P=.03) (Table 6) and anxiety trait and pain interference (R=0.58, P=.02). A clearly positive correlation is noted between postoperative pain score after hospital discharge and pain severity assessed by the MPI (R=0.62, P=.02).

No significant correlation was found between preoperative psychological screening questionnaires and the mean postoperative pain scores or between coping and pain (passive coping index vs pain, R=0.26, P=.32; catastrophizing vs pain, R=0.04, P=.87).

Table 5. Correlation between preoperative psychological screening and postoperative pain.

Characteristics	Postoperative pain scores (inpatient)		Postoperative pain scores (after discharge)		Pain severity		Pain interference	
	R	*P* value	*R*	*P* value	*R*	*P* value	*R*	*P* value
Depressive characteristics	0.01	.96	-0.44	.87	0.11	.70	0.46	.09
Anxiety characteristics	0.26	.30	-0.32	.22	–0.20	.47	0.46	.09
Anxiety trait	0.22	.38	-0.13	.64	–0.08	.78	0.58	.02
Self-esteem	-0.24	.34	0.18	.51	0.09	.75	-0.62	.01

Table 6. Correlation between preoperative psychological screening and coping strategies.

Characteristics	Passive coping		Catastrophizing		Self-control	
	R	*P* value	*R*	*P* value	*R*	*P* value
Depressive characteristics	0.41	.12	0.27	.31	–0.19	.49
Anxiety characteristics	0.55	.03	0.16	.55	–0.01	.99
Anxiety trait	0.04	.89	0.22	.41	–0.28	.32
Self-esteem	–0.02	.95	0.04	.88	0.34	.21

Discussion

Principle Findings

The appearance of a chest wall deformity can decrease a patient's psychological wellbeing such that self-perception is a major contributor to therapeutic decision making [5]. Furthermore, surgical care may cause severe stress or even psychological trauma [8]. Many investigators have shown that preoperative psychosocial factors, such as anxiety, increase postsurgical pain [2-4]. Moreover, patients undergoing thoracic surgery are prone to the development of chronic pain after surgery, which is often neuropathic and therefore more difficult to treat. Although psychological care is finally gaining attention and importance, many health care workers find it difficult to implement these challenging pain reduction strategies [26].

The primary aim was to introduce and evaluate the usefulness of eHealth technology for psychological screening purposes in an integrated surgical care model. Furthermore, 5 questionnaires were evaluated in assessing psychological variables (yellow flags such as depression, anxiety, and coping) involved in the transition from acute to persistent (subacute) pain in adolescent pectus patients. Finally, self-esteem was measured as an indirect parameter for pain persistence, as it is shown to be related with the incidence of yellow flags.

eHealth Technology

eHealth is a relatively new practice in health care that includes electronic processes and communication. Although concerns are rising about user privacy and confidentiality, its importance is growing significantly [27,28]. We conducted this study to investigate its usefulness as part of a holistic surgical care process in adolescent pectus patients.

This study confirmed the easy accessibility of internet-based psychological screening questionnaires. Most patients quoted a low effort for questionnaire completion, reflecting patient compliance. Since we introduced an internet platform, patients can complete their tasks when and where they want, highlighting the importance of patient independency and responsibility.

In general, the implementation of Web-based questionnaires containing a preoperative psychological assessment can improve surgical outcomes for patients and their families if the optimal screening questionnaire depending on the surgical population is chosen.

Psychological Variables and Type of Screening Questionnaire

It is well known that psychological characteristics play an important role in the development of persistent postsurgical pain; previous studies [29] have shown that trait anxiety increased pain after surgery [30-32]. In our data, preoperative depressive and anxiety states did not correlate with pain severity or pain intensity. This result is, however, somewhat inconsistent with the existing literature that shows that these states play a major role in chronification of pain [2-4,32]. One possible explanation is that psychological factors play a role in the development of chronic pain (defined as the persistence of pain for more than 3 months). The questionnaires used in this study protocol were, however, completed in the first week after discharge. Unfortunately, there was no long-term evaluation or a reassessment by retaking the applied screening battery. Consequently, further research is necessary to derive conclusions about chronic pain development and the extrapolation of the results to other patient populations.

Our results showed that anxious patients tended to engage more often in passive coping, which leads to maladaptive behaviors and cognitions about pain. This finding is in accordance with the literature on the chronification of pain. A study by Kaczynski et al [31] evaluated pain coping as a mediator of associations between anxiety and functional disability in adolescents with chronic pain. The authors indicated that relationships between anxiety systems and pain-related outcomes are complex. Their results showed that the association between anxiety and disability was mediated by passive coping [31].

There was no correlation between anxiety, depressive states, catastrophizing, and the experience of self-control. The overall mean catastrophizing score was low. This result is inconsistent with the literature on coping behaviors [33,34]. However, some authors have remarked on the concept of catastrophizing in children and adolescents [35-38]. One general remark should be made on the results of coping behavior and pain intensity and interference. The mean NRS score in the early postoperative phase was 1.89 (SD 0.82). The mean MPI pain severity score and interference after discharge were 1.88 (SD 0.78) and 3.20 (SD 0.69), respectively. These scores were low and could be attributable to the multidisciplinary follow-up before and after surgery (see below). A pain sensation that is acceptable may indicate that the patient was able to cope with it. Conversely, because of the use of more adaptive coping styles, the pain was generally under control. Nevertheless, pain scores increased the first week after hospital discharge.

We found several significant correlations: anxious predisposition and interference of pain, self-esteem and interference of pain, anxiety states and passive coping, self-esteem and anxiety measures, and depressive states and anxious predisposition. It is most likely that the relationships between anxiety, pain coping, and disability are bidirectional and contribute to a vicious circle of increasing pain-related disability, as outlined in the fear avoidance model of pain by Vlaeyen and Linton [39] (Figure 5).

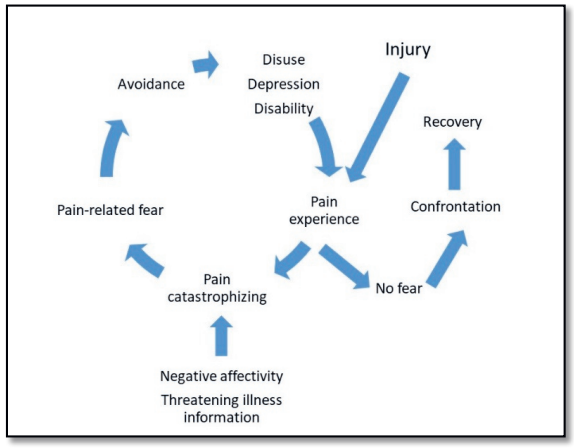

Fig. 5. Fear Avoidance Model of Pain by Vlaeyen and Linton [39].

It is important to note that all study patients followed a specific postsurgical pathway that focused on pain (recovery). All patients had a preoperative consultation in the multidisciplinary pain center in which education about the eHealth system was provided. In addition to this practical information, the medical staff also provided information on acute, subacute, and chronic pain and self-management methods. During hospitalization, a multidisciplinary team of anesthesiologists, surgeons, physiotherapists, and nurses followed the postoperative rehabilitation protocol. Each provider could anticipate the concerns of the patients very quickly. This process of reassurance, encouraging questions, and cognitive reappraisal is important to reduce distress and anxiety, consistent with the findings of Sjoling et al [40]. This personal and specialized approach could be used therapeutically to address the experience of distress associated with hospitalization.

Self-Esteem in Pectus Patients

Our results showed that preoperative anxiety is related to lower self-esteem, which is in accordance with the literature [22,41,42]. The mean self-esteem scores of this study sample were higher than the average Belgian levels of global self-esteem. This result is inconsistent with the expectation that pectus patients experience low self-esteem. Despite these findings, self-esteem played a role in the interference of postsurgical pain.

Self-esteem is an interesting measure in this population. There is a high comorbidity between depression and anxiety disorders. Low self-esteem is a transdiagnostic factor, for example, in both disorders. Improving self-esteem is an important treatment goal for therapy in depressive or anxious patients. Sowislo and Orth [41] evaluated the vulnerability and scar models of low self-esteem and depression, as well as low self-esteem and anxiety. The vulnerability model states that low self-esteem contributes to depression and anxiety, whereas the scar model states that low self-esteem is a consequence of depression and anxiety. The authors meta-analyzed the available longitudinal data. For depression, the findings supported the vulnerability model. For anxiety, the effects were relatively balanced; they found evidence for both theories. The authors speculated on why depression and anxiety were differentially linked to low self-esteem. They described, for example, that self-focused attention as a mediator is differentially related to depression and anxiety [41].

Additionally, many researchers further documented the concept of self-focus and suggested correlations between self-esteem and depressive and anxiety states [43-46].

We can question the use of the RSES in the measurement of self-esteem in children with pectus pathology. The RSES is a frequently used, short, and well-studied measure. In our study sample, all scores were relatively high. The study by Knudsen et al [47] reported the same ceiling effect in the use of the RSES as a measure of self-esteem. The purpose of their study was to assess the effects of surgical corrections of the pectus carinatum on health-related quality of life and self-esteem. Only one of 36 participants had low self-esteem (<15 points) according to the RSES before surgical correction, and self-esteem was within the normal range (>15 points) in all patients at the 6-month follow-up. This ceiling effect could be explained by the use of generic questions, resulting in high scores for self-esteem before surgery [47]. However, the RSES still remains a good measure of self-esteem [48], although some alternative multidimensional measures could be more sensitive

Some authors [49,50] question the factor structure of the RSES. Current debate focuses on whether the RSES has a uni- or bidimensional structure (positive and negative self-esteem). Franck et al [17] evaluated the difference between the 1- and 2-factor models of the Dutch RSES questionnaire, and the questionnaire appears to represent a 1-dimensional construct of self-esteem, contaminated by the method effect primarily associated with the specific nature of the items. The predisposition to answer negatively worded items differently is associated with cognitive ability, age, cultural group membership, lower academic motivation, etc. The positive and reverse negative scores were 11.39 (SD 1.82) and 10.17 (SD 2.53), respectively (P=.06), indicating that patients answered consistently, independent of the positive or negative formulation of the items.

Limitations

The limitations of our exploratory study need to be acknowledged. First, all questionnaires used were self-report instruments. Therefore, response bias may play a role, as results can vary due to small introspective abilities or socially desirable answering [51,52]. Second, we emphasize a potential time bias between hospital pain assessment and psychological evaluation via the MPI and CPQ. However, one may suggest an aberrant self-report from patients with a high postoperative pain score. A more precise evaluation of pain and coping technique could improve outcome variables. Furthermore, the reassessment of the preoperative questionnaires in the postoperative period could be of particular value. Nevertheless, minimal patient effort should be pursued. Third, the design of this proof-of-concept study may not use the questionnaire of choice in the assessment of self-esteem in adolescent pectus patients, as there was no significant difference in scores compared with those of healthy Belgians. To distinguish adolescent pectus patients with respect to self-esteem characteristics, a more sensitive and specific questionnaire is necessary.

Conclusion

If caregivers involved in a surgical care process use innovative eHealth techniques as a simple, accessible psychological screening tool, along with adequate treatment if necessary, postoperative outcome parameters may further improve. As a fast, straightforward, and accessible instrument, an online platform can not only increase patient participation in rehabilitation but also alert the provider when yellow flags are present. To determine if this technique may be helpful in reducing postoperative pain, the length of hospital stay, and the development of chronic pain after surgery, more research is imperative.

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5.2 Implementation of an enhanced recovery pathway for minimally invasive PECTUS surgery: a population-based cohort study evaluating short- and long-term outcomes using mobile health technology.

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Abstract

Background

Pectus excavatum and pectus carinatum are the most common chest wall deformities. Although minimally invasive correction (Minimally Invasive Repair of Pectus, MIRP) has become common practice, it remains associated with severe postoperative pain. Preoperative psychosocial factors such as anxiety and low self-esteem can increase postsurgical pain. Early detection of psychological symptoms, effective biopsychosocial perioperative management of patients and prevention of pain chronification using an enhanced recovery pathway (ERP) may improve outcomes. The incidence of the latter is poorly described in adolescents undergoing MIRP.

Objective

To evaluate an ERP containing early recovery goals and to assess persistent postsurgical pain three months after surgery in pediatric patients undergoing MIRP using a web-based psychological screening questionnaires, and telemonitoring.

Methods

A population-based cohort study was conducted with prospectively collected data from patients undergoing pectus surgery between June 2017 and December 2017. An ERP was initiated preoperatively and included patient education, eHealth-based psychological screening, multimodal preemptive analgesia, nausea prophylaxis as well as early Foley catheter removal and respiratory exercises. After hospital discharge, patients were followed up to ten weeks by an online diary evaluating pain while their rehabilitation progress was monitored via Bluetooth-connected telemonitoring devices.

Results

Twenty-nine adolescents were enrolled using the developed ERP. Preemptive multimodal analgesia pain rating scores were low during hospital admission. Optimal epidural placement occurred in 26 of the 29 participants (90%), defined by T8-9 or T9-10, hereby no motor block or Horner syndrome occurred. Duration of bladder catheterization was 3.41 ± 1.50 vs 4.66 ± 1.18 days (P<.001), in ERP and non-ERP patients who underwent surgery before the ERP introduction respectively. Numeric pain rating scores (NRSs) and incidence of nausea was low, contributing to an improved and faster rehabilitation. NRSs were 2.58 ± 1.77 vs 2.84 ± 1.60 (P = 0.50) on postoperative day (POD) 1, 2.48 ± 1.66 vs 3.24 ± 1.70 (P = 0.05) on POD 2, and 3.14 ± 1.98 vs 2.66 ± 1.40 (P = 0.19) on POD 3 in ERP and non-ERP treated control patients, respectively. Telemonitoring at home was feasible in adolescents after hospital discharge despite adherence difficulties. Although pain scores at the final interview were low (0.81 ± 1.33), 9 out of 27 long-term follow up ERP patients (33%) still experienced frequent disturbing thoracic pain requiring analgesic administration, school absenteeism and multiple doctor (re)visits.

Conclusions

Allocating patients to the appropriate level of care preoperatively and immediately after surgery may improve long-term outcome variables. Internet-based technologies and feasible, objective monitoring tools can help clinicians screen surgical patients for risk factors and initiate early treatment if necessary. Future research should focus on improving risk stratification and including a psychological assessment and evaluation of the effect of perioperative care pathways in children undergoing major surgery.

Trial Registration: ClinicalTrials.gov NCT03100669

Keywords: enhanced recovery, pectus carinatum, funnel chest, telemedicine, persistent postsurgical pain

Introduction

Funnel chest (pectus excavatum, PE) occurs in 1 out of 400 to 1000 live births and is the most common chest wall deformity (80-90%); additionally, it affects four times more males than females. Pectus carinatum (PC) is the second most common anterior chest deformity (15%), with an even more pronounced male predominance [1]. Surgery, frequently during childhood, is often planned for esthetic reasons rather than as a necessary correction due to compression of underlying organs. Although minimally invasive correction (Minimally Invasive Repair of Pectus, MIRP) has become common practice because of the reduced surgical stress response, lower blood loss and smaller incisions [2], it remains associated with severe acute and persistent postoperative pain. Psychosocial factors, including preoperative anxiety and low self-esteem, are identified as risk factors for increased postoperative pain [3-5]. Furthermore, evidence has revealed that patients undergoing thorax surgery are prone to the development of persistent postsurgical pain (PPSP) [6,7], which is often neuropathic and therefore more difficult to treat. However, little is currently known about the precise incidence of PPSP in children after pectus surgery. Despite the increased scientific interest in pain management after pectus surgery [8,9], the provision of adequate pain management and the necessary antiemetic and psychological treatments during the whole perioperative period remains a challenge for healthcare providers.

Recently, enhanced recovery pathways (ERPs) have been implemented worldwide as evidence-based standardized perioperative approaches. ERPs became the standard of care for patients undergoing colorectal surgery [10]. By introducing enhanced recovery programs, multidisciplinary teams began to work together, and the traditional care model was shifted to a more holistic approach, improving many patient-related outcome measurements by reducing the variation of care. The implementation of such ERPs for children and adolescents undergoing MIRP may not only reduce acute pain after surgery and increase overall satisfaction but also early alert caregivers to potential risk factors for increased postoperative pain or PPSP, allowing early treatment that may further improve patient outcomes. Use of one of the most rapidly growing healthcare innovations [11], eHealth technology (smartphone applications, individual online platforms, medical devices), may facilitate biopsychosocial follow-up, especially in the long-term after hospital discharge [12].

In this study, we evaluate a newly developed holistic ERP for adolescents undergoing elective MIRP surgery utilizing eHealth technology for preoperatively psychological screening and long-term patient follow-up.

Methods

Recruitment

Twenty-nine patients scheduled for MIRP between June 2017 and December 2017 were managed via the implemented multidisciplinary perioperative care pathway after written informed consent. All surgical procedures were performed by one attending pediatric thoracic surgeon. The technique used is described by Nuss for pectus excavatum [2] and by Abramson for pectus carinatum [13]. Patients with a history of psychiatric disease, chronic opioid use (more than three months) or revision surgery were excluded from this pilot project. All patients were recruited by the Department of Thoracic and Vascular Surgery, and subsequently selected for this study by in the Anesthesiology Department, Antwerp University Hospital, Belgium. Two patients refused preoperative psychological

screening via online questionnaires and long-term follow-up via individual eHealth technology. None of the patients reported preoperative pain symptoms. Questionnaire reports and medical data obtained before and after hospital admission were recorded by the patient via a specifically designed electronic medical record, supporting an individualized approach.

This population-based cohort study was performed in accordance with the ethical standards of ICH-GCP and the Declaration of Helsinki after obtaining study approval by the Institutional Review Board and Ethics Committee of the Antwerp University Hospital, Belgium (study identifier: 17/08/082) and trial registration (ClinicalTrials.gov NCT03100669).

Multidisciplinary ERP

The components of the multidisciplinary ERP are shown in Figure 1 and 2.

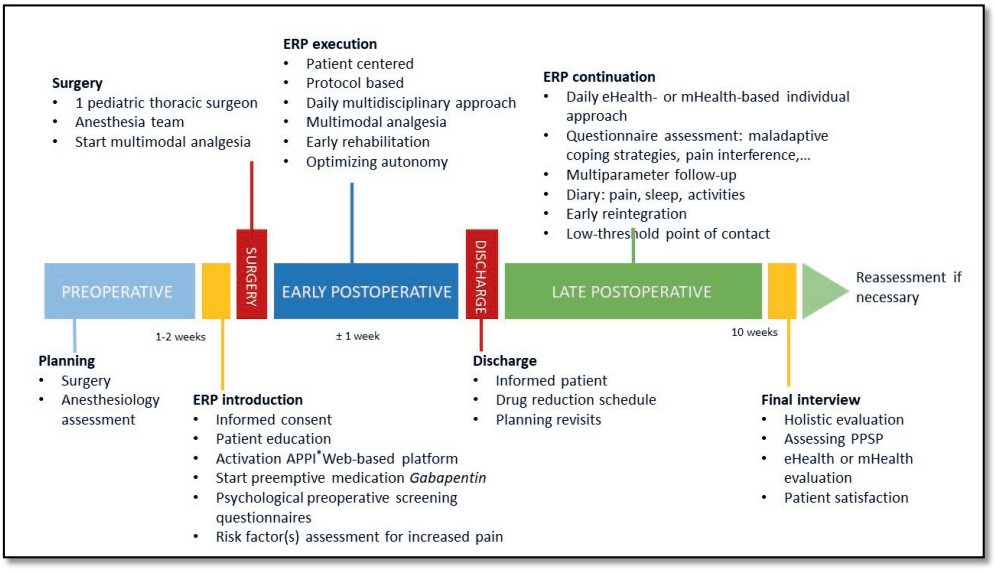


Fig 1. Protocol Design - Timeline. ERP, enhanced recovery pathway; APPI, Antwerp Personalized Pain Initiative; PPSP, persistent postsurgical pain.

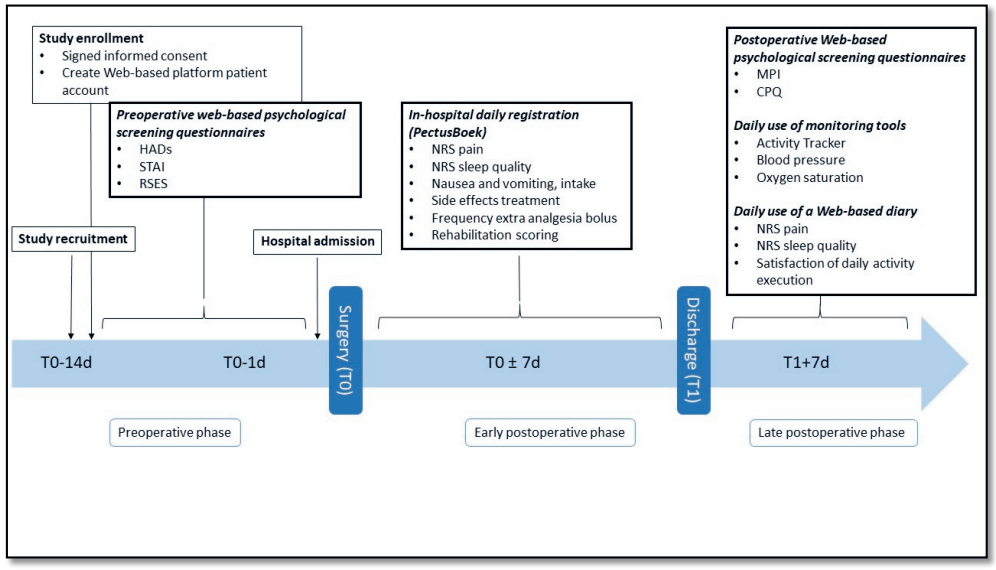


Fig 2. Timeline of the conducted surveys. T0: day of surgery; T1: day of hospital discharge; HADs: Hospital Anxiety and Depression Scale; STAI: State-Trait Anxiety Inventory; RSES: Rosenberg self-esteem scale; NRS: Numeric Rating Scale; MPI: Multidisciplinary Pain Inventory; CPQ: Coping Pain Questionnaire.

Preoperative study phase

A clinical study interview was executed one to two weeks prior to surgery. A preoperative psychological inventory [14] was performed by the patient after activation of the personal online Antwerp Personalized Pain Innovative (APPI) (Appi@Home®) platform (https://appi.uza.be) (Figure 3, APPENDIX III). Validated online Dutch questionnaires (APPENDIX I) included screening for anxiety and depressive symptoms (Hospital Anxiety and Depression Scale, HADs [15]), or trait characteristics (State-Trait Anxiety Inventory, STAI [16]) and self-esteem (Rosenberg Self-Esteem Scale, RSES [17]). Self-assessment through the abovementioned online questionnaires are used in this web-based trial part. If deviating or alarming questionnaire scores were recorded, an appointment with the psychologist was scheduled preoperatively. Alarming scores were defined on normative data and described cut-offs as previously described [14]. If present, the appropriate treatment was performed by a specialized psychologist.

The routine preanesthetic assessment included taking a patient history and a clinical examination, blood collection and technical cardiac and pulmonary investigations if necessary, supplemented by an extensive information session regarding the anticipated surgical trajectory. Key features regarding postoperative pain, pain management with patient-controlled thoracic epidural analgesia (PCEA) and the Foley catheter were included in a procedure-specific information leaflet. The preoperative assessment included the administration of a 7-day regimen of oral gabapentin one week before surgery and alignment of the patient's expectations.

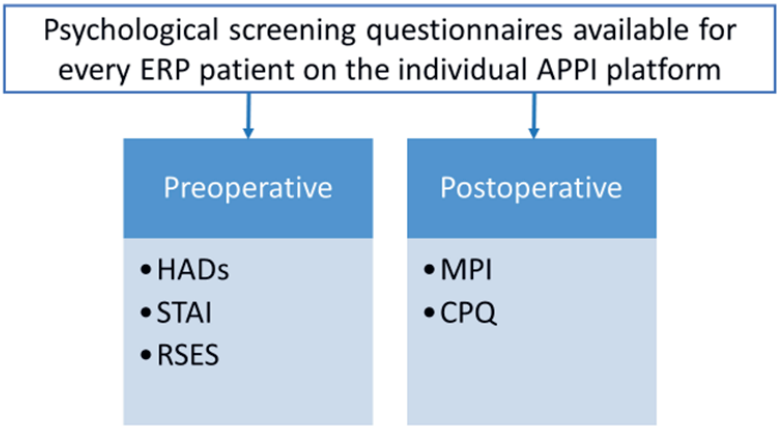


Fig 3. Multidisciplinary enhanced recovery pathway – Psychological Elements. HADS, Hospital Anxiety and Depression Scale; STAI, State-Trait Anxiety Inventory; RSES, Rosenberg Self-Esteem Scale; MPI, Multidimensional Pain Inventory; CPQ, Coping with Pain Questionnaire (see APPENDIX I, II).

Early postoperative study phase

A complete overview of the used ERP protocol during hospital admission is shown in the Multimedia Appendix 1 section.

In brief, the intraoperative treatment included multimodal analgesia using a thoracic epidural opioid-local anesthetic mixture, ketorolac, and acetaminophen based on patient weight. Additionally, the ERP featured a maximal multimodal antiemetic strategy including dexamethasone, ranitidine, dehydrobenzperidol, and propofol for anesthesia maintenance. Immediately after surgery, patients were admitted to the postanesthesia care unit (PACU) and were transferred to the ward when PACU discharge criteria were fulfilled. Postoperatively, ERP patients continued oral gabapentin in addition to PCEA, nonsteroidal anti-inflammatory drugs, and acetaminophen around-the-clock. The use of intravenous morphine or tramadol was strictly avoided, and a rigorous antiemetic strategy included ondansetron administration during the PCEA regimen. If necessary, escape analgesia for breakthrough pain and antiemetic rescue was available. In the subsequent days, PCEA settings were decreased in a stepwise fashion according to the protocol. Implementation of an intermittent bolus regimen (PIB) was applied to diminish rebound pain during the reduction of the PCEA dose. Under the protocol, PCEA was discontinued on postoperative day 6, or if possible on day 5. Urinary catheters were removed as quickly as possible . During hospital admission, daily pain scores, respiratory rehabilitation, and vomiting were recorded in a multidisciplinary fashion. Nausea was noted when persistent. Patients were discharged on acetaminophen, fixed combination of tilidine/naloxone and gabapentin. An analgesic reduction scheme over a two-week period was provided.

Late postoperative study phase

The extended ERP included a follow-up period of 10 weeks after surgery to meet the PPSP working definition proposed by Werner et al. [18]. After hospital discharge, two online questionnaires were provided for completion in the first week after hospital admission to screen for maladaptive coping strategies and pain-rehabilitation interference using their individual Appi@Home® platform. Scores of the validated Dutch questionnaires (APPENDIX II) from the Multidimensional Pain Inventory (MPI) [19] and the Coping Pain Questionnaire (CPQ) [20] were assessed. Using eHealth technology, adolescents used their smartphone to log in to the Appi@Home® smartphone application for direct transmission of the derived objective parameters of three medical rated telemonitoring devices (activity tracker, blood pressure monitor, and oxygen saturation measurement device) in the ubiquitous health monitoring system Appi@Home® (Figure 4 , APPENDIX III). The objective data were supplemented by subjective personal diary answers, including daily pain, sleep and activity assessments on an 11-level scale, which is asked to fill in daily via the Appi@Home® app on his or her smartphone. When no (objective or subjective) data was obtained for one week, the patient received a single reminder via the platform. If no response was given, the patient was contacted by telephone and asked for their well-being, measurement instructions were repeated and the patient was noted as non-adherent. Adherence is referred to the capacity of the patient to abide by mutually agreed recommendations regarding daily monitoring [20-21].

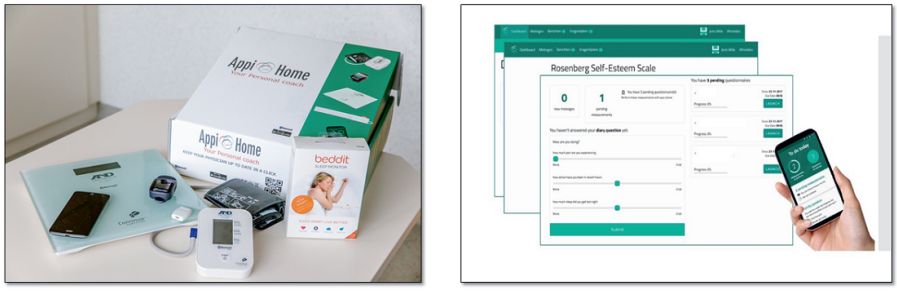


Fig 4. Appi@Home® toolbox and smartphone application. Medical devices for patient monitoring after hospital discharge. Patient enrolled in the ERP protocol after pectus surgery were instructed to link the following devices via Bluetooth connection with a smartphone: activity tracker (small white rectangular device), blood pressure monitor, sleep monitor and noninvasive oxygen saturation monitor. Appi@Home® is an European Union registered trademark under registration No 017610627.

Patients presented for postoperative evaluation visits 1–2 weeks after surgery and 2–3 months after surgery at the Department of Thoracic Surgery according to surgeon preference.

A final study interview was planned three months after surgery for patients on an ERP. In-hospital reassessments were scheduled earlier if necessary. An integrated final assessment was executed by a study physician or team member from the multidisciplinary pain center. Furthermore, the intake of medication and side effects, the presence of sleep disturbances, presence of PPSP, school

absenteeism, and overall satisfaction was recorded. Moreover, a thorough evaluation of the online platform was performed.

Data analysis

All data were recorded using a specific designed, multidisciplinary registration tool ('PectusBoek') and Microsoft Excel for Windows 2016 (Microsoft Corporation, Redmond, WA). Patient characteristics were extracted from the electronic patient record (C-medical record, Cegeka®, Vienna, Austria) during the hospital stay. Questionnaire scores, diary answers and medical devices data were derived from their individual eHealth APPI-platforms and described. Data were analyzed with SPSS Statistics software, version 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Numeric rating scores (NRSs) for pain and nausea symptoms and subjective sleep scores were summarized and described. When multiple pain scores were assessed in a single day, the day's scores were averaged. A supplementary NRS was recorded by a specialized pain nurse, as were PCEA-related side effects or complications. Rehabilitation measures, including flow-oriented spirometry and posture exercises, were evaluated and recorded by a specialized physiotherapist.

Values for the postoperative length of hospital stay, days of PCEA and urinary catheterization of the patients on an ERP were compared to the corresponding values in the cohort of the previous 93 (ratio 1:3 to reduce selection bias) adolescent pectus procedure patients at our institution before the ERP transition period. The relationships between patient characteristics and outcome variables were analyzed using the independent sample T-test and Chi Square test after normality control.

Results

Patient characteristics

Twenty-eight males (97%) and one female (range 12–18 years) underwent MIRP via the ERP protocol. Twenty-three of them were treated for a pectus excavatum deformity. The mean Haller Index was 3.53 (range 2.5–6.8), but this outcome was measured in only 9 of the 23 PE patients. Mean length and body mass index were 174.28 ± 9.14cm and 18.37 ± 2.30 kg m-2, respectively.

Early recovery: Pain assessment and related outcome variables

Nausea symptoms were reduced in ERP patients the first day after surgery compared with previous operated patient data undergoing the same procedure in our hospital (5 of 29 ERP participants (17%) vs. 37 of 93 non-ERP treated patients (40%), P=.03). One ERP-treated patient reported nausea symptoms more than once the day after surgery (3%). The highest incidence of postoperative nausea among patients using the ERP was recorded on postoperative day 3 in 7 of 29 participants (24%), and three of them reported nausea symptoms more than twice that day (10%) despite multimodal antiemetic strategies. In two ERP patients, nausea was associated with vomiting.

If other side-effects were present during the ERP treatment, pruritus was the most frequent (86%) during PCEA administration, followed by dizziness (14%) in the first three postoperative days. Not unexpectedly, the ERP patients had significantly less neuraxial analgesia side-effect (1 out of 29 ERP patients (0.3%) vs. 20 out of 93 non-ERP patients (22%), P=.03) after standardized thoracic catheter insertion. Accurate pain reduction was reflected in a longer PCEA administration period (5.76 ± 1.02 days vs. 4.67 ± 1.20 days, P< .001). Enrolled ERP patients followed the PCEA weaning protocol and

PCEA was discontinued in eleven patients (38%) on postoperative day 5 and twenty-six patients (90%) on day 6, respectively. Patient-controlled epidural analgesia characteristics were compared with previous non-ERP treated patients in our hospital (Table 1). Using a 11-level NRS pain scale (0: no pain, 10: worst pain), average pain scores given by the educated patient, are shown in Table 2.

Table 1. Patient-controlled epidural analgesia (PCEA) characteristics in patients undergoing MIRP with and without an ERP.

Postoperative day	**ERP protocol (N=29)**	**Controls (N=93)**	***P Value***
Thoracic level PCEA			***< .001***
T8-10	90% (N=26)	0%	
Other	10% (N=3)	100% (N=93)	
Problem [a]			
Yes: no (%)	1:28 (0.3%)	20:73 (22%)	***.03***
Horner syndrome (%)	0%	60% (N=12)	
Motor blockade (%)	0%	15% (N=3)	
Prematurely removed (%)	0.3% (N=1)	25% (N=5)	
Length of PCEA (mean ± SD)	5.76 ± 1.02	4.67 ± 1.20	***< .001***

[a] Problem defined as Horner syndrome, motor blockade, or unforeseen premature PCEA discontinuation

Table 2. Average pain scores assessed by a specialized pain care provider in patients treated with and without an ERP.

Postoperative day	**ERP protocol (N=29)**	**Controls (N=93)**	***P Value***
POD 1			
At rest	1.26 ± 1.43	1.24 ± 1.40	.94
During exercise	2.58 ± 1.77	2.84 ± 1.60	.50
POD 2			
At rest	1.08 ± 1.38	1.41 ± 1.62	.36
During exercise	2.48 ± 1.66	3.24 ± 1.70	***.05***
POD 3			
At rest	1.58 ± 2.15	1.16 ± 1.16	.37
During exercise	3.14 ± 1.98	2.66 ± 1.40	.19
POD 4			
At rest	1.73 ± 1.76	1.29 ± 1.74	.26
During exercise	3.71 ± 2.16	2.70 ± 1.79	***.02***
POD 5			
At rest	1.52 ± 1.87	1.00 ± 1.59	.16
During exercise	2.84 ± 1.70	2.23 ± 1.69	.12

Numeric pain rating scores (NRS) assessed by specialized pain team member. NA: no data available.

On the first postoperative day, 18 of 29 ERP participants (64%) (N=18) were able to maximally execute flow-oriented incentive spirometry, twenty-five patients (as were 93%) of ERP patients on the second postoperative day and all of them the third day after surgery. Eight patients were able to execute physical exercises while standing upright on postoperative day two (30%). This number increased during the consecutive days to 67% on day 3 (N=18), 77% on day 4 (N=20) and 96% on day 5 (N=26). Moreover, patients were stimulated to increase mobilization and walk from postoperative day 3. Seven patients were able to walk three days after surgery (26%), 58% were able to walk on day 4 (N=15), and 82% could walk on day 5 (N=22). However, no rehabilitation data were available in patients treated without a standardized perioperative protocol.

ERP-treated patients had a significantly reduced Foley catheterization period (3.41 ± 1.50 vs 4.66 ± 1.18 days, P<.001), and the chest tube was removed earlier in the ERP patients (1.48 ± 1.12 vs 2.34 ± 1.31, P=.002) (Figure 5) compared with retrospective data on non-ERP treated patients in our hospital. However, the length of hospital stay (LOS) was longer in the ERP-treated group (7.66 ± 2.01 vs 6.32 ± 1.26 days, P<.001); patients could have been discharged after 6.59 ± 1.99 days (P=.4) but stayed in the hospital for nonmedical reasons.

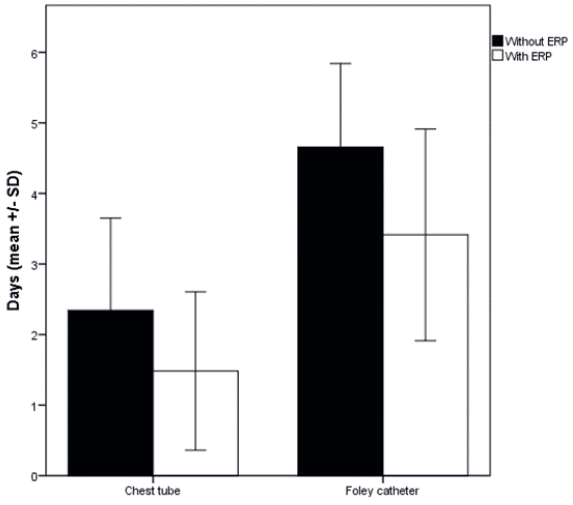


Fig 5. Chest tube and urinary catheter duration in patients treated with and without an ERP. Mean ± SD; standard deviation

Early psychological screening in surgical patients treated with the ERP

The implementation of a psychological screening tools is new in the ERP. The PPSP-defined risk factors for anxiety, depression and low self-esteem were identified using three online questionnaires before surgery. Questionnaire scores and normative 'control' data are summarized in Table 3.

The HADS containing two subscales was used to assess the presence of an anxiety or depressive disorder. The overall mean score for 'fear' was 6.00 ± 3.20 (range: 1-12), indicating the absence of anxiety states prior to surgery. Seventeen patients (71%) scored between 0 and 7 (no anxiety), and

five patients (21%) scored between 8 and 10 (possible anxiety). Two patients (8%) scored 11 or higher (probable anxiety). Screening for depressive disorders showed a mean score of 3.33 ± 2.76 (range: 0-10) and indicated the absence of depressive states prior to surgery. Twenty-two patients (92%) scored 0 to 7 (no depression), and two patients (8%) scored 8 to 10 (possible depression). No patient with an alarming score was identified by either subscale. Additionally, trait anxiety was measured using the STAI-DY-2. The overall mean score of the study sample (38.67 ± 7.99) was compared with available control data of a group of 18-year-old male military recruits (decile 6) [24], which indicated a mean level of trait anxiety in the enrolled ERP patients.

For evaluation of global self-esteem in patients undergoing MIRP with an ERP, the RSES was used. The mean score of the overall patient sample was 21.25 ± 3.49, which was above the theoretical defined cut-off score of 15 [25]. No single patient scored beneath this cut-off. When compared to mean self-esteem levels across 53 nations, we showed higher self-esteem among our patients than the mean Belgian level of 19.66 ± 5.28 [25].

The MPI measures various pain-relevant aspects. This study focused on the 'pain severity' and 'interference' subclasses, therefore, the Dutch version of the MPI questionnaire was used [19]. The mean score of the study sample was compared with available normative data (mean and standard deviation) of the 'IASP Primary Site: Thoracic Region' [26]. The overall mean 'pain severity' score in our patients was 2.27 ± 1.09, which was lower than the mean score of the normative sample (5.01 ± 0.82). The overall mean 'pain interference' score in our patients was 3.41 ± 0.81, which was also lower than the mean score of the normative sample (5.01 ± 0.80).

For assessing various pain coping strategies, the CPQ was used [23]. The mean raw subscale scores were compared with those of the normal group of patients with chronic low back pain/neck pain since an identical control group was missing [27]. The decile scores are written in parentheses below. The overall mean 'diverting attention' score was 21.32 ± 12.89 (decile 4). The overall mean 'reinterpret pain sensation' score was 8.18 ± 6.41 (decile 2). The overall mean 'catastrophizing' score was 10.45 ± 8.96 (decile 2). The overall mean 'Ignore Pain sensation' score was 23.09 ± 12.44 (decile 3). The overall mean 'praying/hoping' score was 20.00 ± 15.37 (decile 5). The overall mean 'coping self-statements' score was 38.09 ± 11.52 (decile 5). The overall mean 'increased behavioral activities' score was 19.95 ± 10.26 (decile 3). The overall mean 'perceived pain control' score was 10.65 ± 5.69 (decile 7). Note that these scores represented the pain coping ability of the study sample. The mean postoperative pain during the first week after discharge was low (NRS: 3.68 ± 0.22, MPI pain severity: 2.27 ± 1.09), reflecting the need to develop strategies to cope with pain.

Table 3. Detailed questionnaire scores from online psychological screening.

Questionnaire variables	Questionnaire outcome[a]	Available data[b]
HADS		
Fear (mean)	6.00 ± 3.20	
No anxiety	17 patients (71%)	Cut-off: ≤ 7
Possible anxiety	5 patients (21%)	Cut-off: ≥ 8, but < 10
Probable anxiety	2 patients (8%)	Cut-off: ≥ 10
Depression (mean)	3.33 ± 2.76	
No depression	22 patients (92%)	Cut-off: ≤ 7
Possible depression	2 patients (8%)	Cut-off: ≥ 8, but < 10
Probable depression	0 patients	Cut-off: ≥ 10
STAI		
Trait Anxiety	38.67 ± 7.99	decile 6
RSES	21.25 ± 3.49	Midpoint cut-off: 15
MPI		
Pain Severity	2.27 ± 1.09	5.01 ± 0.82
Pain Interference	3.41 ± 0.81	5.01 ± 0.80
CPQ		
Diverting Attention	21.32 ± 12.89	decile 4
Reinterpret Pain sensation	8.18 ± 6.41	decile 2
Catastrophizing	10.45 ± 8.96	decile 2
Ignore Pain sensation	23.09 ± 12.44	decile 3
Praying/Hoping	20.00 ± 15.37	decile 5
Coping Self-statements	38.09 ± 11.52	decile 5
Increased Behavioral Activities	19.95 ± 10.26	decile 3
Perceived Pain Control	10.65 ± 5.69	decile 7

Results are presented as the mean ± standard deviation. [a] Questionnaire outcome scores are reported as the mean ± standard deviation or number of patients per category and percentages. [b] Normative data and cut-off scores from previous literature, see text for references. HADS: Hospital Anxiety and Depression Scale; STAI: State-Trait Anxiety Inventory; RSES: Rosenberg Self-Esteem Scale; MPI: Multidimensional Pain Inventory; CPQ: Coping Pain Questionnaire.

Long-term rehabilitation: subjective and objective variables

There was a large variability in the use of the telemonitoring devices in the study sample. As patients were asked to use the devices every day during the 10-week follow-up period, we would theoretically receive at least 70 results from each patient's monitoring tool when the patients' adherence is maximal. On average, patients used the devices half as much as expected, only 38 times (Table 4).

Table 4. Per patient use of coupled telemonitoring devices that are asked to actively use once a day and an eDiary in the follow-up period.

Parameter	Minimum times used per patient	Maximum times used per patient	Mean ± SD
Oxygen saturation monitor	8	77	38.00 ± 21.93
Blood pressure monitor	7	78	38.50 ± 23.12
Diary	1	67	19.88 ± 16.03

There was very little evidence of vital sign problems in the study group (Figure 6), even during the first week when opioids were prescribed. Mean oxygen saturation, heart rate, and systolic blood pressure were 97.85 ± 1.06% (range: 93-100), 81.69 ± 12.60 beats per minute (range: 55-112), and 111.72 ± 9.99 mmHg (range: 90-159), respectively, during the first week after discharge. No alarming vital signs, defined as a systolic blood pressure < 95 mm Hg or > 140 mm Hg, oxygen saturation < 95%, tachycardia > 140 beats per minute, bradycardia < 45 beats per minute, or more than 10% deviating from last parameter control before hospital discharge, were recorded during the long-term study follow-up.

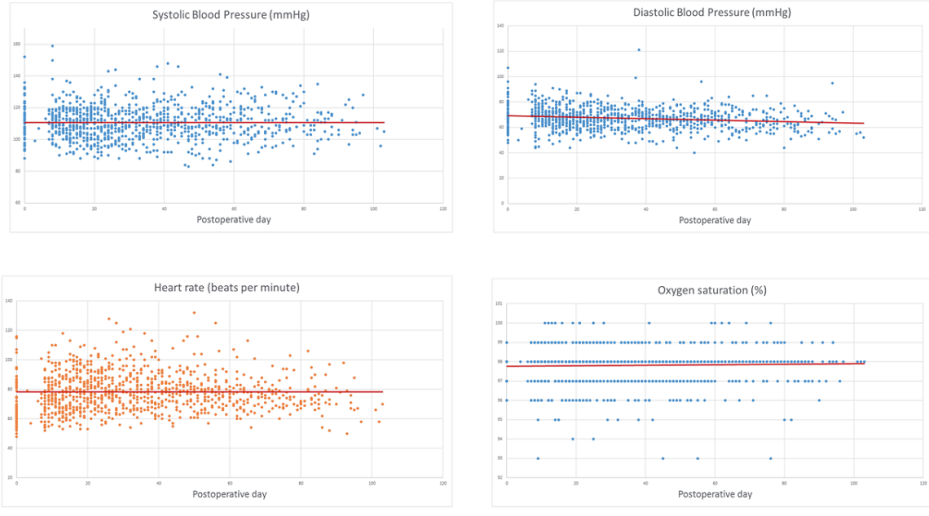
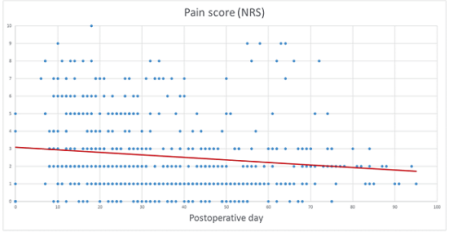


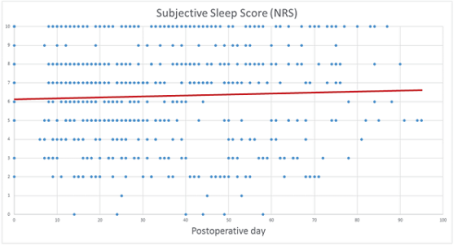
Fig 6. Vital signs during patient follow-up at home. Note that patients did not use the devices when admitted to the hospital during the early postoperative period.

Mean NRSs for pain intensity, daily activity execution and subjective sleep quality in the first week after hospital discharge were 3.68 ± 0.22, 4.54 ± 0.19, and 6.10 ± 0.22, respectively. Table 5 gives an overview of the overall mean pain scores, daily activity execution capabilities, and subjective sleep quality during out of hospital follow-up. All of these parameters favorably evolved in each patient during the postoperative phase (Figure 7) with decreasing pain scores and increasing scores for sleep quality and satisfaction with performance of daily activities.

Table 5. Mean scores of pain, rehabilitation and sleep quality of ERP patients after hospital discharge.

Number of Weeks at home	No. of results [a]	NRS Pain	NRS Daily activity	NRS Sleep quality
Week 1 (≤ 7 days)	97	3.68 ± 0.22	4.54 ± 0.19	6.10 ± 0.22
Week 2 (day 8-14)	70	3.14 ± 2.34	5.29 ± 2.57	5.29 ± 2.54
Week 3 (day 15-21)	58	2.62 ± 1.92	4.43 ± 2.42	5.93 ± 2.26
Week 4 (day 22-28)	52	2.71 ± 2.39	5.54 ± 2.36	6.40 ± 2.33
Week 5 (day 29-35)	50	1.92 ± 1.88	5.52 ± 3.13	6.80 ± 2.52
Week 6 (day 36-42)	38	1.89 ± 1.57	6.03 ± 2.92	6.50 ± 2.85
Week 7 (day 43-49)	35	1.91 ± 2.37	5.51 ± 3.04	5.77 ± 3.26
Week 8 (day 50-56)	25	2.60 ± 2.55	5.40 ± 2.83	6.36 ± 2.77
Week 9 (day 57-63)	25	2.24 ± 2.28	5.24 ± 2.79	6.16 ± 2.78
Week 10 (day 64-70)	17	2.18 ± 1.38	6.06 ± 2.14	7.41 ± 2.60





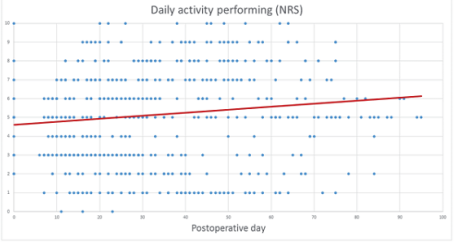


Fig 7. Subjective outcome variables per patient during postoperative rehabilitation at home (after hospital discharge). Note that patients did not use the individual diary when admitted to the hospital during the early postoperative period.

Mean results from daily patient activity generated by the objective activity tracker are shown in Figure 8. Expected long-term postoperative rehabilitation is given in Figure 9, which is showed by the activity tracker data from patient Y.J.

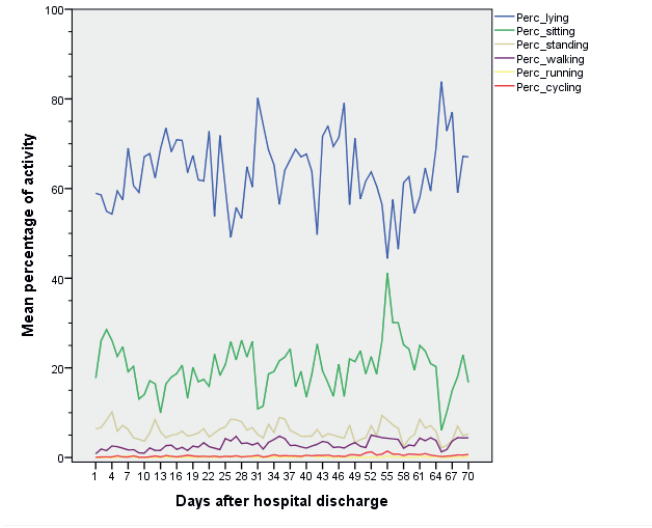


Fig 8. Study population mean objective activity variables during postoperative rehabilitation after hospital admission. Data are shown as mean percentages of daily activity evaluated in 6 categories; lying (blue), sitting (green), standing (dark yellow), walking (purple), running (yellow), and cycling (red).

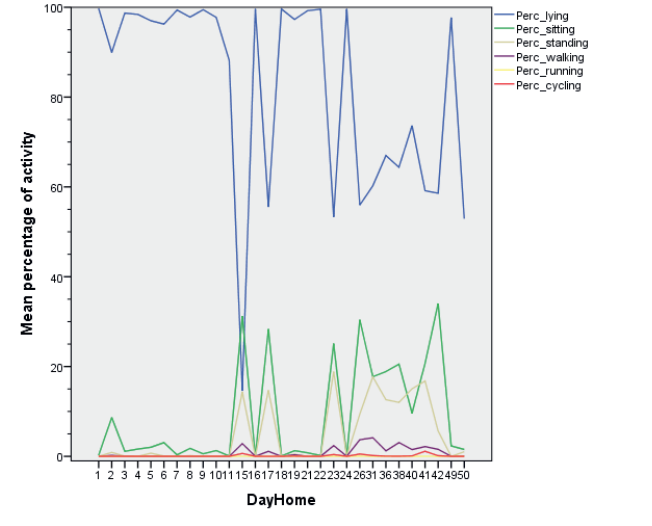


Fig 9. Evolution of daily activities during rehabilitation. Patient Y.J. mean objective activity variables during postoperative rehabilitation after hospital admission. Data are given as mean percentages of daily activity evaluated in 6 categories; lying (blue), sitting (green), standing (dark yellow), walking (purple), running (yellow), and cycling (red).

Twenty-four patients used the activity tracker monitoring tool (Table 6). Results were registered in six different categories; lying, sitting, standing, walking, running, and cycling. They were able to track their activity in 39.79 ± 5.12 days after surgery, with a large range in patient individual monitoring use (minimum 1 day, up to maximal use during study period). Theoretically, the 27 included ERP patients carried the activity tracker during at least 70 days, generating activity measurements during a total of 1890 days. During this pilot study, the activity of the ERP patients was tracked solely in 955 days (51%). Moreover, only 873 tracked days were evaluated as representative data; i.e. activity day logs containing 24 hours of 'lying' were interpreted as 'tracker not used' and were excluded for data analysis. Patients were registered as 'lying down' most frequently during the day. Moreover, 'lying down' frequency did not decrease during the consecutive weeks after hospital discharge. Not surprisingly, patients seldom performed more intense activities such as running or cycling during the follow up period.

No single patient-reported side effects from the perioperative intake of oral gabapentin was observed. Twenty of the 26 patients (77%) did not report side effects from oral opioid administration on the final interview. When asked about symptoms, four patients reported drowsiness, and all others experienced dizziness. All of these symptoms disappeared after dose reduction (Multimedia Appendix 2) during the first two weeks after their hospital discharge.

Although mean pain scores were low at the final interview (NRS: 0.81 ± 1.33), 3 out of 27 participants (11%) still took analgesics on a routine basis. Moreover, 10 of 27 MIRP operated patients (37%) still experienced frequent disturbing pain 10 weeks after surgery leading to sporadic intake of analgesic drugs, school absenteeism and multiple doctor (re)visits. All located the pain at the midaxillary thoracic region (5 patients even reported bilateral pain), and all described neuropathic pain characteristics.

Questions regarding Appi@Home® satisfaction were asked at the final interview, three months after surgery (Table 7) in this pilot trial. Twenty-seven ERP treated patients rated the smartphone application, the individual online platform usability and platform the accessibility as "good" or "excellent" in 78% (N=21), 85% (N=23) and 89% (N=24), of cases, respectively. No individual scored the platform usability or the accessibility as "insufficient". Regarding the time burden for psychological assessments, 15 of the 27 participants (56%) indicated a (rather) low effort for questionnaire completion, and 5 patients (19%) mentioned an average effort was required. Overall, 21 of the 27 ERP patients (78%) were able to complete the online questionnaires within the imposed deadlines.

The overall satisfaction after ERP was high. Seventeen patients rated the in-hospital care as "very good", eight as "good" and only one patient evaluated the overall care as "sufficient". The overall satisfaction with the long-term follow-up was rated as "very good" in thirteen patients, "good" in ten patients and "sufficient" in three adolescent pectus patients.

Table 6. Mean activity levels in six different intensity categories registered by the activity monitoring tool over 24 hours per week after hospital discharge. Results were collected using the online platform during the defined follow up period of 10 weeks after surgery. [a] Overall number of included measurement days. Data are given as day % and mean hours ± SD.

Number of Weeks at home	No. of days [a]	Lying	Sitting	Standing	Walking	Running	Cycling
Week 1	123	59.10%	23.51%	7.27%	1.86%	0.07%	0.16%
		14.18 ± 6.30	5.64 ± 4.21	1.74 ± 1.65	0.45 ± 0.46	0.02 ± 0.12	0.04 ± 0.06
Week 2	121	65.44%	15.29%	5.08%	1.65%	0.05%	0.21%
		15.71 ± 6.78	3.67 ± 3.69	1.22 ± 1.80	0.40 ± 0.612	0.01 ± 0.05	0.05 ± 0.12
Week 3	115	66.42%	17.78%	5.38%	2.34%	0.04%	0.30%
		15.94 ± 5.91	4.27 ± 3.86	1.29 ± 1.31	0.56 ± 0.72	0.01 ± 0.03	0.07 ± 0.14
Week 4	80	60.01%	21.47%	6.76%	3.07%	0.12%	0.23%
		14.40 ± 5.82	5.15 ± 3.85	1.62 ± 1.71	0.74 ± 0.84	0.03 ± 0.10	0.05 ± 0.09
Week 5	84	67.16%	18.55%	6.32%	3.35%	0.09%	0.35%
		16.12 ± 5.57	4.45 ± 3.90	1.52 ± 1.50	0.80 ± 0.82	0.02 ± 0.09	0.09 ± 0.17
Week 6	79	64.25%	19.51%	5.79%	2.81%	0.16%	0.39%
		15.42 ± 6.22	4.68 ± 4.02	1.39 ± 1.40	0.67 ± 0.68	0.04 ± 0.15	0.09 ± 0.15
Week 7	61	70.16%	18.33%	4.94%	2.84%	0.06%	0.44%
		16.84 ± 7.01	4.40 ± 4.56	1.19 ± 1.53	0.68 ± 0.77	0.02 ± 0.72	0.11 ± 0.17
Week 8	51	57.68%	25.35%	6.25%	3.76%	0.12%	0.86%
		13.84 ± 5.61	6.08 ± 4.30	1.50 ± 1.21	0.90 ± 0.75	0.03 ± 0.86	0.21 ± 0.21
Week 9	57	58.08%	24.01%	5.77%	3.41%	0.11%	0.68%
		13.94 ± 6.92	5.76 ± 5.45	1.38 ± 1.49	0.82 ± 0.83	0.03 ± 0.07	0.16 ± 0.21
Week 10	46	70.37%	15.69%	4.62%	3.41%	0.12%	0.44%
		16.89 ± 6.01	3.76 ± 3.93	1.11 ± 1.31	0.82 ± 0.82	0.03 ± 0.11	0.11 ± 0.15

Table 7. Applicability of the of eHealth technology for monitoring patients at home after surgery. [a]2 patients did not complete this questionnaire.

Device or application	Rating
Smartphone	
Insufficient	5 (19%)
Sufficient	6 (23%)
Good	8 (31%)
Excellent	7 (27%)
Oxygen saturation monitor	
Insufficient	0
Sufficient	2 (8%)
Good	5 (19%)
Excellent	19 (73%)
Blood pressure monitor	
Insufficient	6 (23%)
Sufficient	6 (23%)
Good	10 (39%)
Excellent	4 (15%)
Activity tracker	
Insufficient	5 (19%)
Sufficient	3 (12%)
Good	6 (23%)
Excellent	12 (46%)
Sleep monitor	
Insufficient	3 (11%)
Sufficient	1 (4%)
Good	10 (39%)
Excellent	12 (46%)
Application (daily measurements)	
Insufficient	1 (4%)
Sufficient	5 (19%)
Good	12 (46%)
Excellent	8 (31%)
Online platform (questionnaires)[a]	
Insufficient	0
Sufficient	2 (8%)
Good	8 (31%)
Excellent	14 (54%)
Main reason for nonadherence	
Time-consuming	1 (4%)
Remembering	19 (73%)
Empty battery	2 (8%)
Device failure	4 (15%)

Discussion

This pilot study evaluated different outcome variables of the implemented ERP after surgery in early recovery and assessed the occurrence of PPSP three months after surgery in pediatric patients undergoing MIRP using eHealth technology. We demonstrated the possibilities of eHealth screening and monitoring tools in a perioperative enhanced recovery program. Using Appi@Home®, patients can be monitored during the (long-term) rehabilitation period.

Acute pain and short-term-related variables

The use of ERPs has gained major attention in recent years. However, many clinicians struggle to appropriately describe and dose postoperative analgesics while tackling the real needs of acute pain [29]. Litz and colleagues [32] recently described the potential benefit of an in-hospital ERP in patients undergoing thoracic wall deformity repair. Optimal treatment by a preemptive multimodal management protocol covering biopsychosocial needs improved patient-related outcome measures whereas under-treatment of acute pain increased the risk of pain chronification [3]. Possibly more important than the ongoing debate on the optimal peroperative and immediate postoperative treatment in the ERP (for example epidural versus intravenous analgesia) [33], novel research suggests a more structured holistic care pathway of routine elective major surgery, understanding the relation between medication initiation, dosage and duration, focusing on early appropriate treatment of yellow and red flags. This requires multidisciplinary follow-up of patients, maximizing patient and parent satisfaction. Our data showed that the implementation of the ERP positively affected early rehabilitation with low pain scores, even with thorough epidural analgesia administration. Pain scores were even lower when compared with data from Litz and colleagues using also gabapentin but preferred early systemic opioid administration instead of epidural analgesics [32] which are 5.2 ± 1.7, 3.8 ± 2.1, and 3.8 ± 2.2, on postoperative day 0, 1, and 2 respectively. Furthermore, clinicians are urged to remove chest tubes and Foley and epidural catheters as soon as possible. Therefore, the risk of potential urinary or epidural infections and delayed rehabilitation can be reduced.

In this study, the patient and his/her family members were instructed and educated early in the perioperative trajectory, reducing anxiety and identifying additional risk factors for increased or prolonged postsurgical pain as suggested by Williams et al. using a management pathway including biopsychosocial formulation [7]. The establishment of a constructive relationship between care giver, patient and family as recommended by Liossi and colleagues [35], also provided a platform to provide perioperative context and explain interventions and expectation as indicated by the patients and parents on the final interview. Furthermore, the implementation of the holistic surgical care pathway was positively assessed by the adolescents and their parents during hospital admission as well as after discharge.

Persistent pain and long-term rehabilitation

Our study differs from other studies in terms of the biopsychosocial evaluation and the extended daily follow-up even after hospital discharge. To date, little data concerning subacute, persistent or chronic pain in children after surgery have been collected, despite growing knowledge regarding risk factors [7]. Our project included the recording of objective parameters such as vital signs and subjective variables concerning pain, daily activities and sleep quality after hospital discharge. Hence,

medical intervention could be planned early if necessary. Despite the low pain scores in our population three months after surgery, 9 out of 27 participants (33 %) of the adolescents reported a continuing daily intake of analgesics, repeated visits to general practitioners or specialized healthcare services, and even school absenteeism due to thoracic neuropathic pain symptoms. Furthermore, the dependency of children on their parents and school absenteeism during young vulnerable life increases the importance of these numbers. A possible explanation may be that increased body length growth or surgical correction of an asymmetrical deformity may lead to consequent increased (unilateral) pressure after fixation with potential intercostal nerve damage as suggested by Wildgaard et al. [36]. However, more research with long-term evaluation is necessary to decipher causal variables.

Implementation of eHealth and mobile healthcare

Digital applications are on the rise in healthcare. The need for such applications is apparent due to the increasing tendencies towards early recovery after surgery with reduced hospital stay lengths [37]. Through applications, mobile technology [38] and wearables, the health of patients can be monitored more accurately and faster [39]. Consistent with our data, efficient care using this technology was positively evaluated by various patient-related outcome measurements such as pain, daily activities and overall satisfaction. In fact, mobile health can be a facilitator of evolution towards a value-based approach to care. In this first implementation trial, patients reported the monitoring tools as feasible devices, and they indicated that rather low effort was required for online questionnaire completion. However, in addition to the need to optimize the performance of the individual wearables, research should be devoted to increasing patient adherence. The use of gamification techniques and other approaches could accelerate implementation [40]. The use of such game design elements can increase the motivation of people to adhere to telemonitoring actions and web-based questionnaires as part of their individual follow-up and therapy.

However, little is known about the possibilities of eHealth in this specific patient group of pectus adolescents. However, many of them could benefit from improved perioperative care. This pilot project combines various suggestions reported in other target groups such as psychological screening, structured care and PROM. Nevertheless, more detailed research through well-designed study protocols is necessary towards postoperative (long-term) application of e-Health modalities in adolescents after major surgery.

Limitations

We recognize that our implementation study has some limitations. First, we compared ERP-treated patients with retrospective data in our hospital before such protocols were used for MIRP patients. Therefore, data between 2010 and 2014 were used. It should be mentioned that the Abramson technique has been introduced in recent years. Moreover, although recognized as most important risk factor for pain, those historical controls have only been matched for age and pathology. Furthermore, additional research is needed to further clarify the differences in multiple patient related outcome measurements treated with the used ERP protocol in the two MIRP categories, pectus excavatum and carinatum. Secondly, the adherence to the different telemonitoring devices should be further increased. The daily use of the devices is mainly diminished due to 'forgot to use it'. This could be a possible explanation of the high reported activity tracker category 'lying down'. Thirdly, the design of this study focused on adolescent pectus patients without a history of opioid use or psychiatric disease. Ideally, patients diagnosed with autistic spectrum disorders or other mental

illnesses should be included in an ERP, as they could benefit the most from standardized care. Our findings must, therefore, be evaluated in larger comparative descriptive studies and randomized controlled trials.

Conclusion

Our results offer a potential approach for optimizing holistic patient care, consequently improving patient-reported outcome measures. Early risk factor identification and structured individual medical (long-term) follow-up after discharge may further enhance rehabilitation. Healthcare providers should extend their knowledge of and embrace available eHealth technologies for biopsychosocial care.

Our platform provides a framework for optimizing patient- and procedure-specific psychological online screening questionnaires, individual patient monitoring and treatment (re-)assessment. Furthermore, it may contribute to scientific research by offering reliable long-term data.

The implementation of holistic surgical care pathways using a multidisciplinary eHealth-based approach is a combination that merits further investigation in various surgical patient groups.

Acknowledgments

We would like to acknowledge Joris Wille and Dries Oeyen, members of BeWell Innovations® (IT, Ranst, Belgium), for the development of the online platform and for providing continuous technical support. Moreover, the implementation of this ERP was made possible by the collaboration between the Department of Anesthesia & Multidisciplinary Pain Center and the Departments of Physical Medicine and Rehabilitation, Thoracic and Vascular Surgery and Pediatrics of the Antwerp University Hospital (UZA). In addition, an educational grant (Dehousse mandaat) was received from the University of Antwerp (UA).

Conflicts of Interest

None declared.

Appendix I

Preoperative Psychological Screening Questionnaires

The Hospital Anxiety and Depression Scale (HADS)

The HADS was developed for detecting states of depression and anxiety in a hospital setting [410,42]. It assesses core components of anxiety and depression without involving the physical complaints. The questionnaire has two subscales, anxiety and fear, and both subscales consist of seven items. Higher scores indicate more emotional complaints. A validated Dutch version by Spinhoven et al. was used [15].

The State-Trait Anxiety Inventory (STAI) Form Y

The STAI was used to assess state and trait anxiety [24]. In this questionnaire, state anxiety is defined as fear, nervousness and discomfort temporarily induced by situations perceived as dangerous or threatening in which the autonomic nervous system is activated. Trait anxiety refers to rather stable individual differences in the predisposition to experience fear, stress and discomfort. People with high trait anxiety characteristics will experience certain situations such as surgery as more threatening or dangerous compared to people with low trait anxiety. Van Der Ploeg et al. developed a Dutch translation [16].

The Rosenberg Self-Esteem Scale

The Rosenberg Self-Esteem Scale (RSES) is a screening instrument for negative body image perception [43]. Self-esteem is an important measure for screening problems of social adaptation and predicting mental health problems. Furthermore, screening for body image disturbances can already be a necessary intervention in patients with a thoracic wall deformity. The RSES is a self-report measure for self-esteem containing 10 items constructed for investigating a person's feelings about themselves in terms of self-confidence and intrinsic value. The Dutch version by Franck was used [17].

Appendix II

Postoperative Psychological Questionnaires

Multidimensional Pain Inventory (MPI)

The Dutch version of the (West Haven Yale) Multidimensional Pain Inventory (MPI) was used to assess different pain-relevant aspects [19,26]. The first part used in this project assesses the psychosocial aspects of pain and consists of five subscales: pain severity, interference, life control, affective distress and social support.

Coping with Pain Questionnaire (CPQ)

The second postoperative questionnaire is the Dutch version of the Coping Strategies Questionnaire (CSQ), the Coping with Pain Questionnaire (CPQ), which was developed by Spinhoven et al. [23]. The CPQ contains 44 items in eight subscales: diverting attention, reinterpreting pain sensations, using coping self-statements, ignoring pain sensations, praying/hoping, catastrophizing, increased behavioral activities and perceived control over pain. The respondent answers questions on a visual analog scale (VAS) (CPQ) instead of a 7-point Likert-type scale (CSQ). CPQ active and passive coping indices were calculated according to the method described by Soares and Grossi [44] and Nicholas et al. [45]. The scores of five subscales that reflect active coping, were calculated to determine an active coping index. Two scales that refer to passive coping were used to create a passive coping index.

Appendix III

Appi@home® digital platform

Consulted by https:/home.uza.be and available introduction movie via the link below.

UZA@home, jouw persoonlijk patiëntenportaal van het UZA - YouTube

Appi@Home® is an award-winning eHealth tele-monitoring system, allowing physicians to keep tabs on patients even after they return home. Patients can easily measure their vital parameters through our user-friendly smartphone application, as well as completing diaries or filling questionnaires. The resulting data is then made available to physicians in the web platform, where it can be used to evaluate the patient's therapy. The application also proactively tracks down possible issues with patients and alert their physicians if necessary. Appi@Home® supports our approach to subacute and chronic pain by offering a platform for continuous follow-up. Patients are provided with a toolbox and an app that continuously collects objective outcome data. Earlier (unpublished) results clearly indicate an increase in patient responsibility and self-management, with a significantly shorter treatment period and earlier functional reintegration as a result.

Meanwhile, the digital platform has been further renewed and this personal patient portal can be found under uza@home. It supports and guides individuals during their care process in our hospital. Accounts are created a few days before a planned visit and an inviting text message is sent with the link to the platform. Registration instructions are shown and the login procedure via Itsme or digipass can be followed. An alternative registration procedure is provided for patients without a Belgian passport.

How it works in reality

1. Patients are asked to start using the application after the preoperative consultation when an informed consent is obtained
2. Patients receive a box with wireless medical measuring devices.
3. The patient downloads our app for Android or iOS, which guides the patient through the set-up procedure, necessary to connect the wireless bluetooth connected devices with their smartphone. As an alternative, questionnaires and diaries can also be accessed by using the web-based platform
4. Measurements are securely transmitted to the hospital. Data only gets stored on-premises.
5. Physicians can sift through the data and receive proactive alerts if predefined problems arise. Therefore, limits for measurement results are predefined when a caregiver is activating the platform of a patient.
6. Patients receive messages asking them to complete validated questionnaires on fixed time points, throughout the entire perioperative period.

Multimedia Appendix 1

Multidisciplinary Enhanced Recovery Pathway – Medication Components. PCEA, patient-controlled epidural anesthesia; TCA, target controlled anesthesia; PACU, post-anesthesia care unit; POD, postoperative day; IV, intravenous; PO, per os; PIB, programmed intermittent bolus regimen.

Preadmission

- Gabapentin, starting 7 days prior to surgery, < 50 kg, daily 300 mg; > 50 kg, daily 900 mg
- Day before surgery, admission to the floor, where all healthcare providers are familiar with the postoperative protocol

Day of surgery

- Multimodal analgesia
  - PCEA, optimal placement T8-T10. Ropivacaine bolus 3.75 $mgml^{-1}$, 1 ml per 10 cm above 1 m patient length
  - IV Acetaminophen 20 $mgkg^{-1}$, 15 $mgkg^{-1}$ repeated every 6 hours
  - IV Ketorolac 0.5 $mgkg^{-1}$
- Multimodal antiemetics
  - IV Dexamethasone 5 mg
  - IV Dehydrobenzperidol 0.625 mg
  - IV Ondansetron 4 mg
  - TCA Propofol
- Chest tube and Foley catheter placement
- When awake: incentive spirometry as frequently as possible
- PACU admission overnight: continuous pulse oximetry and supplemental oxygen if necessary to maintain saturation
- Stimulation early intake as tolerated

POD 1 - 2

- PCEA mixture ropivacaine 0.2 % + fentanyl 10 μgml^{-1}, 6 ml/h continuously, 4 ml/h bolus if necessary every 30 minutes (6/4/30) – coadministered with ondansetron 4 mg every 8 hours
- IV Acetaminophen 15 $mgkg^{-1}$ repeated every 6 hours
- IV Ketorolac 0.5 $mgkg^{-1}$ every 8 hours – coadministered with ranitidine 2–4 mg/kg/day
- Continue gabapentin administration according to preoperative scheme
- Laxative association
- Early mobilization (supine position POD 1, sitting and standing position POD 2) and incentive spirometry
- Remove chest tube POD 1 after thoracic X-ray, remove Foley catheter if PCEA settings have been reduced on POD 2

POD 3

- PCEA (ropivacaine 1.6 % + fentanyl 10 μgml^{-1}) setting reduction 4/3/10 - coadministered with ondansetron 4 mg every 8 hours
- Convert to PO acetaminophen and NSAID
- Continue gabapentin and laxative administration
- Intensify mobilization (standing position and walking) and incentive spirometry
- If not already done, remove Foley catheter

POD 4

- PCEA (ropivacaine 1.6 % + fentanyl 10 μgml^{-1}) setting reduction PIB 5/120/3/10
- Escape buprenorphine 0.2 mg if necessary for breakthrough pain during PCEA weaning
- Continue PO medication
- Increasing mobilization and rehabilitation

POD 5

- PCEA (ropivacaine 1.6 % + fentanyl 10 μgml^{-1}) setting reduction 0/3/10
- Escape buprenorphine 0.2 mg if necessary for breakthrough pain during PCEA weaning
- Start tilidine/naloxone slow release 50 mg every 12 hours in preparation for PCEA discontinuation
- Continue PO medication
- Evaluates patient for completion of activities of daily living

POD 6

- If not already done, discontinue PCEA and ondansetron administration
- Stop NSAID and coadministration of ranitidine
- Discharge patient when
  - pain is well controlled on PO medication,
  - given education on medication reduction scheme and long-term eHealth follow-up,
  - emphasize physical activity exercises and precautions preventing implanted material dislocation

Multimedia Appendix 2

Standard medication reduction scheme, recommended after hospital discharge. NSAID: non-steroidal anti-inflammatory drug. All drugs are administrated taking into account the weight of the patient.

Hospital discharge
- Stop NSAID and coadministered ranitidine

After 7 days
- Reduce tilidine/naloxone slow release 50 mg two times a day to one a day regimen, earlier reduction is recommended if excessively sleepy.
- Continue acetaminophen

After 12 days
- Reduce gabapentin from three times a day, to twice a day
- Continue acetaminophen

After 13 days
- Reduce gabapentin from two times a day, to once a day
- Continue acetaminophen

After 14 days
- Stop tilidine/naloxone
- Stop gabapentin
- Acetaminophen can be administrated if necessary

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5.3 Enhancing recovery after minimal invasive surgery of the pectus. A review of the literature.

Trongthiang N, Wildemeersch D, Mertens P, Hendriks J.

Published in Acta Anaesth Belg (72) 149-159 (2021).

Abstract

Background

Pectus excavatum (PE) and pectus carinatum (PC) are the most frequent chest wall deformities presenting for a minimal invasive repair of pectus (MIRP). Enhanced recovery protocols (ERP) could improve postoperative recovery and reduce complications, however there is little uniformity in the management of patients undergoing MIRP. The aim of this review is to present an overview of the different ERPs. Our primary outcome is the effect of these ERPs on length of hospital stay (LOS), secondary outcomes include, but are not limited to, the effect on pain scores, urinary catheter requirement and duration, post-operative opioid usage and its side effects.

Method

Data were collected through a Pubmed/ MEDLINE literature search. The main inclusion crite-rium for each study was the implementation of a clearly defined ERP consisting of a multimodal approach in a population requiring MIRP.

Results

In total six articles were included, each of them containing a cohort study population before and after implementing an ERP. All control groups were historical cohorts with data extracted from medical files, prior to implementation of an ERP. Thus, all articles were retrospective comparative cohort studies, with a level IV of evidence.

Most studies suggest that the implementation of an ERP could reduce LOS and reduce the incidence of urinary catheter requirement and duration, without an increase in complications. A reduction in opioid usage and the incidence of its side effects and a reduction in pain scores could not be uniformly achieved.

Conclusion

There is promising evidence that implementing an ERP may improve short-term outcome in a young population undergoing minimal invasive repair of pectus. Large prospective multicentred trials are needed, using proper controls and implementing multiple aspects of the ERP (pre-, peri- and postoperatively).

Keywords

Enhanced recovery pathway/protocol (ERP); early recovery after surgery (ERAS); pectus excavatum (PE); pectus carinatum (PC); minimal invasive repair of pectus (MIRP).

Introduction

Pectus excavatum (PE) and pectus carinatum (PC) are the most frequent chest wall deformities presenting for surgical correction (1). PE is described as the depression of the anterior chest wall and occurs in 1 out of 400-1000 live births. PC is less common and occurs due to progressive outward growth of the anterior chest wall. Both deformities have a pronounced male predominance (2). There are two commonly known surgical techniques. The classic open "Ravitch" procedure, which involves exposure of the anterior thorax region with resection of the costal cartilages affected bilaterally combined with a transverse sternal osteotomy (3). However, after Donald Nuss published his Nuss procedure (minimal invasive repair of pectus excavatum, MIRPE) in 1998, whereby 1-3 curved bars are inserted behind the sternum to position it anteriorly, it has changed the treatment of PE and become the most commonly used technique (Fig. 5-6) (4). The severity of the pectus deformity may become more noticeable during pubertal growth spurs and repair is therefore usually performed in the teenage years. In 2005, Horatio Abramson added the Abramson procedure as a minimal invasive repair of pectus carinatum (MIRPC), in which one subcutaneously placed bar is fixed to the ribs with retrograde traction to reduce the PC.

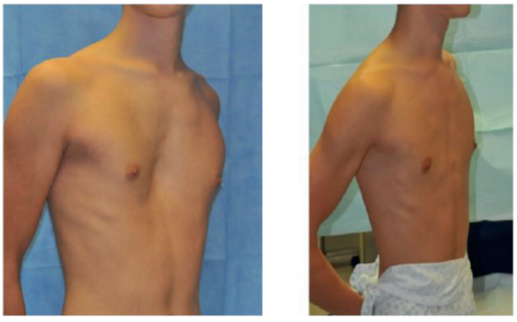

Fig. 5. — Patient with pectus excavatum before (left) and after (right) Nuss procedure.

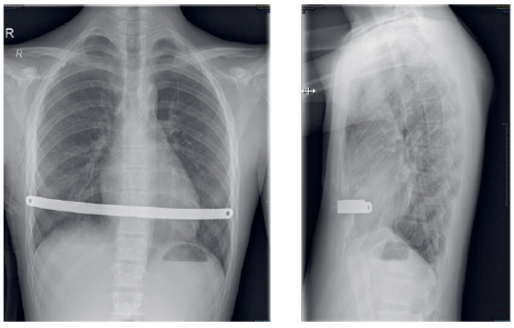

Fig. 6. — Chest X-ray showing anterior and lateral view after correction of pectus excavatum using Nuss procedure.

Reasons for surgical intervention range from cardiopulmonary problems, such as chest pain, fatigue, dyspnoea, exercise intolerance due to compression or restriction of lung and cardiac structures and cosmetic correction (5, 6).

Even though there are smaller incisions, reduced blood loss and reduced stress response using the MIRP technique, it is still correlated with significant postoperative pain due to the constant pressure on the sternum and potential intercostal neuropraxia. Therefore, the post-operative pain management can be quite challenging (7). Notably, effective pain management in the acute post-operative period significantly influences length of hospital stay (LOS) (8). Currently there is little uniformity in the clinical management of these patients (9). Furthermore, there is little literature available on the effect of the implementation of an enhanced recovery protocol (ERP) in a paediatric population (10). Meanwhile there is also a growing tendence towards reduction of resource utilisation by reducing length of stay, without sacrificing the patient's well-being and without increasing postoperative complications. In view of these challenges, many ERPs have been proposed for MIRP. The aim of this review is to present an overview of the different ERPs. Our primary outcome is the effect of these ERPs on LOS, secondary outcomes include, but are not limited to, the effect on pain scores, urinary catheter requirement and duration, post-operative opioid usage and its side effects.

Method

Articles for review were identified via Pubmed and Medline following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). Filters were used to show only articles in English, published between February 2016 and 2021, involving human patients aged between 0 and 35 years. There were no eligible studies published before 2016. The search terms "pectus", "enhanced recovery", "early recovery" and "ERAS" were used. Screening and eligibility analysis were performed by one reviewer (N.T.). Of the results yielded after the initial search, further screening of each title was performed using keywords such as "enhanced recovery", "perioperative management", "analgesic considerations", and "analgesia modalities". The main inclusion criterium for each study was the implementation of a clearly defined ERP consisting of a multimodal approach in a population requiring MIRP. After full-text reading, the main reasons for study exclusion included the absence of a clearly defined multimodal enhanced recovery protocol and interventions related to only singular elements of ERPs. Elements of the ERP, study population, study duration, inclusion and exclusion criteria, and primary and secondary outcomes such as LOS, pain scores, opioid requirements, and post-operative complications were reviewed in each study. The quality of conduct of each study was assessed using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist, also assessing for possible selection and information bias (12).

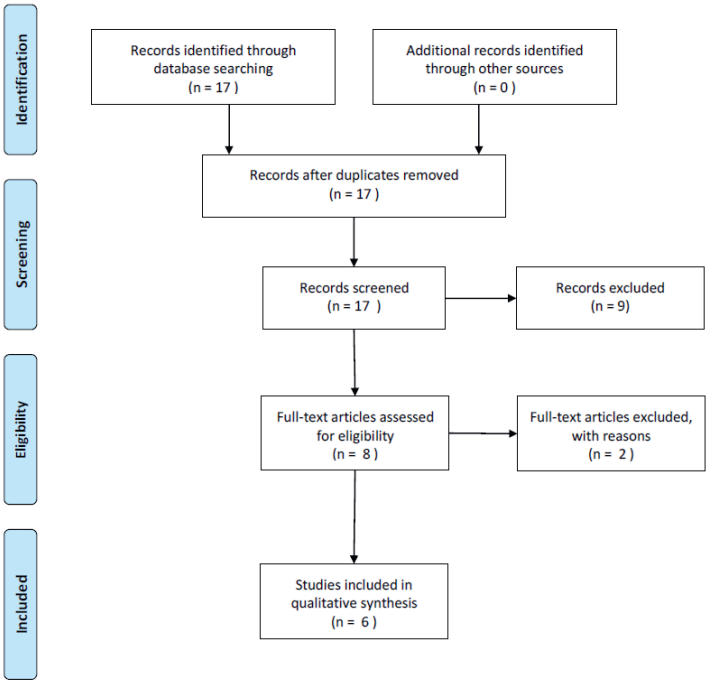

Fig. 1. — Flow chart study selection.

Results

The initial search yielded 17 results of which 9 were excluded by screening titles and abstracts. After reading full-texts 2 more articles were excluded due to a different research scope. In total 6 articles were included, each of them containing a cohort study population before and after implementing an ERP. These articles were assessed for quality and omission using the STROBE Statement checklist for cohort studies (12). Details of this assessment can be found in Appendix 1. A flow chart of the screening process is detailed in Figure 1. An overview of the author, title, study type, population and limitations of the included studies can be found Table 1. Four studies took place in the USA (13-16), one in Belgium (17) and one in China (18). All were single centre and largely single surgeon studies.

The studies were conducted between 1998 and 2019. All control groups were historical cohorts with data extracted from medical files, prior to implementation of an ERP. Thus, all articles were retrospective comparative cohort studies, with a level IV of evidence according to Sackett et al (19). Four studies collected data from a period between 3 – 5 years (13-15, 18). Wildemeersch et al. prospectively collected data for their ERP group between June 2017 and December 2017, however they did not specify during which period they extracted data for their historical cohort (17). Holmes et al. collected data between 1998 and 2017, thus having the longest period of data collection (16). Four studies were conducted on patients who underwent MIRPE, one study by Mangat et al. also included patients undergoing the Ravitch procedure for PE, mixed PE/PC and PC (15). The study by Wildemeersch et al. included patients undergoing MIRPE as well as those who needed surgical correction of PC using Abramson's technique (MIRPC) (17). Study sizes differed between studies

ranging from 41 patients to 436 patients. We limited the data extracted from the Mangat et al. study to the cohort that underwent a Nuss procedure, excluding the results of the Ravitch cohort, which is not a minimal invasive technique. This resulted in study size of 41 patients. Holmes et al. achieved a study size of 436 patient by including the patients from the transition period between the pre-ERP and the ERP periods, however we did not consider the results of the transition period in our review, reducing the study size to 332 patients. Ages were comparable between studies, with a total range between 6 and 30 years. Wharton et al. did not present exact numbers, but presented the population characteristics in charts (13). Wildemeersch et al. expressed the age range, but no mean age for their population could be found in the article (17). The different proposed ERPs are presented in Table 2. Three studies included preoperative patient education in their ERP (13, 14, 17), of which one included aerobics and stretching exercises one month prior to surgery. Wildemeersch et al. included a preoperative web-based psychological screening and the assessment of risk for persistent postsurgical pain (PPSP). They had the longest follow-up time up to 3 months for their ERP cohort, with further assessment of risk factors using their web-based tool (17). Wildemeersch et al., Wharton et al. and Mangat et al. implemented a pre-emptive analgesic strategy using gabapentin prior to surgery. Holmes et al. introduced gabapentin into their postoperative management, they did not describe a preoperative or perioperative protocol (16). One study by Yu et al. implemented an ERP for they perioperative management, not describing a pre- or a postoperative protocol (18). All studies included acetaminophen and nonsteroidal anti-inflammatory drugs (ketorolac or ibuprofen) in their multimodal analgesic approach. Wildemeersch et al. strictly deferred the use of postoperative intravenous morphine and tramadol, instead they relied on analgesia with a patient-controlled epidural anal-gesia (PCEA) on top of their multimodal approach. In contrast, Litz et al. and Wharton et al. used a patient controlled narcotic analgesic (PCA) of either hydromorphone or morphine respectively, the latter also including a ketamine PCA. Mangat et al. implemented the use of an epidural catheter in their strategy, but also included oxycodone after discontinuation of the epidural. Holmes et al. extended their multimodal analgesic regimen with a narcotic PCA during admission and lidocaine infused bilateral paravertebral catheters that were placed perioperatively and remained until 2 to 3 days after discharge and removed at home. Table 3 summarizes an overview of results commonly reported between studies.

Table 1

Overview of included articles with study type, study size, population sample, population age and limitations. ERP (enhanced recovery protocol); MIRPE (minimal invasive repair of pectus excavatum); PE (pectus excavatum); PC (pectus carinatum); PVB (paravertebral catheter).

AUTHOR YEAR COUNTRY	JOURNAL	STUDY TYPE	STUDY SIZE	POPULATION SAMPLE	AGE, YEARS, (RANGE)	LIMITATIONS
LITZ N. ET AL., 2017 USA	Pediatric surgery international	Retrospective comparative cohort study	64 patients 27 pre-ERP 37 ERP	MIRPE between 2010-2015. Pre-ERP: 2010-2012 ERP: 2014-2015	Mean pre-ERP 15.3 ± 1.6 (9.9-7.6) Mean ERP 15.5 ± 1.8 (8.9-18.1)	Data extracted retrospectively from medical records. Unclear description of missing data, inclusion or exclusion criteria Transition period (2012-2014), possible bias towards lower opioid use Single centre
WILDEMEERSCH D. ET AL. 2018 BELGIUM	JMIR perioperative medicine	Population based cohort study	112 patients 93 pre-ERP 29 ERP	ERP: recruitment in 2015 (June-December) Exclusion criteria: psychiatric disease, chronic opioid use, revision surgery Pre- ERP: Historical cohort: Age < 18 y, pathology requiring MIRP	ERP - (12-18)	Retrospective data, matching only by age (<18y) and pathology (PE and PC). No procedure segregated analyses (PE vs PC). Single centre, single surgeon. No description of opioid use.
HOLMES D.M. ET AL. 2018 USA	Journal of Pediatric Surgery	Retrospective comparative study	436 patients 146 pre-ERP 104 transition 186 ERP	MIRPE between January 1998 and December 2017 Pre-ERP 1998-2006 Transition 2007-2011 ERP 2012-2017	Mean total 15 ± 2.7 (6.1-25.6) Mean pre-ERP 14.2 ± 3.3 (-) Mean ERP 15.3 ± 2.3 (-)	Retrospective design, missing data. High correlation between factors ex. PVB + nursing protocol simultaneously implemented. Transition period, possible bias towards lower opioid use. No rate of events for nausea/vomiting. Single centre, largely single surgeon.
MANGAT ET AL. 2020 USA	Pediatric surgery international	Retrospective review	41 patients 13 pre-ERP 28 ERP	Nuss procedures between 2014 and 2018. Pre-ERP (2014-2015) ERP (2015-2018)	Med. pre-ERP 15 (13.5-16) Med. ERP 16 (14-17)	Retrospective design (missing data and bias) Single institution, small cohort
WHARTON ET AL. 2020 USA	Journal of Pediatric surgery	Retrospective comparative study	109 patients 51 pre-ERP 58 ERP	Nuss procedures between 2015 and 2018. Pre-ERP (2015-2016) ERP (2017-2018) Exclusion: age >21 and combined surgeries.	-	Retrospective design. Statistical methods not mentioned. No clear presentation of population Unclear how data are extracted and presented. No description op opioid use. No stratification based on compliance. Single centre.
YU ET AL. 2020 CHINA	Journal of Thoracic Disease	Retrospective comparative study	148 patients 75 pre-ERP 73 ERP	Nuss procedures between 2016 and 2019. Exclusion: patients with comorbidities and requiring thoracotomy, patients with anterior chest wall severe asymmetry and depressions, chest CT showing CT index < 3.0 and mild depression patients without related symptoms, complex patients with other thoracic deformities, patients with severe scoliosis, patients with Marfan syndrome and skin or soft tissue infection near incision, incomplete medical record.	Total 15 (6-30)	Retrospective design Small population, selection bias Only comparative for perioperative protocol. Single centre.

Overview of included articles with study type, study size, population sample, population age and limitations. ERP (enhanced recovery protocol); MIRPE (minimal invasive repair of pectus excavatum); PE (pectus excavatum); PC (pectus carinatum); PVB (paravertebral catheter)

Table 2

Overview of enhanced recovery protocols. POD (postoperative day); LMA (laryngeal mask airway); PCA (patient controlled analgesia); PCEA (patient controlled epidural analgesia); PACU (post anaesthesia care unit); NSAID (nonsteroidal anti-inflammatory drugs).

	LITZ ET AL.	WILDEMEERSCH ET AL.	HOLMES ET AL.	MANGAT ET AL.	WHARTON ET AL.	YU ET AL.
PREOPERATIVE	Preoperative information, education and counselling Standardized analgesic protocol Antimicrobial prophylaxis	Planning surgery Anaesthesiology assessment. Patient education Activation Web-based platform Start gabapentin 1 week preoperatively Psychological screening Risk factor assessment for increased pain	-	Carbohydrate drink 2hours prior to surgery Fluid bolus Multimodal pain management Start gabapentin night before surgery	Patient education incl. preop handbook Counselling by surgeon Aerobic and back/chest stretching exercises 1 month prior to surgery 3 days prior to surgery – Gabapentin – Polyethylene glycol	-
INTRAOPERATIVE	Standardized anaesthetic protocol Maintenance of normovolemia and normothermia Avoidance of arterials lines, epidurals, routine ordering of blood products and perfusion services	Standardized anaesthetic protocol with epidural catheter Maximal multimodal antiemetic strategy	-	Standardized anaesthetic protocol with epidural catheter	Three level bilateral intercostal nerve blocks and field block around incision (intraoperative care unaltered between ERP and pre-ERP cohort)	LMA Diapers instead of urinary catheter Indwelling drainage of the right pleural cavity or subcutaneous with 15-F drainage
POSTOPERATIVE	Admission to medical/surgical floor Standardized multimodal analgesic protocol incl. PCA Nausea and vomiting prophylaxis Bowel regimen Urinary retention protocol Early mobilization on POD 0 Early oral nutrition, clear liquids on POD 0 One postoperative chest Xray with additional imaging only as needed No routine labs	"Pectusboek" with post-operative trajectory: PACU until discharge criteria fulfilled Standardized multimodal analgesic protocol incl. PCEA Continuation gabapentin Antiemetic strategy. Discontinuation of PCEA on POD 6 latest. ASAP removal of urinary catheter Follow-up after discharge through Web based platform	Standardized multimodal analgesia incl. lidocaine infused bilateral paravertebral catheters and PCA Start gabapentin Early ambulation Foley catheter removal Diet initiation POD0	PACU until discharge criteria fulfilled Early ambulation Encourage nutrition according to diet tolerance Standardized multimodal pain management incl. epidural analgesia of PCA if epidural failed Continuation gabapentin Discontinuation epidural and urinary catheter removal POD 3	Postsurgical handout given at discharge Standardized multimodal analgesia protocol, incl. narcotic and ketamine PCA Continuation gabapentin Bowel regimen Gut prophylaxis for chronic NSAID use	

Overview of enhanced recovery protocols. POD (postoperative day); LMA (laryngeal mask airway); PCA (patient controlled analgesia); PCEA (patient controlled epidural analgesia); PACU (post anaesthesia care unit); NSAID (nonsteroidal anti-inflammatory drugs)

Table 3

OUTCOME	LITZ ET AL. PRE-ERP	LITZ ET AL. ERP	WILDE-MEERSCH ET AL. PRE-ERP	WILDE-MEERSCH ET AL. ERP	HOLMES ET AL. PRE-ERP	HOLMES ET AL. ERP	MANGAT ET AL. PRE-ERP	MANGAT ET AL. ERP	WHARTON ET AL. PRE-ERP	WHARTON ET AL. ERP	YU ET AL. PRE-ERP	YU ET AL. ERP
LOS (DAYS)	4*	2,8*	6,32*	7,66*	4,9*	3,1*	5	5	3,49*	2,897*	7,71*	4,96*
PAIN SCORE POD0	4,1*	5,2*	-	-	-	-	-	-	5,527*	4,488*	-	-
PAIN SCORE POD1	3,2	3,8	1,24 (R) 2,84 (A)	1,26 (R) 2,58 (A)	4*	3,2*	-	-	-	-	-	-
PAIN SCORE POD2	3,6	3,8	1,41 5 (R) 3,24* (A)	1,08 (R) 2,48* (A)	-	-	-	-	-	-	-	-
PAIN SCORE DISCHARGE	3,2	3,5	-	-	-	-	4	2	-	-	-	-
OPIOID USAGE (MG KG^{-1} [B] OR MEDD KG^{-1} [C])	3,38*	1,2**	-	-	0,74[C]*	0,49[C]*	1,51[B]*	2,61[B]*	-	-	-	-
URINAY RETENTION REQUIRING CATHETER (INCIDENCE)	33%	14%	-	-	10,9%	16,7%	23%	4%	47%*	21%*	-	-
URINARY CATHETER DURATION (DAYS)	-	-	4,66*	3,41*	2,5*	1,1*	3,97*	3,25*	-	-	-	-
NAUSEA (INCIDENCE)	63%	43%	40%*	17%*	-	-	54%	72%	-	-	-	-
DAYS OF NAUSEA (DAYS)	-	-	-	-	0,7*	1,1*	-	-	-	-	-	-
RETURN TO ED (INCIDENCE)	0%	13%	-	-	-	-	8%	11%	-	-	-	-
READMISSION (INCIDENCE)	0%	8%	-	-	7,50%	5,10%	0%	7%	37,30%	13,80%	-	-

Overview of commonly assessed outcomes, comparing cohort without enhanced recovery protocol (pre-ERP) and with enhanced recovery protocol (ERP). Pain scores assessed according to numerical rating scales (NRS) 0= no pain, 10 worst imaginable pain. Opioid usage expressed in (B) morphine equivalents per kg (mg kg-1) or (C) morphine equivalents daily dose per kg (MEDD kg-1). (*) difference reported as significant $p<0.05$, (-) = no data LOS (length of stay); POD (postoperative day); R (rest); A (activity); ED (emergency department).

LOS, our primary outcome, was significantly reduced after implementing an ERP in every study except two (Fig. 2) Wildemeersch et al. showed a significant increase in LOS after implementing an ERP (7.66 ± 2.01 ERP vs 6.32 ± 1.26 days pre-ERP), while Mangat et al. could produce no difference between their cohorts (17).

When looking at our secondary outcomes, pain scores were significantly higher in Litz et al.'s study in the ERP group on postoperative day (POD) 0 (4.1 ± 1.6 pre-ERP vs 5.2 ± 1.7 ERP, $p< 0.01$), only to be similar at discharge (3.2 ± 1.7 pre- ERP vs 3.5 ± 2.2 ERP, $p = 0.6$) (14). Wharton et al, however, showed a significant decrease in pain scores on POD 0 (5.527 pre-ERP vs 4.488 ERP, $p = 0.0065$). Other postoperative days failed to show a difference after implementation of their ERP (13). There was a significant reduction in pain scores after protocol implementation at all time points except the morning of POD 3 in the study by Holmes et al., but no significant difference could be found at discharge. They did not present exact scores, except for the morning after surgery (4.0 ± 2.0 pre-ERP vs 3.2 ± 1.4 ERP) (16).

Opioid usage was quantified in three studies. Litz et al. and Mangat et al. calculated morphine equivalents (ME, mg kg-1), while Holmes et. al used morphine equivalent daily dose per kg (MEDD kg- 1). Litz et al. and Holmes et al. showed a reduction in opioid usage (3.3 ± 1.4 mg kg-1 pre-ERP vs 1.2 ± 0.5 mg kg-1 ERP, $p < 0.01$; 0.74 ± 0.77 MEDD kg-1 pre-ERP vs 0.49 ± 0.20 MEDD kg-1 ERP, $p < 0.05$ respectively), while Mangat et al. reported a significant increase of opioid usage (1.51 mg kg-1 pre-ERP vs 2.61 mg kg-1 ERP, $p = 0.02$).

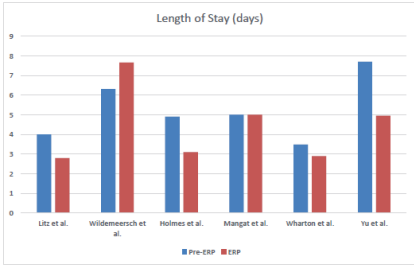

Fig. 2. — Comparing length of stay with enhanced recovery protocol (ERP) and without ERP (pre-ERP).

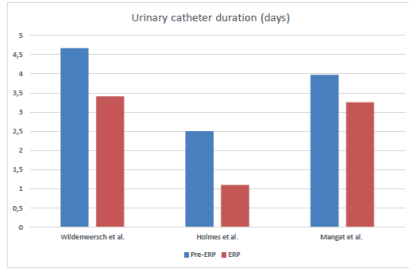

Fig. 3. — Comparing number of days requiring urinary catheter with enhanced recovery protocol (ERP) and without ERP (pre-ERP).

Urinary retention requiring catheterization was mentioned in four studies. Litz et al. reported a decrease in incidence, but this decrease was not significant (33% pre-ERP vs 14% ERP, p= 0.07). Similar results were produced by Wharton et al. with a significant reduction in incidence (41% per-ERP vs 21% ERP, p= 0.0044). Mangat et al. also showed reduction in need for urinary catheterization, while Holmes et al. reported an increased need. Both results were of insignificant value (Fig. 3) Three studies discussed the duration of indwelling urinary catheter (IDUC), all of which showed a significant reduction in duration (15-17). Notably, Yu et al. refrained from placing an IDUC and used diapers perioperatively instead (18).

When considering nausea postoperatively, two studies showed a decrease in incidence after ERP implementation, with a significant reduction from 40% to 17% (p= 0.3) in the study of Wildemeersch et al.(17). However, in Mangat et al.'s study the incidence was higher after ERP implementation, although this was not significant (15). Unlike Wildemeersch et al. they did not include an anti-emetic strategy in their ERP . Holmes et al. did not report incidence of nausea, but days of nausea. In their study, there was an increase of days of nausea after ERP implementation (0.7 ± 1.2 pre-ERP vs 1.1 ± 1.2 ERP, p <0.05) (16) (Fig. 4)

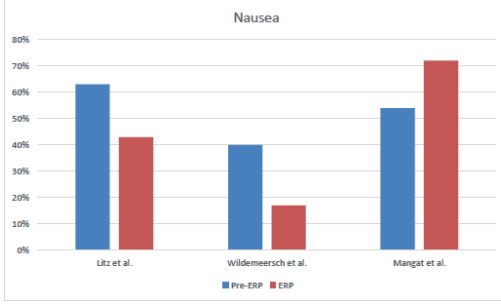

Fig. 4. — Comparing incidence of nausea with enhanced recovery protocol (ERP) and without ERP (pre-ERP).

With reducing LOS one must also take into account that patients may return to the emergency department or need readmission, due to "late" complications or uncontrollable pain. Holmes et al. and Wharton et al. showed a reduction in re-admissions (7.5% vs 5.1% p = 0.2; 37.3% vs 13.8%

respectively) (13, 16). In contrast, Litz et al. and Mangat et al. reported no readmissions in their pre-ERP cohort compared to 8% and 7% in their ERP cohort respectively.

Discussion

With enhanced recovery protocols gaining popularity in different types of surgery, it may be interesting to focus on the applicability of this on MIRP and on its relatively young population. Promising evidence is emerging showing that a paediatric population could also benefit from an ERP in different types of surgery (10). Furthermore, there is a growing tendence towards reduction of resource utilisation by reducing length of stay, without sacrificing the patient's well-being and without increasing postoperative complications. After the results of the study conducted by Wilde-meersch et al. in our centre, we implemented an ERP with preoperative, perioperative and post-operative elements increasing adherence in the different departments. However, due to the re-duced availability of monitoring tools and lack of psychosocial resources, the web-based monitoring application has been left out of the ERP, which is still standard of care (17).

All but two studies presented a significant re-duction in LOS, of which two also showed a decrease in opioid usage, thus possibly also a reduction in resource utilisation. However, Litz et al. and Holmes et al. both implemented a transition period between the pre-ERP and the ERP cohort, allowing them time to alter their ERP towards a lower narcotics usage and a lower LOS. This transition period may potentially bias study results toward the desired outcomes (14, 16). Yu et al. implemented strict exclusion criteria for their study population as summarized in Table 1, creating the opportunity for a selection bias with the preferred outcome of reducing LOS (18). Wildemeersch et al. showed an increase in LOS, they however mentioned most patients could have been discharged earlier (6.59 days p=0.40), but stayed in the hospital for nonmedical reasons (17). This further underlines the need for biopsychosocial management strategies, such as discussing patient expectations preoperatively.

While the study conducted by Wharton et al. showed promising results with a reduction in LOS, pain scores, urinary retention requiring catheterization and less readmissions, it remains un-clear which statistical analyses they used on their data. Precise measurement op opioid usage was not conducted in their analysis, although they mention to explore it in a further examination of their data (13). Mangat et al. (15) could not produce the desired outcome with their ERP. They contributed the lower pain scores at discharge to the increased opioid usage in their ERP cohort. Every proposed protocol is unique in its combination of interventions, although some interventions are found in most, if not all of the protocols, such as the use of acetaminophen and NSAIDs. It could be interesting to compare the different analgesic strategies implemented in these studies. There is a *lack of evidence* showing which analgesic modality is superior for MIRP. In a study by Schlatter et al. (20) comparing three analgesia modalities (epidural vs PCA and intercostal nerve block vs scheduled oral pain meds and intercostal nerve blocks), they were able to reduce LOS from 4.4 days with epidural analgesia to 1.6 days with oral pain medication and an intercostal nerve block. They also mention that an enhanced preoperative consultation, patient education and setting the right expectations might be as important as the analgesic modality used for the reduction in LOS and pain scores. This philosophy was also applied by Wildemeersch et al. and Holmes et al. (16, 17), with the first also screening for preoperative risk factors. When comparing epidural analgesia to PCA, a meta-analysis from 2014 including 3 randomized controlled trials (RCT) and 3 retrospective cohorts concluded that epidural analgesia may initially provide superior pain control, however without any significant difference secondary outcomes such as LOS, adverse event, opioid side-effects and epidural complications (21).

Currently, there a few centres implementing intercostal cryoanalgesia for analgesia after MIRP. A small single institution randomized clinical trial (22) compared intercostal cryoanalgesia to epidural analgesia after a Nuss procedure. Their data showed that cryoanalgesia resulted in reduction in LOS and systemic opioid consumption, while providing equivalent pain control. Comparable results were found in a study by Harbaugh et al. (23), where there was a reduction in LOS and an increased perioperative opioid use in the cryoanalgesia cohort, but no difference in postoperative narcotic requirements. Furthermore, there was a reduction in prescription doses of opioids after intercostal cryoablation vs epidural. However, patients can develop neuralgias and numbness up to 2 months after surgery with a gradual return of sensation presumably during axonal regeneration of the intercostal nerve (20). More RCTs are required to assess if this analgesic approach could be implemented in future ERPs. Currently, there is a clinical trial in the Children's Hospital Colorado which started in May 2020, aiming to compare the use of video-assisted intercostal nerve cryoablation, erector spinae block, and thoracic epidural for postoperative analgesia after MIRPE (https:// clinicaltrials.gov/ct2/show/NCT04211935). The risk of developing PPSP is quite high after pectus surgery, as described by Williams et al., where higher pain scores during the first 3 post-operative days and at 2 weeks predicted slower recovery and higher pain scores at 4 and 12 months (24). Therefore it might be interesting to asses if the proposed ERPs could also affect the incidence of PPSP although there is limited data on the precise incidence in children after MIRP. Furthermore, pragmatic studies that asses the feasibility of implementation of an ERP and include long-term patient related outcome measurements could be of value, such as the one conducted in our centre by Wildemeersch et al.

Limitations of our review is that we only included six studies, of which one was conducted in our own centre. We also focused exclusively on MIRP technique, the most commonly conducted technique in our centre, which rendered a smaller study population. The studies presented are all limited by their small study population and their retrospective design, with a historical control cohort, creating opportunity for selection bias.

The question could also arise if the proposed ERPs are universally applicable, seeing all of them are implemented in a single centre, with the surgery largely done by one specific surgeon. Because all ERPs contains both similar and very different analgesic modalities, it is difficult to extract which specific elements of the ERP is superior. We must also address the likelihood of publication bias of reports demonstrating no efficacy of ERPs in MIRP.

It would be inappropriate to propose a proper universal protocol with such limited evidence. Thus, it is cautious to conclude that the implementation of an ERP could significantly reduce resource utilisation such as LOS and opioid usage and improve outcome.

Conclusion

There is promising evidence that implementing an enhanced recovery protocol may improve short-term outcome in a young population undergoing minimal invasive repair of pectus. Large prospective multicentred trials are needed, using proper controls and implementing multiple aspects of the ERP (pre- , peri and postoperatively). Furthermore, more research is needed to assess which analgesic moda-lity is superior and should be implemented in an ERP.

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Appendix

Appendix 1. Assessment of articles according to 22 point STROBE checklist items

ITEM NO	LITZ ET AL.	WILDEMEERSCH ET AL.	HOLMES ET AL.	MANGAT ET AL.	WHARTON ET AL.	YU ET AL.
1A	1	1	1	1	1	1
1B	1	1	1	1	1	1
2	1	1	1	1	1	1
3	1	0	1	1	1	1
4	1	1	1	1	1	1
5	1	1	1	1	1	1
6A	0	1	1	1	1	1
6B	1	1	0	0	0	0
7	0	0	1	1	1	1
8	0	1	1	1	0	1
9	0	1	0	0	0	1
10	1	1	1	1	1	1
11	0	1	1	1	0	1
12A	1	1	1	0	0	1
12B	0	0	0	1	0	1
12C	0	0	0	0	0	1
12D	0	0	0	0	0	1
12E	0	0	0	0	0	0
13A	1	1	1	1	1	1
13B	0	1	0	0	0	1
13C	0	0	0	0	0	1
14A	1	0	1	1	1	1
14B	0	1	1	0	0	0
14C	1	1	0	1	1	0
15	1	1	1	1	1	1
16A	1	1	1	1	0	1
16B	0	1	0	0	0	1
16C	0	1	1	0	0	0
17	0	0	1	1	0	0
18	1	1	1	1	1	1
19	1	1	1	1	1	1
20	1	1	1	1	1	1
21	1	1	1	1	1	1
22	1	1	0	1	0	1

0 = incomplete, 1 = complete. Explanation of each item can be found further in this appendix.

STROBE Statement — Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, explain how loss to follow-up was addressed
		(e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

5.4 Introduction of an enhanced recovery program for young adults undergoing posterior spinal fusion surgery for idiopathic scoliosis: a single-centre pilot study evaluating short term outcomes

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Abstract

Background

The large surgical incision and extensive tissue trauma in posterior spinal fusion for adolescent idiopathic scoliosis causes severe acute postoperative pain. Furthermore, posterior spinal fusion is associated with a risk of persistent postsurgical pain. Six months after posterior spinal fusion, the incidence of persistent postsurgical pain is as high as 22% of the patients. Optimizing pain management therefore remains crucial, but challenging.

Objective

The study objective is to design and implement an enhanced recovery pathway for patients with adolescent idiopathic scoliosis undergoing posterior spinal fusion integrating all aspects of biopsychosocial care. Its outcomes are assessed, including its effect on postoperative pain and early mobilization.

Design and settings

A prospective cohort study was performed at the Antwerp University Hospital.

Methods

In December 2019, a prospective cohort study was set up in which an enhanced recovery pathway substitutes more than the patient controlled intravenous analgesia containing morphine postoperatively. This pathway consists of m/eHealth based psychological screening questionnaires, patient education, early mobilization, and a multimodal analgesia protocol consisting of preemptive gabapentin, an intraoperatively given single dose of methadone (0.2 mg kg-1), non-steroidal anti-inflammatory drugs, and acetaminophen.

Results

We treated 25 adolescents (10 males and 15 females) with the developed enhanced recovery pathway with a mean age of 16.5 years (range 12-22). The mean number of spinal levels fused was 10 (range 6-13). Mean numerical rating scale scores were 4.17 at postoperative day 1, 4.46 at postoperative day 2, and 3.74 at postoperative day 3 in enhanced recovery pathway treated patients. Mean bladder catheterization duration was 3.04 days and enhanced recovery pathway patients stayed in the hospital for an average of 7.4 days.

Conclusions

Using an enhanced recovery pathway for patients undergoing posterior spinal fusion could not only reduce the acute and chronic opioid consumption and its side effects, but could also result in less postoperative pain, shorter hospital stay and higher patient satisfaction. Further reevaluation and improvement focused on these variables will likely further improve the effectiveness of enhanced recovery pathways.

Trial registration: ClinicalTrials.gov NCT04038229.

Introduction

Adolescent idiopathic scoliosis (AIS) is a three-dimensional deformation of the spine affecting 1-3% of adolescents with a female predominance (8:1) [1,2]. AIS is a benign condition, but is frequently associated with back pain and psychosocial difficulties. A Cobb angle greater than 45° is an indication for surgery [3] . Posterior spinal fusion (PSF) is characterized by a risk of severe blood loss, extensive tissue trauma, and inflammation resulting in central and peripheral nerve sensitization and ensuing severe acute postoperative pain. Inadequate pain management not only causes a delay in rehabilitation and patient dissatisfaction, but is also an important risk factor of persistent postsurgical pain (PPSP)[4] . The incidence of PPSP after PSF is 22% at 6 months postoperatively and 11-15% after 1 to 5 years. Next to severe acute pain, other predicting factors for PPSP include preoperative pain intensity, patient anxiety, patient pain coping efficacy, and parental pain catastrophizing [5] . Postoperative pain protocols play an important role in enhanced recovery and improved prognosis and are an important area for (re)evaluation and improvement [6] . Traditional analgetic management after PSF consists of intravenous opioids, despite significant adverse effects [4] . In recent years, multimodal analgesia (MMA) has been introduced to decrease postoperative opioid consumption, diminishing postoperative gastrointestinal concerns (mainly nausea and ileus) postponing hospital stay and recovery Moreover, optimizing peroperative pain management protocols should include PPSP prevention strategies. MMA contributes to enhanced recovery programs (ERP), which allow a more holistic approach, improving many patientrelated outcome measurements [7] .

Objective

In this study, we aimed to design and implement an ERP for patients with AIS undergoing PSF integrating all aspects of biopsychosocial care and evaluate its outcomes in comparison with the conventional pain management strategies.

Methods

Study design

A prospective cohort study was conducted with the approval of the Ethics Committee of the Antwerp University Hospital, Belgium (study identifier EC19/14/183, chair P Cras, May 2019) after trial registration (ClinicalTrials.gov NCT04038229). Based on the postoperative treatment protocol received, two cohort groups were compared.

Patients of one cohort were operated between August 2018 and October 2019 and received the standard of care pain management protocol at our institution with patient controlled intravenous analgesia (PCIA) without ERP. On the other hand, patients of the other cohort were operated between December 2019 and July 2021 and treated with the newly designed ERP. All surgeries were performed by a single orthopedic surgeon. All patients were recruited by the Department of Orthopedics and selected for this study by the Anesthesiology Department, Antwerp University Hospital, Belgium. Inclusion criteria included AIS patients under 26 years of age, scheduled for elective PSF. Patients with non-idiopathic scoliosis, preoperative chronic opioid use (> 3 months), and known unstable psychiatric history with the use of psychotropic drugs were excluded. This manuscript adheres to the applicable CONSORT guidelines. This study which contains a descriptive analysis of the early rehabilitation process after spinal surgery according to a specifically developed and implemented enhanced recovery care path is part of a comprehensive biopsychosocial trajectory including pre and postoperative psychosocial screening and long term follow up to evaluate

persistent postsurgical pain in adolescents after spinal fusion surgery. Results of the entire holistic path can be expected in the near future.

Control group

Figure 1 shows the standard of care in the control group. Patients were scheduled by the department of Orthopedics and since they received standard of care. They consulted an anesthesiologist for a standard preoperative assessment. Intraoperative neuromonitoring involved performing a wake-up test, which is why a short-acting volatile anesthetic (desflurane) in combination with remifentanyl was used for maintenance of anesthesia. The traditional analgetic management consisted of intravenous ketamine (loading dose of 0.5 mg kg-1 at induction and 0.2 mg kg-1 h-1 after wake up procedure), ketorolac and acetaminophen. Postoperatively, PCIA containing morphine was started, next to continuation of the intravenous ketorolac and acetaminophen.

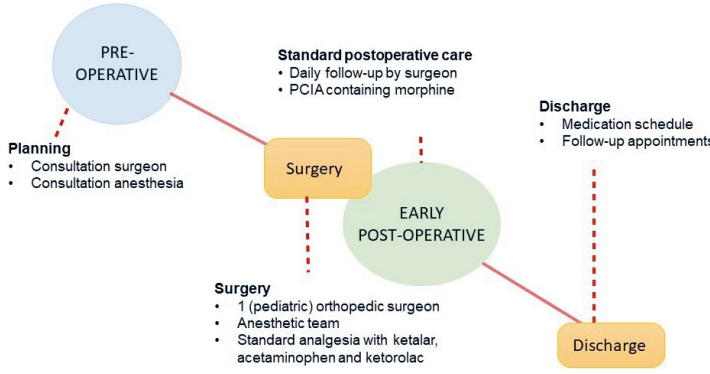


Fig. 1 – Standard of care in control group.

Enhanced recovery pathway

Figure 2 presents the designed multidisciplinary ERP.

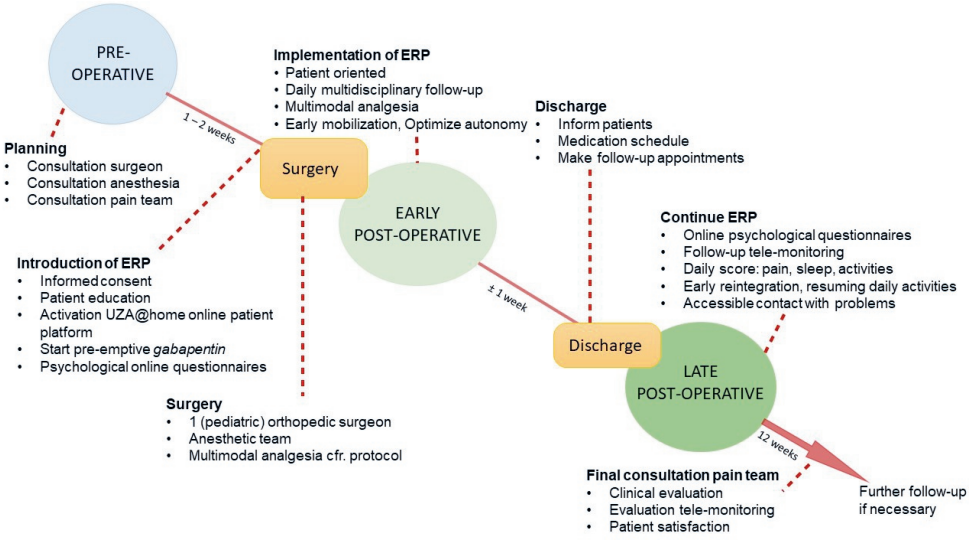


Fig. 2 – Design multidisciplinary ERP.

Preoperative study phase

Once patients with AIS were scheduled for PSF by the department of Orthopedics, they were invited for a clinical study interview 1 to 2 weeks prior to surgery. The ERP was explained and informed consent obtained. A key component of this interview was patient education regarding the anticipated surgical trajectory. The online patient platform uza@home was activated and patients replied to an online preoperative screening psychological inventory. This inventory consisted of different screening tools for anxiety and depression (State-Trait Anxiety Inventory or STAI), pain and psychosocial aspects (Multidimensional Pain Inventory or MPI and Child and Adolescent Social and Adaptive Functioning Scale or CASAFS), depression (Childhood Depression Inventory or CDI) and coping mechanisms (Pain Response Inventory or PRI).

After negative screening for QT-prolongation on 5 lead electrocardiography before peroperative methadone administration, ERP was started and oral pre-emptive gabapentin was started 7 days prior to surgery and increased over time up to a dose of 5mg kg-1 3 times a day.

Intraoperative study phase

Intraoperative multimodal analgesia consisted of a single dose of methadone (0,2mg kg-1) at induction, in addition to clonidine, ketorolac, and acetaminophen based on patient weight. To prevent postoperative nausea and vomiting (PONV), dexamethasone and dehydrobenzperidol were administered, next to maintenance of anesthesia with TCI/TIVA propofol Marsh model.

Early postoperative study phase

Immediately postoperative, patients were admitted to the post-anesthesia care unit (PACU). When PACU discharge criteria (Aldrete) were fulfilled, they were transferred to the ward, usually on postoperative day (POD) 1. Standard MMA included intravenous acetaminophen every 6 hours and nonsteroidal antiinflammatory drugs (NSAIDs) every 8 hours, next to the continuation of oral gabapentin tree times a day. The conversion of intravenous to orally administration of medication took place on POD 3. Pantoprazole and macrogol to enhance bowel movements were also part of the ERP. If necessary, escape analgesia for breakthrough pain and antiemetic rescue were available. Urinary catheters were removed as soon as possible. During hospital admission, patients were evaluated multidisciplinary on a daily basis. Pain, nutrition status, nausea and vomiting were scored 3 times a day by ward nurses. Additionally, daily follow-up by specialised pain nurses was provided and physiotherapists evaluated patients' rehabilitation.

Patients were discharged on acetaminophen, NSAIDs, and gabapentin. A reduction scheme of gabapentin within 2 weeks after discharge was provided.

Late postoperative study phase

To get a picture of a patients pain sensation as well as its psychosocial aspects, the above mentioned questionnaires (MPI, STAI, CDI, PRI and CASAFS) were provided again after 4 and 12 weeks post-surgery. Patients were asked to fill in a daily online questionnaire up to 3 months postoperatively containing subjective revalidation characteristics including pain, sleep quality and activity progress. The study was completed after a final study interview 12 weeks postoperatively.

Statistical analysis

11 level Numerical Rating Scale (NRS) scores for pain between 0 (no pain) and 10 (worst imaginable pain), subjective sleep scores between 0 (worst possible sleep) and 10 (best possible sleep), and presence of nausea were described by ward nurses in a specific designed registration tool (ScolioseBoek). This tool was also used by specialized pain nurses for an additional NRS and by physiotherapist to describe rehabilitation, including mobility and flow-oriented spirometry [7] . Patient characteristics and values for hospital length of stay (LOS) and urinary catheterization were extracted from the electonic patient record (C-medical record, Cegeka, Vienna, Austria and Millennium, Cerner, North Kansas City, MO, United States) SPSS Statistics software version 28.0 for Windows (IBM Corp, Armonk, NY, United States) was used for statistical analysis. After normality control, independent sample t-test and chi-square were used where appropriate. Due to the novelty of the design and implementation correct data for power analysis are lacking.

Patient characteristics

Table I summarises the patient characteristics. Overall, 23 AIS patients (2 males and 21 females) who had undergone PSF were included in the conventional group and 25 patients (10 males and 15 females) were treated according to the ERP. Figure 3 shows the process of inclusion and exclusion of patients in the intervention group. Mean age of the conventional group was 14.5 years (range 11-18) at the time of surgery and 16.5 years (range 12-22) in the ERP group. Mean body mass index in the conventional and ERP group were 21.4 (range 16.3- 35.9) and 20.4 (range 13.7-37.4) respectively. The mean number of spinal levels fused was 10 (range 6-13) in the conventional group and 9.6 (range 7-15) in the ERP group.

Table I. – Patient characteristics.

	ERP-treated patients (n=25) Mean (SD)	Controls (n=23) Mean (SD)
Gender, n (%)		
Male	10 (40)	2 (9)
Female	15 (60)	21 (91)
Age (years)		
Mean ± SD	16.52 ± 2.82	14.48 ± 1.78
Range	12-22	11-18
Body mass index (kg/m2)		
Mean ± SD	20.40 ± 4.97	21.36 ± 4.97
Range	13.70-37.40	16.30-35.90
Fused levels (n)		
Mean ± SD	9.60 ± 2.14	10.00 ± 2.13
Range	7-15	6-13

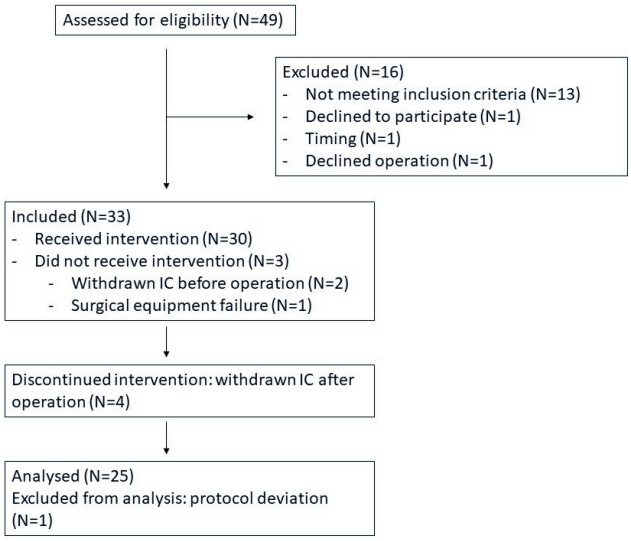
Early recovery

PNRS scores for pain and sleep are summarised in Table II. On POD 1, NRS score for sleep was significantly better in the control group than in the ERP group (7.2 vs 4.9, p=0.003). During the remaining time of hospitalisation, NRS score for sleeping was similar between both groups. Time to removal of urinary catheter was significantly shorter in the ERP group with a difference of 2.14 days (5.18 days vs 3.04 days, p<0.001). LOS on the other hand did not differ between the both cohorts (7.5 days in the control group vs 7.4 days in the ERP group). Of all patients in the ERP group, 24% were able to execute physical exercises while standing upright on POD 2. This number increased the following days to 67% at POD 3, 92% at POD 4 and 100% at POD 5. This in contrast to the control group where only 5% of patients were able to do these exercises at POD 2, 39% at POD 3, 65% at POD 4 and 93% at POD 5. Moreover, 12% of all ERP participants were able to walk at POD 2, 39% at POD 3, 70% at POD 4 and 87% at POD 5 compared with none of the patients in the control group at POD 2, 17% at POD 3, 18% at POD 4 and 50% at POD 5. Those differences were statistically significant for POD 1 and POD 4 (p=0.004 and p=0.003). Concerning respiratory rehabilitation, 75% of ERP patients were able to maximally execute floworiented incentive spirometry at POD 1 and 94% at POD 2. In the control group, this was only possible for 67% of the patients t POD 1 and 80% at POD 2.

Table II. – Mean NRS scores for pain and sleep by ward nurses.

	ERP-treated patients (n=25) Mean (SD)	Controls (n=23) Mean (SD)	P-value
NRS pain			
POD 1	4.17 (1.28)	3.87 (1.33)	0.23
POD 2	4.46 (1.56)	3.44 (1.53)	0.01a
POD 3	3.74 (1.50)	3.41 (1.37)	0.22
POD 4	2.78 (1.11)	3.11 (1.44)	0.20
POD 5	2.40 (1.09)	2.89 (1.57)	0.36
NRS sleep			
POD 1	4.88 (2.55)	7.20 (1.26)	0.003a
POD 2	5.45 (2.18)	5.41 (2.11)	0.94
POD 3	5.56 (1.98)	6.00 (2.07)	0.47
POD 4	6.20 (2.17)	6.11 (1.78)	0.73
POD 5	7.21 (1.58)	6.45 (1.99)	0.25

Fig. 3 – CONSORT flow diaphragm showing patient selection process.



Discussion

PSF for AIS is an extensive operation, presenting several perioperative challenges including effective pain control, management of opioid related side effects, and delay in mobilization [8]. We present a possible ERP including biopsychosocial care and it's results on outcome. Average LOS after PSF was 5-6 days [9,10]. Gauger et al [11] identified postoperative pain scores of 5.3, 5.1, and 4.6 in the first 3 POD in patients treated with PCIA. Walker et al5 described an incidence of PPSP of 22 % 6 months after PSF and 11-15% at 1 to 5 years. With acute postoperative pain being one of the risk factors for PPSP, this emphasises the importance of MMA with pre-emptive medication, blocking central sensitisation mechanisms. Other risk factors included preoperative pain intensity, patient anxiety, patient pain coping efficacy, and parental pain catastrophizing revealing the need for a biopsychosocial approach. In recent years, the use of ERP, integrating biopsychosocial care with MMA and early mobilization, has gained extensive attention. Fletcher et al [12] was the first to implement and evaluate an accelerated discharge pathway in paediatric spinal surgery following the example of colorectal surgery and joint arthroplasty. Potential benefits of early mobilization and early discontinuation of (intravenous) opioids were shown as reduced LOS and costs without increasing number of complications. Sanders et al [13] assessed the effect of ERP on postoperative pain scores, which were 3.40, 4.08, and 3.57 in the first 3 POD. With the implementation of an ERP, some caregivers succeeded in reducing LOS to only 2.2 days [14]. Our data show an earlier mobilization defined by standing upright and walking being achieved after implementation of the ERP, although this did not result in shorter LOS. Furthermore, Foley catheters were removed as soon as possible to reduce the risk of potential urinary infections and delayed rehabilitation. Postoperative pain scores were slightly higher in the ERP group for POD 1 to 3 compared with the control group with a statistical significant difference for POD 2. This may possibly be related to early ambulation.

Moreover, a trend toward slightly lower NRS scores on POD 4 and 5 were seen, but these were not statistically significant.

We acknowledge that our implementation study has some limitations. First limitation of this study encompasses that the type of surgery (including peroperatieve neuromonitoring) differed between the historical control group and the intervention group. In the control group, patients underwent a wake-up procedure with associated possible recall and psychological trauma. Fortunately, this was not reported by any patient in this study protocol. In the intervention group however, neuromonitoring consisted of somatosensory and motor evoked potentials. According to the literature, intraoperative awareness is not associated with sleep disturbances or higher postoperative pain scores in children, but results are conflicting [15-17]. Second, the COVID-19 pandemic made implementing an ERP very challenging. Patients under the age of 16 years are normally admitted to the paediatric ward. However, due to shortage of hospital beds, patients of the intervention group were occasionally admitted to different surgical wards. These teams were not familiar with this surgery, nor with the ERP, causing suboptimal implementation and unsatisfactorily date for hospital discharge communication. Third, patients with non-idiopathic scoliosis, known unstable psychiatric disease and preoperative chronic opioid use were excluded from this study. Considering patients diagnosed with mental illnesses could benefit the most from standardized care, they should ideally be included in further pragmatic ERP evaluation research.

Conclusion

Implementing an ERP for patients undergoing PSF leads to earlier mobilization as shown in this prospective study. Further reevaluation and improvement could not only reduce the acute and chronic opioid consumption and its side effects, but could also result in less postoperative pain, shorter hospital stay, faster recovery, and higher patient satisfaction.

Conflicts of interests

The authors have indicated they have no conflicts of interest to disclose.

Source of financial support for the project: This was supported through external funds from the Antwerp University Hospital.

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Appendix

ERP – medication component.

Preoperative

Preemptive oral gabapentin started 7 days preoperatively and gradually increased:

Day -7: 1x 5mg kg-1
Day -6: 2x 5mg kg-1
Day -5: 3x 5mg kg-1
Day -4 until day of surgery: 3x 5mg kg-1, and continued afterwards

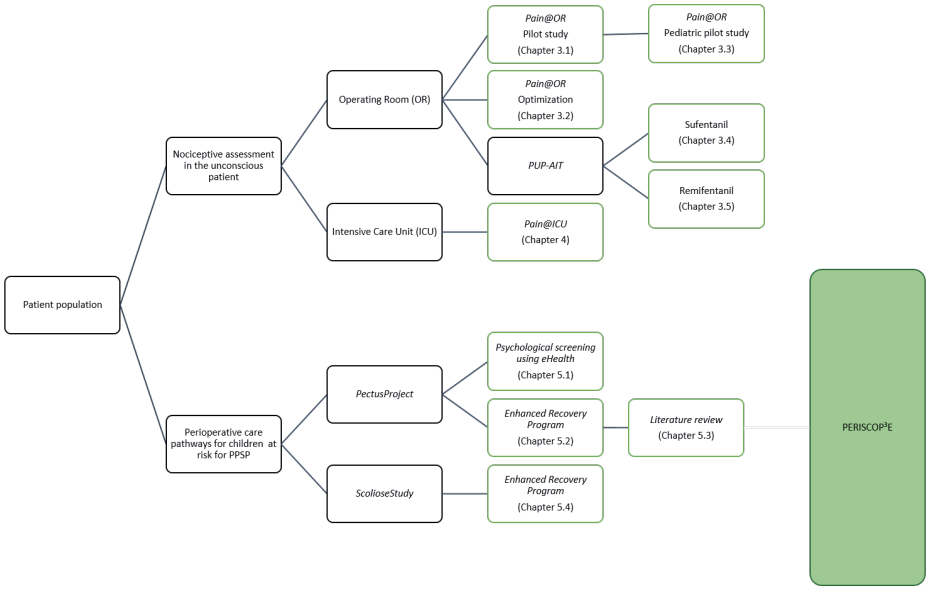
Peroperative

- Induction with propofol 1% 2-3 mg kg-1 IV, rocuronium 0.6mg kg-1 IV and fentanyl 2 mcg kg-1 IV
- Maintenance of anesthesia with propofol IV according to MARSH model
- Cefazolin 30mg kg-1 IV at induction, repeat after 4 hours or with major blood loss
- Tranexamic acid 20mg kg-1 IV
- Methadone 0.2mg kg-1 IV (at induction; after ECG screening for QT prolongation)
- Acetaminophen 20mg kg-1 IV
- Ketorolac 0.5mg kg-1 IV, max 30mg
- PONV prophylaxis: dexamethasone 0.1mg kg-1 iV (at induction) dehydrobenzperidol 0.02 mg kg-1 IV (standard dose 0.625mg)
- Clonidine 1 mcg kg-1 IV

Postoperative

- Acetaminophen 15mg kg-1 4x/day IV. If oral nutrition was resumed, switch to oral acetaminophen 60 mg kg-1 day-1 over 3-4 gifts
- Ketorolac 0.5mg kg-1 3x/day IV. If oral nutrition was resumed, switch to oral ibuprofen 10mg kg-1 3x/day
- Rescue pain: 1st night stay at PACU: piritramide 0.02 mg kg-1 IV (or 1-2 mg bolus) ward: buprenorphine 0.1- 0,2mg sublingual , max 6x/day
- Rescue PONV: first choice: ondansetron 0.1 mg kg-1 IV up to 3x/day second choice: alizapride 1mg kg-1 IV up to 4x/day third choice: dehydrobenzperidol 0.02 mg kg-1 IV up to 3x/day
- Continue oral gabapentin (same dose as preoperatively until 12 days postoperatively, then reduce over 3 consecutive days and completely stopped 14 days after hospital discharge)
- Cefazolin 30mg kg-1 3x/day IV during the first 24 hours postoperatively. The first dose is given 8 hours after the initial dose, regardless of any repeat doses
- Macrogol 1 bag 2x/day in constipation prevention
- Remove urethral catheter on POD1 and monitor spontaneous miction

Chapter 6. PERIoperative Holistic RIsk Factor SCreening in the Prevention of Persistent Pain (PERISCOP^{3}Ecare)



This chapter focusses on the first part of the PERISCOP³E research project (protocol, still recruiting at the time of dissertation publication). A risk factor screeningbattery is being validated in an adult surgical patient group. Furthermore, wellbeing is being surveyed pre- and postoperatively. In addition, a cutoff score will be defined for participation in a "perioperative biopsychosocial enhanced vigilance program".

6.1 Protocol for a risk factor screening assessment tool and cut-off determination for participation in a transmural perioperative care program.

Study protocol (recruiting)

Study Description

Brief Summary

Assessment and management for improved wellbeing after elective surgery (PERISCOP³E-Care) Diagnostic assessment tool evaluation and cut-off determination for participation in a transmural perioperative care program

Detailed Description

Adult patients (≥ 18y) who are planned to undergo an elective surgery at the University Hospital Antwerp, will be invited to participate. After signing the informed consent, they will be asked to complete PERISCOP^{3}E-care questionnaires: Kalkman & modified-Althaus, DN4, HADS, Stait-trait, NRS, MPI, and EQ-5D-5L that involve screening of the risk to develop persistend postoperative pain (PPSP). The questionnaires will be completed via a survey link to the RedCap platform. Invites will be send out via the patient's e-mail.

Demograpic data and relevant medical history, surgery history, concomitant medication will be registered. One month and three months post surgery the patients will be contacted to identicate if they developed PPSP. They will also be asked to complete quesionnaires (MPI, HADS, Stai-Trait, NRS, MPI, DN4). Based on this info, the cut-off value will be defined for the preoperative questionnaire. Analysis will be done for the sensitivity and specificity of the questionnaires.

Study Design

In this prospective observational cohort study 560 participants will be enrolled. Inclusion started in December 2022.

Patients with planned elective surgery will be asked to complete the PERISCOP3E-Care questionnaire (modified-Althaus & Kalkman, DN4, HADS, Stait-trait, NRS, MPI, EQ-5D-5L) preoperative. One month and three months post op the patients will be contacted to check if they developed persistend postoperative pain and they will also complete questionnaires (DN4, HADS, Stait-trait, NRS, MPI and EQ-5D-5L).

Outcome measures

Primary Outcome Measures

1. Cut-off determination (preoperative assessment)

   Cut-off score determination for Kalkman and modified-Althaus riskfactor screening in the prevention of persistent postsurgical pain (PPSP). Determination of inclusion and exclusion in a transmural care path.

Secondary Outcome Measures

1. Postoperative pain (postoperative on day of surgery, day after surgery)

   Determination with numeric rating scale, NRS on the 11-level pain scale

2. Persistent postoperative pain (1 month and 3 months after surgery)

   Determination of persistent postoperative pain via NRS on the 11-level pain scale.

3. The use of opioids (1 month and 3 months after surgery)

   Need for daily intake of opioids (started postoperative) after surgery

4. Patient well-being (preoperative assessement and repeated at 1 month and 3 months after surgery)

   Evaluation of the well-being measured with EQ-5D-5L questionnaire (5-level EQ-5D version). Each dimension has 5 levels of response. (Level 1); slight; moderate; severe; and extreme problems (Level 5). Here are 3,125 possible health states defined by combining one level from each dimension, ranging from 11111 (full health) to 55555 (worst health).

5. Fear and Depression (preoperative assessement and repeated at 1 month and 3 months after surgery)

   Evaluate the core complaints of fear and depression (without physical complaints) using the HADS questionnaire. Seven questions related to fear and seven questions related to depression. Every question can be answered with 0-1-2-3. If the score for the questions with fear is >8, this will indicate a psychiatric condition. If the score for the questions related to depression >8, this will indicate a psychiatric condition.

6. State anxiety and fear predisposition (preoperative assessement and repeated at 1 month and 3 months after surgery)

   Evaluation of the state anxiety and fear disposition using the Stai-Trait questionnaire. The range of scoring goes from a minimum of 20 untill a maximum score of 80. STAI scores are commonly classified as "no or low anxiety" (20-37), "moderate anxiety" (38-44), and "high anxiety" (45-80)

7. Pain complaints (preoperative assessement and repeated at 1 month and 3 months after surgery if the NRS ≥ 3)

   The MPI questionnaire part 1 measures the impact of pain on an individual's life, quality of social support and general activity. Each item is rated on a 0-6 scale, and the scoreds for each subscale are calculated by adding the score for each item in that subscale, devided by the number of items that subscale to yeald a mean score.

8. Neuropatic pain (preoperative assessement and repeated at 1 month and 3 months after surgery if the NRS ≥ 3)

   Evaluation of the presence of neuropatic pain components using the DN4 quesionnaire. When the score ≥ 4, neuropatic pain is likely.

Eligibility Criteria

Study population includes adults, 18 years and older of both sexes. The first 560 patients registered for elective surgery at the Antwerp University Hospital and have a preoperative consultation with an anesthesiologist.

Exclusion criteria include: language barrier to complete the study questionnaires, cognitive deficit that makes completion of the study questionnares impossible.

Study registration details

EC UZA: EC3410

EDGE UZA: EDGE002575

ClinicalTrials.gov: NCT05526976

Chapter 7. General discussion

This pragmatic research work has focused on an integrated pain evaluation and the design of surgery-specific pain care pathways, for an improved outcome in patients vulnerable to developing chronic pain syndromes. As explained in the introduction, the presence of pain can have tremendous consequences in the short and long term both for patients and those widely involved. During the last decades, chronic pain has evolved into a public health challenge with a profound negative clinical and socioeconomic impact. Although the knowledge of pathophysiology, pain assessment and treatment are increasing, the incidence of chronic pain, including PPSP, remains high. Knowing that chronic pain can have such a significant negative impact and is often more challenging to treat than acute pain due to its complexity, accurate risk identification, improved integrated assessment, early diagnosis of persistent symptomatology as well as prediction of future hurdles to rehabilitation, are of critical importance to patient management.

In recent years, more objective nociceptive monitoring tools for analgosedated patients have been evaluated but still lack validation due to its use in a very diverse patient population and its challenging applicability in highly technological environments such as ICUs and ORs. In addition, the interpretation and consequences for patient management appear to be insufficiently clarified. In this research work, we focused on two nociceptive reflex (pupil dilation reflex (PDR) and nociception flexion reflex (NFR)) monitoring tools that were already available in our center and have been promoted by their ease of use.

Furthermore, to improve patient-related outcomes after painful procedures such as surgery or during intensive care admission, great effort has been put into the identification of risk factors for chronic pain conditions. However, there is still a great gap between the knowledge of these theoretical risk factors and implementation of that knowledge in daily routine to identify patients at risk. To our knowledge, a biopsychosocial optimization of surgical care pathways for patients undergoing high risk surgery in the development of PPSP and introducing interdisciplinary teams are important first steps. In addition, risk factor screening in a broad surgical population undergoing all types of surgery should be evaluated as part of PPSP prevention strategies.

In this chapter we will discuss, considering the results of the research presented in this thesis, the possibilities for monitoring nociception and pain and for holistic biopsychosocial pain care programs, elaborating on ways to improve patients' wellbeing after hospital admission.

Monitoring nociception and pain in analgosedated patients

During general anesthesia

Several monitors have been developed to assess intraoperative nociceptive state, all with the objective to optimize analgesic administration. All these monitoring tools are based on the evaluation of the sympathetic-parasympathetic activity, although their physiological substrates and methods of analysis differ. Moreover, they provide retrospective information on the analgesia level (insufficient/excessive) resulting in analgesic management adjustements afterwards. Recently, a novel pupillometric index named Pupillary Pain Index (PPI) was designed to assess the level of intraoperative analgesia. Although the physiological principle on which the PPI is based has been described earlier,[297,298] we were one of the first to evaluate the pupil dilation reflex (PDR) using a PPI protocol during routine surgical procedures in 2018 (chapter 3.1).[1] We demonstrated that after opioid administration, propofol-sedated patients needed a higher stimulation intensity to obtain a pupillary reflex in response to the standardized automated nociceptive stimulus. Consequently, PPI

score was reduced by 32.16% after opioid analgetic treatment. Moreover, the elicitation of PDR by this low-intensity standardized noxious stimulation protocol was performed without changes in vital signs before and after opioid administration in adults under propofol-based general anesthesia (chapter 3.2).[299] In addition, we described PDR via a PPI protocol in children under general anesthesia in our university hospital, and concluded that measurements were feasible in this surgical subpopulation (chapter 3.3).[2] Evaluation of the PPI assessing the level of intraoperative analgesia after a bolus of alfentanil in children under sevoflurane general anesthesia was conducted by French colleages.[300] In this pilot study they described a significant decrease in PPI after alfentanil administration in 20 healthy children (6 at baseline, and a score of 2 after opioid administration). Our results were in line with the latter, as PPI scores decreased after administration of an opioid bolus and no significant changes in heart rate or blood pressure were found. Subsequently, PPI was further evaluated during surgical procedures under general anesthesia using sufentanil (chapter 3.4).[3] In this single-center double-blind randomized controlled trial we evaluated if pupillometry-controlled sufentanil use is superior to free choice sufentanil administration by the attending anesthesiologist. In this study, the intervention group of pupillometry-controlled opioid usage received significantly more sufentanil (20.1 mcg vs 14.8 mcg, p = 0.017) and, not unexpected, patients had a longer recovery time (52 min vs 40 min, p = 0.025). None of the patients reported PONV symptoms during the follow-up period. Postoperatively during the first 5 consecutive days, patients were questioned daily about their pain (NRS), analgesic consumption, and wellbeing. No significant differences were seen in postoperatieve pain intensity scores, analgetic usage, and no differences in wellbeing were recorded. Upon these results, no additional value can be identified using a sufentanil administration protocol depending on PPI monitoring results in outpatient surgery. Study protocol was repeated with the short-acting opioid remifentanil (chapter 3.5). Comperable results were seen, barring that there were no opioid dose differences in both groups. Both studies showed that there was no significant difference in analgetic administration after hospital discharge and health state. Our data are conflicting with the results from pupillometry-dosed remifentanil during major gynaecological surgery regarding intraoperative remifentanil consumption, but postoperative pain scores did not differ.[298] In addition, research dedicated to the additional value of pupillometry on postoperative pain the first hours after recovery have been conducted, and results are conflicting as well.[301] Up to now, large studies evaluating the additional value of intraoperative pupillometry on analgetic consumption after discharge and postoperative wellbeing are lacking. Subsequently, recent research evaluating pupillometry in the prediction of opioid requirements was disappointing.[302]

In future years, research should be further oriented on identifying confounding factors such as medication interaction and usefulness of pupilreflex evaluation in optimizing individualized opioid administration. A comprehensive literature review on the effect of different nociception monitoring tools on anesthesia practice was conduced and recently published.[303] However, most included studies were single-center, of small sample size and with a considerable variability in surgical procedures and anesthesia techniques. This again underlines the novelty of the research topic. In line with our research data, no consistent effect of nociception-guided anesthesia on postoperative pain and pain treatment could be established up to now.

Major hurdles for research are the often inability to fully blind investigators due to the nature of the intervention (using monitors and performing the 'intervention') and the often heterogeneity of patients and surgical procedures, and differences in 'standard anesthesia care'. Furthermore, the complexity of pain in contrast to nociception might give the impression that nociception is easier to

measure, but it is nothing less than a complex assignment. The challenging task remains for measuring nociception under general anesthesia, where the magnitude of the autonomic nerve system and behavioral responses depends on the presence of any alleviating agents. And nociception monitors invariabily use one or more autonomic variables as algorithm input for nociceptive index generation. Even more complex, autonomic variables are not uniquely related to nociception, further reducing the specificity of available monitoring tools.

In sedated critically ill patients

In the ICU, routine nociceptive evaluation in the sedated patient is carried out by using the BPS, also in mechanically ventilated patients.[216] However, this assessment is limited by medication use (e.g., NMB administration) and the inherent subjective character of nociceptive evaluation by third parties. In our study, which was one of the first studies investigating the usability of PDR and NFR measurements in critically ill patients, we showed that these tools are non-invasive and well tolerated in this group of patients (chapter 4.1).[4] The NFR, as a polysynaptic spinal withdrawal reflex, can be elicited after the activation of nociceptive A delta afferents. To quantify the reflex threshold, the electromyographic activity of the biceps femoris muscle is monitored during the application of varying intensities of electrical stimulation to the ipsilateral sural nerve. The required stimulation intensity to elicit the NFR is used to define the nociceptive threshold.[304] Both devices, measuring PDR and NFR, can provide researchers and clinicians with objective information regarding two different nociceptive processing pathways: (1) the ascending component of the somatosensory system and (2) the related autonomic reactivity. More recently, Vinclair reported a positive correlation between PPI scores and the standard pain assessment by the BPS in response to endotracheal suctioning.[305] Not unimportant, this research group concluded that in contrast to endotracheal suctioning, tetanic stimulation had no effect on intracranial pressure in the brain-injured group. The results of this proof-of-concept study,[305] showed that the nociceptive response to endotracheal suctioning could be accurately predicted using the PPI score in sedated critically ill patients whether they have brain injury or not. Similarly, the correlation between BPS and NFR was recently studied.[306] The authors concluded that NFR measurement is negatively associated with BPS assessment in patients with Richmond Agitation-Sedation Scale (RASS) below -4. However, behavioural reactions to both investigated clinical procedures can be predicted by observational scales or nociceptive reflexes.[307]

Results regarding the shift from NFR threshold monitoring in a perioperative setting to the mechanically ventilated, analgosedated critically ill remains unclear,[283,284,308,309] despite the more extensive possibilities for measurement outside a surgical environment (accessible leg for measurement of the NFR, no NMB administration).[236,310] Additionally, Linde and colleagues[311] recently published a scoping review proposing a methodology for NFR measurement in chronic pain patients. They concluded a significant difference in NFR threshold between chronic pain conditions and controls. As such, NFR threshold evaluation can be of potential value in different conditions. However, the evidence upon titrating analgosedatives depending on NFR threshold and its effect on patient-related outcome measures is inconclusive or lacking. Although NFR threshold assessment, may be less prone to the confounding effects of the concomitant routine used ICU or OR medication (excepting NMBA), the more unknown set-up and the perchance limited access to the patient's leg may still pose a significant hindrance to its routine use. Solutions for eluciding the NFR on other body locations or adjusting the patient positioning results in different threshold values.[311] Therefore, such modifications do not appear to be a conclusive solution for a broader roll-out in clinical practice as different standards should then be available.

Recommendations for future research to improve individualized nociception and pain monitoring

As reasoned above, one might assume that combining nociceptive monitors could result in less pain intensity and chronification after noxious procedures. This suggested *improved care* offers theoretical possibilities, but real-life data are lacking up to now. One of the major difficulties of integrated nociceptive evaluation in the analgosedated patient in general is that many devices are characterized by a laborious and often time-consuming set-up, making the translation from the clinical lab to daily practice cumbersome or even impossible. Nevertheless, they might have the potential to further improve individual pharmacological treatment and PROMs. However, future research should primarily focus on further validation of these tools in large, well-designed clinical trials in a real-life environment.

Most commercially available monitors (for a comprehensive report see Appendix A) are based on the detection of an increase in sympathetic activity or decrease in parasympathetic tone in response to surgical stress and defined it as the 'reaction' to nociceptor activation. Of course, this assumes that nociception will trigger a shift in the sympatho-vagal balance towards a stress response with changes in cardiac autonomic control, increased peripheral vasocontriction, pupillary dilaton, and increase in galvanic skin conductance. Most monitors focus on the evaluation of one or two of the aforementioned parameters, except for the nociception level index (NoL) which uses a multi-parameter approach. Multiple modalities are beginning to demonstrate its usability. But results regarding a decrease in intraoperative opioid usage, lower postoperative painscores and consequently postoperative opioid requirements are conflicting, which is hampering widespread adoption.[312,313] One of the major limitations in defining the power of nociceptive monitoring devices is to titrate analgetics in individual patients, and how to predict their postprocedural pain.

The main question, however, remains: "*what is the clinical added value of the routine use of nociception monitors*?".[314,315] They often have a high degree of error or usability compared to the more well-known gold standard pain assessment tools in conscious awake adults. Furthermore, they may not even be available or relevant for many cases. Moreover, there is a lack of high-quality evidence for efficacy in improving postoperative PROMs using intraoperative nociception monitors. In addition, these outcome measurements include not only postoperative pain scores evaluation and adapted treatment, but also postoperative psychosocial and psychiatric factors assessment including delirium, anxiety and depression that may delay rehabilitation and wellbeing. Although intraoperative nociception monitoring guidance may reduce intraoperative opioid administration and therefore might be a viable strategy to titrate opioids intraoperatively,[7] to date, there is a paucity of evidence regarding the impact of opioid minimization or total avoidance on long-term analgetic use and outcomes that are meaningful for our patients (chronic pain, functionality, wellbeing). Accordingly, despite advances in nociception monitoring technology and availability in recent years, up to now, their limitations override their benefits in routine anesthesia care. Future research should focus on defining how the balance between nociception and analgesia may affect PROMs, and consequently, maybe a critical balance can be identified were we positively or negatively affect patient outcomes. It is not until then that we can evaluate timing, frequency, and amount of analgetic titration and its impact on patients' recovery. Additionally, when focusing on our patient's recovery, perhaps the postoperative rehabilitation and wellbeing should play a more central role as primary outcome measurement taking the entire biopsychosocial package into account, in contrast to solely focusing on nociceptive monitoring, which appears up to now to be just a drop in the ocean.

To our opinion, recent eHealth developments can contribute to a high-quality long term patient follow-up taking all aspects of preoperative risk factor screening, perioperative analgesic titration, and postoperative wellbeing into account. The way for nociceptive, pain and prolonged pain research is more than ever open in this digitized era.

Designing care pathways focusing on a holistic pain approach

In our preliminary evaluation of a Web-Based psychological screening tool in adolescents undergoing minimally invasive pectus surgery (chapter 5.1),[5] we showed that perioperative online screening of psychological symptoms and trait characteristics could further inventorize patients at risk for prolonged pain conditions. Today, it is common knowledge that early identification and management of biopsychosocial risk factors and holistic care can improve postoperative pain, overall health status and well-being.[46,316-318] Embedded surgical pain treatment protocols or so-called enhanced recovery after surgery (ERAS) protocols have been described since the 2000s. These ERAS protocols are multimodal perioperative care pathways designed to achieve early recovery after surgical procedures by maintaining pre-operative organ function and reducing the profound stress response following surgery.[205,319] Mainly these protocols are designed from a surgical point of view and includes key elements such as preoperative (nutritional) counseling, optimization of nutrition, use of standardized analgesic and anesthetic regimens and early mobilization.[320-322] Despite the significant body of evidence indicate that ERAS protocols lead to improved outcomes,[323-326] they challenge traditional surgical doctrine (concerning fasting and postoperative immobilization schemes, pain-relieving catheter handling, length of stay). As a result, their implementation for optimizing pain prevention and management has been slow. Although most of the data arise from colorectal surgery, the evidence is applicable to many types of surgery. Our results are in line with the latter, despite inclusion of a small group in highly specific surgery (chapter 5.2).[6]

After our trial, Holmes et al. implemented an enhanced recovery pathway (ERP) in a high volume center for patients undergoing pectus excavatum repair, hypothesizing it is associated with a decrease in opioid requirements and a shorter hospital stay.[327] Patients were categorized similarly to our trial in a pre-ERP (1998-2006), a transition (2007-2011) and an ERP (2012-2017) cohort. ERP was shown to be associated with a decrease in hospital opioid use (morphine daily dose per kilogram) and a shorter median length of stay, despite equal pain scores at hospital discharge (all below three to ten). However, no further follow-up after discharge was provided, nor a biopsychosocial approach was performed. Later, Schlatter and collegues incorporated more attention to the psychosocial component of rehabilitation and wellbeing.[328] They invested in an enhanced preoperative consultation aiming to educate patients about anxiety and reframe pain expectations. This research group was able to decrease length of stay to 1 day and reduced postoperative narcotic usage measured 2 weeks after discharge. We would remark that this is one of the very few studies who evaluated an implemented psychosocial strategy in addition to intraoperative intercostal nerve block using an ERAS protocol. This reflects that despite the frequently underlined importance of holistic care, implementation and broad roll-out remains difficult.[329,330]

Sharma and collegues described three large core barriers for clinical implementation of a biopsychosocial model.[331] First, mental health aspects are seldom fully considered which impairs the full recognition of the pain problem. Secondly, training in the interdisciplinary use of validated

biopsychosocial pain assessment protocols is underrated and insufficiently used, and thirdly, the clinical assessment often fails to recognize the fundamental sensory and emotional dimensions of pain. An additional reason for difficult implementation is the time-consuming nature of pain education and psychosocial evaluation. This is also underlined by the Schlatter study describing initial consultations for patients ranged from 60 to 80 minutes in length[328] which confirms previous findings from psychiatric research.[332] Notwitstanding, it is well known that high preoperative individual expectations can precede unfulfilled pain outcome measurements.[333-337]

Rosenberg and Mullin described in depth some of the foundational skills in integrated healthcare that can be incorporated into training across the professional lifespan, in order to promote effective integration in modern healthcare which is still based on the biomedical model of disease.[338] Allocating patients to the appropriate level of care preoperatively and immediately after surgery may improve long-term outcome variables (chapter 5.2).[6] Internet-based technologies and feasible, objective monitoring tools can help clinicians screen surgical patients for risk factors and initiate early treatment if necessary (chapter 5.1 and 5.2).[5,6] Future research should focus on improving risk stratification and including a psychological assessment and outcome evaluation after including surgical patients in perioperative care pathways. Also, the rapid increase on eHealth technology, even for psychological care, might accelerate the wider roll-out of such a digital holistic pain care program.[339,340] With the PERISCOP³E project (chapter 6), the previously described lessons learned about risk factor identification, preventive and early biopsychosocial care are bundled. Within this new and rapidly evolving research topic, new methods for prediction of PPSP[341-344] and widespread implementation will be further explored.[200,345,346] In addition, the impact of this on many PROMs will also be an important decisive factor in the broad roll-out of holistic pain assessment with the aim of monitoring patients' wellbeing after surgery accompanying the frequently earlier hospital discharge.

Recommendations for future research to improve holistic pain care for patients at risk

Numeric pain rating scores and visual analogue scales are widely known and fortunately part of standard paincare. As mainly assessed by nurses, it needs to be stressed that all physicians have to take responsibility in optimal and repetitive pain assessment. Furthermore, future research should focus on the implementation and validation of different assessment techniques based on the capabilities of a patient. Moreover, not only the subdivision of patient group (types of pathology) for pain evaluation but also the holistic approach should be further examined in the next few years. An urgent need to explore all different dimensions of pain (cognitive, sensory, behavioral, autonomic responses) is critical for preventing pain chronification, rehabilitation evaluation after surgery and improving PROMs.[347] Moreover, clinicians should increase focus on known patient behavior and intercultural differences. The latter will be one of the many challenges of this century as more and more working hours go to administrative tasks and less to direct patient contact. Therefore, it will be imperative to develop guidelines for pain assessment following a hierarchical structure evolving over time given the novelty of such approaches with fewer healthcare resources. Additional to the validation of prediction models, there is a need for validation of the clinical impact of such a predictive score on the patient management and outcomes. Preferably, by performing large-scale high-quality studies reflecting the daily clinical practice we would be able to evaluate the effectiveness of preventive interventions that to date have often proved to be insufficiently successful. In addition, by improving the early identification of patients at risk in a simple and feasible way for a large group of individuals undergoing painful procedures (chapter 6), clinical trials can subsequently focus on the design of such heightened vigilance programs. Verret and collegues

recently published their protocol in which intraoperative pharmacological opioid minimization strategies and patient-centred outcome after surgery will be reviewed, and results are still expected.[348] In this long way to go, the rise in digital healthcare facilities can be of great added value, as seen during the COVID-19 pandemic.

During the COVID-19 crisis, multiple telemonitoring systems were developed to monitor SARS-CoV-2-infected patients in their home environment.[340,349,350] This knowledge has also been used to humanize patient care during the 2022 monkeypox outbreak[351] but can also be very useful not only for the management of future viral outbreaks but also in extensive pragmatic postoperative pain prevention programs to broadly roll out a practical tool for caregivers involved in a surgical trajectory. Such an e-health platform connects general practitioners, surgeons, anesthesiologists, pain doctors, and nurses and supports early detection of persistent pain complaints when preventive strategies have failed. Patient-central care, enabled through e-health technologies, offers opportunities for thorough psychosocial care and patient empowerment where necessary. Large-scale testing for risk factors in a preoperative pragmatic setting, and subsequently introducing pain-specific protocols are some of the next steps to evolve to a perioperative holistic risk factor screening in the prevention of persistent pain with assessment and management for improved wellbeing after surgery. The evolution of implementing a biopsychosocial approach led inevitably to teamwork. In practice, clinicians may become adept at assessing the biological, psychological and social components of health, yet patients with more complex biopsychosocial needs might benefit from collaboration of experts in the biological, psychological and social spheres of healthcare.[352] Once these interdisciplinary teams providing biopsychosocial care are available, the most vulnerable may be the first to benefit.

Chapter 8. Conclusion

"Coming together is a beginning,

keeping together is a progress,

working together is a success."

Henry Ford

This PhD thesis aimed to evaluate the additional value of nociception monitoring during surgery and ICU stay. Consequently, perioperative biopsychosocial care pathways were designed and implemented according to the knowledge at the time of execution and its effect on PROM were studied. During our study period (2016-2022) the interest in understanding nociception and pain, has increased more than ever.

First, the pupillary pain index (PPI) as a novel pupillometric index, is designed to assess intraoperative analgesia and can be used as a usable monitoring tool in children and adults under general anesthesia (chapter 3) whithout significant changes in cardiovascular parameters. However, research should be further oriented on confounding factors such as medication interaction and its usefulness in optimization of individualized analgetic administration and finally its relevance to the emergence of postoperative pain symptoms. Additionaly, in our research projects, which were of the first studies investigating the usability of pupil dilation reflex (PDR) and nociception flexion reflex (NFR) measurements, the use of these nociception monitoring tools confirmed to be non-invasive and well tolerated in analgosedated patients (chapters 3 and 4). Yet, the added value for nociceptive monitoring during general anesthesia still remains unclear and the different research questions concerning validation and the impact on analgetic titration should be first elucidated before nociception monitoring can be considered valuable for extensive postoperative pain care and patient related outcome measurement (PROM) evaluation.

Secondly, holistic paincare programs including a perioperative far-reaching pain policy appeared to be feasible in an elective surgical setting (chapter 5). Based on the findings reported in this PhD thesis, attention has to go to early biopsychosocial risk factor screening focusing on a more preventive approach for each surgical patient. Subsequently, structured adequate (preventive) pain management protocols could further improve perioperative wellbeing (outside the scope of this PhD). In our experience, interdisciplinary teams are of the utmost importance. Given the magnitude of the complex pain problem (inter)nationally with increasing psychosocial stressors (health and wellbeing, financially), it is our suggestion to further shape and develop this holistic approach in the prevention of persistent pain complaints. Stimulating the development and implementation of transmural perioperative care pathways will further play its crucial role for early interventions in the rise of pain syndromes.

Although the importance of a better nociceptive assessment no longer needs to be explained, and future opportunities considering nociceptive monitors integrated in closed-loop systems for analgesia titration are promising, the greatest gain in the prevention of PPSP appear to be in the development of holistic pain care pathways that span the complex pallet of pain.

Considering the state-of-the-art regarding perioperative medicines we can conclude that interdisciplinary teams can additionally use digital health systems to ameliorate (longlasting) patient follow-up. And, catalyzed by a viral outbreak pandemic, this digital revolution might even further deploy unprecedentedly. As such, we believe that it is more prudent to focus on forming collaborating teams that translate the evidence-based science into daily practice in achieving a better wellbeing after surgery or intensive care admission. This subsequent more pragmatic research should further design and optimize pain care pathways besides the identification of quality indicators like PROMs and patient related expectation measurements, reducing persistent pain complaints and increasing wellbeing and reintegration in the patients consulting us.

In conclusion, in the current work-up for perioperative holistic pain care starting with an early preprocedural persistent pain risk factor screening is virtually the only chance for an optimized preventive approach, interdisciplinary biopsychosocial care will be a keystone for improved wellbeing in the pursuit of perioperative paincare excellence. Clinicians, medical researchers, basic scientists, and industry should continue collaborating to foster the exchange of medical science information in the field of pain assessment.

Many oppurtunities lay ahead.

"If you can't fly, then run, if you can't run, then walk, if you can't walk, then crawl, but by all means keep moving"

Martin Luther King

Appendix A. An overview of the available objective monitoring tools

[in draft, prepared in 2015-2016 after analysis of nociceptive monitoring possibilities]

Introduction

As pain but also nociception is a complex spectacle including various transductions, synapses, reflexes and mediators; its research remains challenging. Creating an easy-to-use, quick to measure, sensitive and specific variable will probably be futuristic, as a complex assessment of pain also includes inter –and intra-individual variations.

Clinicians consider findings about pain important and many of them are aware of the clinical consequences. Therefore, they should move beyond classical pain scores and combine (1) NRS/VAS or behavior pain scales if self-report by the patient is not possible, (2) physiological pain assessments, and (3) acceptability of pain, satisfaction of pain reduction(strategies), overall health status, and pain interference of daily live to get a clear indication of the pain.[353] Patient care implies the holistic multidisciplinary approach with all patient related outcome measurements and its importance is growing. As stated by Van Boekel et al.,[354] the use of only NRS for pain assessment is rather limited to reflect all multidimensional aspects of pain.

Meanwhile, the choice of individual assessment techniques is not easy. In the past decades, many developers invested in physiological pain measurements techniques as the knowledge about the adverse effects of long-lasting pain in the short and long-term period became clearer. To date, the available methods can be subdivided into EEG derived variables, autonomic nociceptive responses such as PDR, somatosensory system reflex analyses such as NFR, descending inhibitory modulating system evaluation and biomarker assessment. In the next paragraphs the most common techniques are discussed. Figure A1 gives a not limited overview of the available (research) pain assessment techniques.

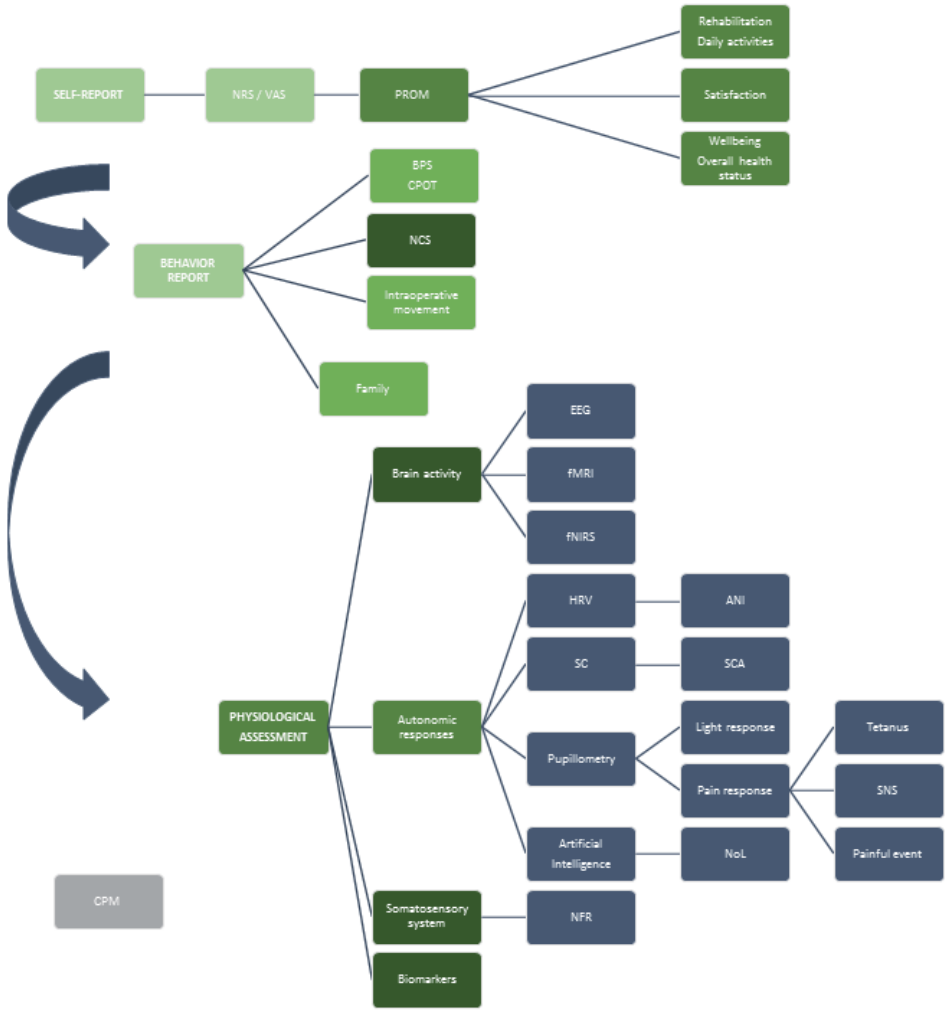


Figure A1. Overview of pain assessment hierarchy. NRS: Numeric Rating Scale; VAS: Visual Analogue Scale; PROM: Patient Reported Outcome Measure; BPS: Behavior Pain Scale; CPOT: Critical-Care Pain Observation Tool; NCS: Nociceptive Coma Scale; EEG: Electroencephalogram; fMRI: functional Magnetic Resonance Imaging; fNIRS: functional Near-Infrared Spectroscopy; HRV: Heart Rate Variability; ANI: Analgesia Nociception Index; SC: Skin Conductance; SCA: Skin Conductance Algesimeter; SNS: Standardized Nociceptive Stimulation; NFR: Nociception Flexion Reflex; CPM: Conditioned Pain Modulation or DNIC (Descending Noxious Inhibitory Control). The arrows indicate the hierarchical tracking structure, implying pain self-report when possible. The fading in green represent the knowledge of pain assessment tools, the darker the more unknown. CPM is in grey where it requires a fully cooperative patient.

Brain activity-derived variables

As a more practical alternative for neuroimaging, physicians can use evoked potentials in the direct evaluation of cerebral activity. Moreover, EEG signal amplitudes correlate with nociceptive stimulation intensity and may represent peripheral and central processing of nociceptive inputs. Furthermore, analgesic drugs appear to alter those amplitudes.[355,356]

More practically, electroencephalography directly measures brain activity by voltage fluctuations due to extracellular ionic currents.[357] More specifically, processed EEG is used to monitor sedation depth under general anesthesia. For example, the BIS is a dimensionless number from 0 to 100, derived from several cortical EEG indices based on the cortical activity and the presence of burst suppression. Further research in the appliance of classically derived EEG for nociception assessment states that there is no correlation between nociceptive stimulation or opioid administration and EEG variables.[358,359]

Fortunately, those special brain imaging techniques and evoked potentials to measure pain are impractical at the bedside.[360,361] Therefore, these techniques remain within the research setting.

A commercially available monitoring tool in this subdivision is the qNOX® (QuantumMedical, Barcelona, Spain) and is designed for monitoring the level of analgesia during general anesthesia. The index is obtained from electroencephalogram (EEG) signals analyzed using an advanced digital processing algorithm.

Other techniques for measuring brain activity as a response to noxious stimulation are: magnetic resonance imaging (MRI) and fMRI or functional near-infrared spectroscopy (fNIRS).[362] The first allows quantification of neural activity in specific brain areas. Moreover, metabolic changes during cell activity are associated with localised haemodynamic responses. Although recently optimizing neuroimaging techniques, its use in daily practice is unattainable due to its expensiveness, long investigations times and risk at artefacts. The second has its main advantage of no necessity to exposure to ionising radiation. Therefore, clinicians can use it for repeated use over extended periods. Results of fNIRS shows promising information in assessing pain in adults and children when self-reporting is impossible.[363,364]

Autonomic response analyses

There is evidence supporting the rationale of a neuroanatomical overlap between nociceptive and autonomic pathways.[365] Moreover, pain exacerbate the autonomic response to stress by increasing circulating stress hormones.[366] A number of assessment tools are developed based on this knowledge. Those devices derive indices from heart rate variability, skin conductance, pupillary changes or a combination of those methods.

Heart rate variability (HRV)

Computational analysis detects measures of HRV as a potential interacting between the sympathetic and parasympathetic nervous system. Changes to time and frequency between consecutive heart beats may reflect nociception after a painful stimulation [367]. As measured by a classic ECG monitor, it is easy-accessed and non-invasive. However, HRV is non-specific and can thus be influenced by numerous physiological and psychologic conditions such as age or sex,[368,369] co-morbidities,[370-373] during general anesthesia and surgery,[374,375] or by medications.[376] As a result of these confounders, steps are made to overcome above mentioned disadvantages by example using respiratory-evoked

heart rate fluctuations [377], or integrated real-time algorithms. Despite many efforts from the industry to many variables are overtaken its accuracy in pain detection. As such it remains unclear whether the complex algorithms are sufficient enough to evaluate nociception in a clinical peroperative setting.

Example for this type of nociception evaluation is the "Analgesia Nociception Index" (ANI). The ANI combines ECG and respiratory rate with high-frequency HRV.[378-380] Commercially available as A.N.I monitor® (MDoloris Medical System, Loos, France).

Skin conductance (SC)

As a result of autonomic nervous system activation by noxious stimulation sweating occurs. Consequently, the electrical resistance of the skin is reduced and its conductance it increased. Fluctuations in skin conductance can be used to assess pain,[381] however those signals are not pain specific and emotional sweating can occur.[382,383] When the skin sympathetic nervous system is activated from the cerebral cortex, sweat glands (palmar and plantar) are filled through muscarine receptor activation via acetylcholine release by the sympathetic nerves. As a result, the skin resistance is reduced. It is the conductance, the inverse of resistance, which is specific for the stimulus. Nevertheless, due to the sweating response, many technical problems arise as electrode dislocation. Although many efforts have been made for optimizing environmental temperature and skin quality, there are inconsistencies in reproducibility in pediatric patients and patients under general anesthesia.[384,385]

Examples for such measurement methods are the Skin Conductance Algesimeter™ (SCA; Med-Storm Pain Monitor) and SudoScan® (ImpedoMedical, Paris, France) for small fiber evaluation which is based on the electrochemical reaction between the chloride ions in sweat and stainless steel-based plate electrodes, on which the subject's hands and feet are placed. A low-voltage current (<4 V) is applied through the electrodes, attracting chloride ions from the sweat glands (which are densely concentrated on the palms and soles). A measurement of conductance for the hands and feet is generated from the derivative current associated with the applied voltage.

Pupillometry

Pupil reflexes are seen in response to light (pupillary light reflex, PLR) and to nociceptive stimulation (pupil dilation reflex, PDR). Certainly, PDR has potential value to the extent that it can be used for nociceptive evaluation in the non-communicative patient during analgo sedation. Anesthesia results from anesthetic (sedation, unconsciousness) and anti-nociceptive effects (analgesia) on cortical and subcortical brain areas. Despite a mainly GABA (γ-Aminobutyric acid)-receptor effect of common used anesthetics, cellular and molecular pharmacological are still partly elucidated. What we do know is a that most anesthetics act on the central nerve system as a whole, cortical and subcortical brain network. In contrast to the non-conscious processes such as memory or nociception are integrated almost exclusively in the subcortical area. Among these structures we find the limbic system ensuring emotional components, thalamus as a relays station for sensory information to cortex areas, and medulla for autonomous regulation of vitals (blood pressure, heart rate, respiration). The spinal cord is a conjoint target for anesthetics and anti-nociceptive drugs. The first, are responsible for motor response to a nociceptive stimulus. As anesthetics reduce the level of

consciousness by cortical inhibition, larger doses even provide loss of motor response by spinal inhibition and influences the autonomic regulation by subcortical effects.

A major advantage over other indices which assess analgesia derived from autonomic responses such as blood pressure or heart rate neither of which is sensitive or specific [386]. The APPENDIX chapter is fully dedicated to automated infrared portable pupillometry as in my PhD fellowship I gained knowledge in the mechanism of action and clinical possibilities for pupil evaluation in the context of nociceptive evaluation. Example for this index is the NeuroLight AlgiScan® (ID Med, Marseille, France) (Figure A2) or NPi® (NeurOptics, Irvine, California, USA).

Figure. A2 Default setup for the measurement of the pupil dilation reflex (PRD) in analgosedated patients during surgery or mechanical ventilation at the Intensive Care Unit (ICU) in this research thesis.

Proprietary artificial intelligence algorithms

Those algorithms convert the physiological data to a real-time Pain Index. A novel multidimensional index of nociception, the “Nociception level index” (NoL), derived from the nonlinear composite of heart rate (HR), HRV, amplitude of the photoplethysmogram, SC, fluctuations in SC, and their time derivatives. This innovative NoL index has been shown to be a reliable measure of moderate and intense noxious stimulation, outperforming HR and MAP in differentiating noxious from non-noxious stimuli [387]. In contrast to HR and MAP, the NoL may not be affected by the hemodynamic effects of remifentanil [388]. Furthermore, the NoL unique pain index was found to be highly correlated with estimated pain level and outperformed any other pain existing related indicators [389]. This innovative technology enables non-invasive, objective, pain monitoring by measuring multiple pain-related physiological parameters. The data is then integrated using state-of-the-art signal processing and pattern recognition algorithms to identify a patient’s unique signature of pain [390]. The estimated parameter, derived from computing analysis of this physiological signals, gives a number between 0 to 100 to produce the NoL . This index appears to give an indication of nociception than each of the physiological signals alone. For this measurement is no patient cooperation necessary. This NoL was initially developed for the combination of stimulus/analgesia measurement and has been used in patients under anesthesia during surgical procedures [388].

Somatosensory system reflex

In this research project, the Dolosys Paintracker® (Berlin, Germany) was used to objectively measure the NFR. This novel technique of automatic pain reflex measurement provides not only specific and sensitive information about the extent of pain control in such non-communicative patients but as a continuous technique, it enables monitoring of the course of the analgesia over a longer period, in addition to determining the extent of the analgesia at a particular time point. Electrical stimulation will be performed through bipolar surface Ag/AgCl-electrodes placed just distal to the lateral malleolus at the innervation area of the sural nerve. Electromyographic (EMG) reflex responses to electrical stimulation were recorded from the middle of the biceps femoris and the rectus femoris muscles via 3 Ag/AgCl-electrodes at the ipsilateral side (Figure A3). Via the inbuilt threshold tracking program, stimulation intensity is increased until NFR is detected.

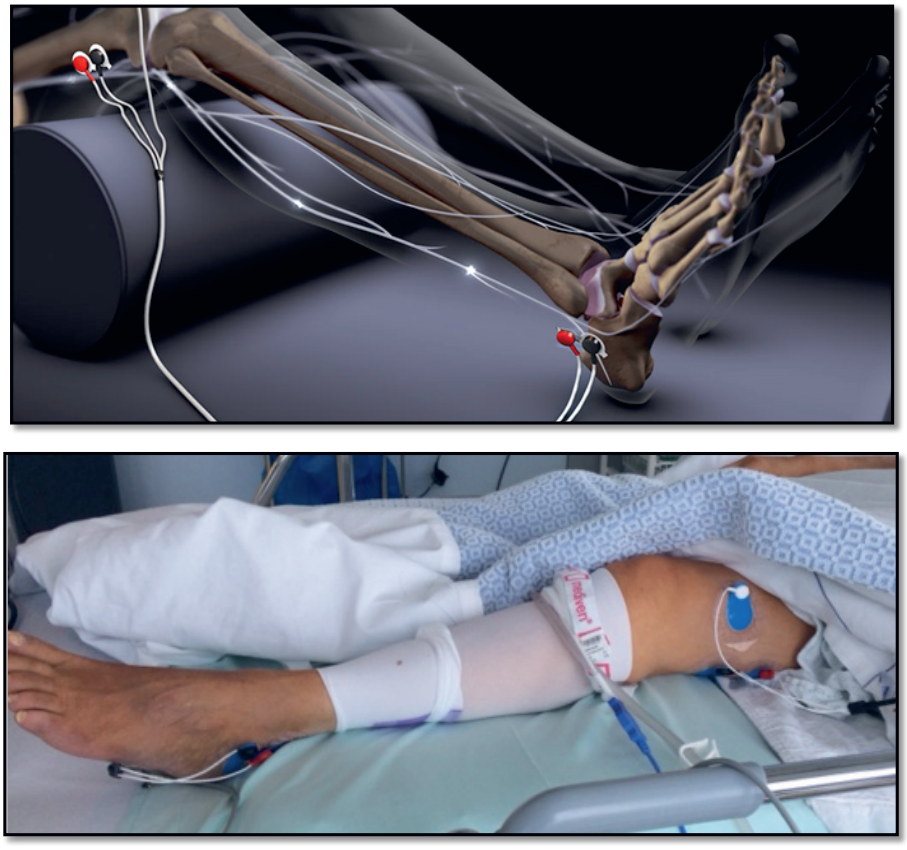


Figure. A3-1. Overview of electrode placing for nociceptive flexion reflex (NFR) assessment. *Photo taken with permission for Dolosys GmbH.*
Figure. A3-2. Presentation of the measurement of the NFR in a critically ill patient. Installation of a subject in supine position for the *Pain@ICU* trial. Distal stimulation electrodes at the skin area innervated by the sural nerve (sensory nerve of the calf) located at the lateral side of the malleolus. For signal (= EMG) capture, electrodes are placed at the biceps femoris muscle on the ipsilateral leg. A reference electrode (white) is placed at the area above the patella at the rectus femoris and the recorded muscle. Negative (black) electrodes are placed distal to the positive (red) electrodes.

Biomarkers

Translational pain research in patient populations with communicative impairments has been hampered by the unreliable nature of pain assessment based on self-reportage. The development of reliable and objective biomarkers would not only improve pain treatment and individually analgesic titration, it may also increase the understanding of pain mechanics.

A biomarker is defined as[391]: "a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or pharmacological responses to a therapeutic intervention", and its use in pain research is relatively new. By using this definition from the Biomarkers Definition Working Group, many variables can be included as they all have the potential to objectively asses pain. As we know that pain is multidimensional and complex, a systems biology approach including transduction principles, neurotransmitters and mediators seems well suited.

A number of biopathways can be eligible for measuring nociception. In literature, two main systems are described: the hypothalamic-pituitary axis and the sympathetic nervous system as the most important. As the strong relationship between pain and stress response has already been cited before in this thesis, serum catecholamine levels reflect sympathetic activation or the alternative salivary alpha-amylase could be measured as done by a Belgian research group [392,393], moreover injury induced pain has been linked to increasing levels of cortisol, adrenaline associated with a decrease in insulin sensitivity [366]. Furthermore, cytokines are released in inflammatory pain and could serve as potential biomarker, but results are still complex and not always consistent in acute and chronic pain syndromes [394,395]. However, pain may only represent a small part in this equally complex neuroendocrine response, and therefore the strength of the link has been questioned in pain research [396]. Many efforts are still made in the pharmacological discovery.

Appendix B. Introduction to two nociceptive reflex measurements

[in draft, prepared in 2015-2016 after analysis of nociceptive monitoring possibilities]

Physio(patho)logy of pain: points of reference

In non-communicative patients, pain assessment is more challenging, and surrogate markers based on behavioral or physiological parameters are used. Although they point towards extremes as no pain or maximal pain intensity, they have their own shortcomings. [397,398] The sympathetic response of tachycardia can be easily obtunded met β-adrenergic blocking agents, curarization prevents patient movement, hypertension can be a reflex effect of peritoneal stretch. This clinical evaluation does not mean that a patient has no pain. One can say that the nociception- anti-nociception balance is unknown. With a single simple retraction of the eyelid, anesthesiologists are allowed to observe pupil diameter and reflex to light or noxious stimulation, which are regulated by nuclei in the midbrain. Consequently, pupillometry can be used to quantify pupil reflex response towards a noxious stimulation. Despite often easy eye access in sedated patients, many anesthesiologists do not use this information.

Until today, an objective measure of a complete pain perception does not exist. However, physicians can measure different aspects of nociceptive processing and pain perception, but these techniques are often time-consuming and therefore exclusively used for research purposes. Experimental pain models often only involved induction of cutaneous pain using a single stimulus modality. Recently new experimental models have been developed eliciting various modalities of deep and visceral pain which more closely resemble clinical pain conditions such as acute postoperative pain. Ideally, multi-modal and multi-structure pain induction and assessment techniques are used, because a simple model cannot describe the very complex and multi-factorial aspects of clinical pain.

Nociceptive stimulation causes (mostly via inflammation mediators) activation of specific thermomechanic myelinated A-δ – and multimodal non-myelinated C fibers by transduction. Non-noxious stimulation of skin, joints or muscle are mainly conducted by large diameter myelinated A-β fibers. Nociceptive information is after detection and conversion to electrochemical signals transported from the nociceptor at the place where the pain is worn, up to the spinal cord by primary afferent sensory neurons. Those called *peripherally nociceptive afferents* enter the dorsal horn of the spinal cord and are organized for neuron synapses. They then make contact with second-order neurons and cross to the opposite side of the spinal cord. Consequently, the information is transmitted upwards through the spinothalamic tract to the thalamic region, which is known as a relay station, and the reticular activation system. This is the **ascending component of the somatosensory system**. Thereafter, the information is transmitted via the limbic system and postcentral gyri towards the hypothalamic region by medullary reflex arcs. The latter are responsible for the **autonomic processing** by a noxious stimulation. Visible reactions are the occurrence of tachycardia, hypertension, and pupillary dilation. A third system modulating pain transmission is the individual specific **descending (inhibitory modulating) part of the somatosensory system**. Fibers form this system, originating from different nuclei at the midbrain (nucleus raphe magnus, nucleus reticularis) and locus coeruleus. By its inhibiting and exciting synapses, temporal summation (representing excitatory modulation processes), and diffuse noxious inhibitory controls (DNIC) (representing the inhibitory modulation) occurs.

Treating pain implies optimal assessment which depends on a clinician's ability to perform a reproducible and objective pain assessment. Adequately identifying and treating pain all patients require a renewed and focused attention from the translational research community.

Nociceptive Flexion Reflex

In order to assess the ascending component of the somatosensory system, one can rely on the evaluation of the Nociceptive Flexion Reflex (NFR). The NFR paradigm has been used in pain research to investigate pharmacological modulation of nociception, spinal and supraspinal influences on nociception, and individual differences in nociceptive processing in participants with and without pain disorders.[399] The NFR is a polysynaptic spinal withdrawal reflex that is elicited following activation of nociceptive A-δ afferents.[400] The reflex arc is mediated by a complex network of interneurons at spinal level, including the wide dynamic range neurons and multireceptive neurons located in lamina V of the dorsal horn of the spinal cord.[401] The nociceptive flexion reflex consists of an early response (RII reflex) and a late response (RIII reflex). Although the RII reflex is a non-nociceptive A-β fiber-mediated response, the RIII reflex is a high-threshold nociceptive A-δ fiber-mediated reflex. The RIII reflex response is recorded electromyographically over the biceps femoris muscle after the application of electrocutaneous stimuli to the ipsilateral sural nerve. To assess the NFR, biceps femoris muscle activity is monitored using electromyogram (EMG) during the application of varying intensities of electrocutaneous stimulation to the ipsilateral sural nerve (see Figures B1 and B2).[304]

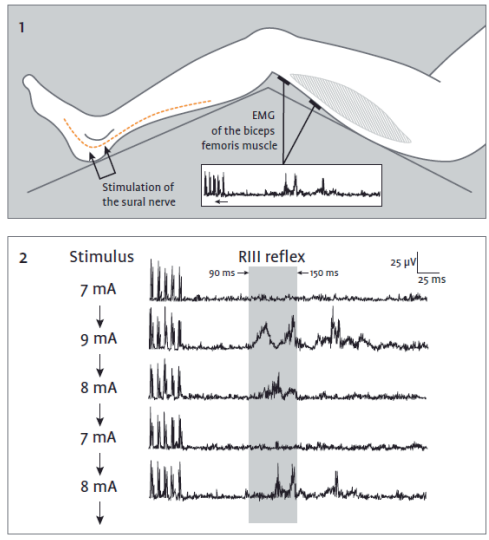


Figure B1. Transcutaneous electrical stimulation near the sural nerve located at the lateral malleolus is applied and the reflex response is measured by EMG of the biceps femoris muscle (1). By varying the intensity of the stimulation current (2) the reflex threshold is determined. *Adapted from Dolosys GmbH - Paintracker® promotional material.*

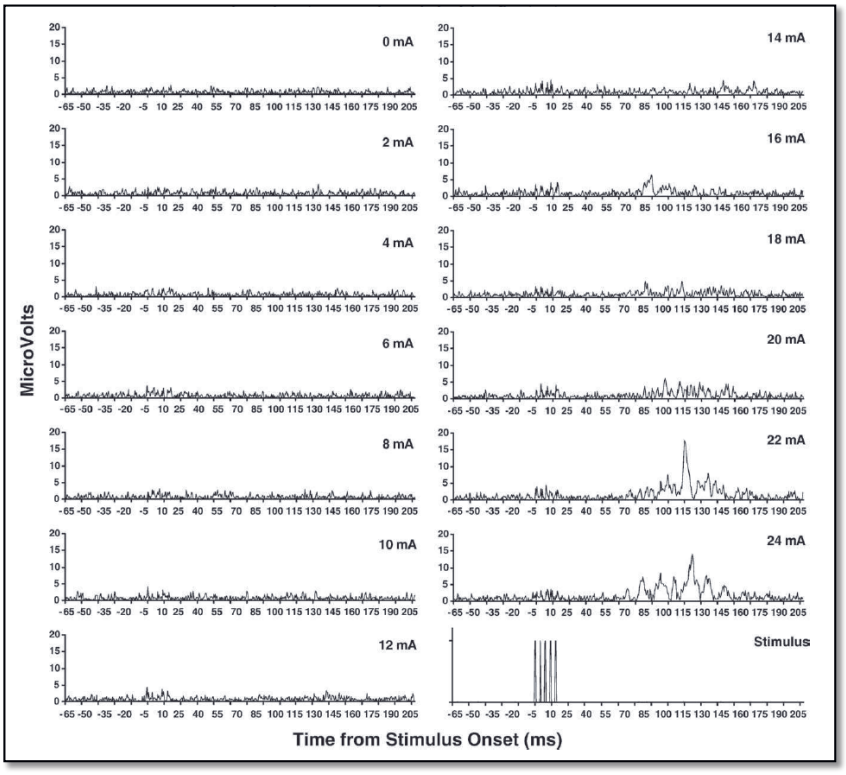


Figure B2. Overview of NFR threshold tracking. Different graphs are the results of biceps femoris electromyogram (EMG) following sural nerve stimulation in one individual (increasing stimulation intensity). Typically, the NFR is assessed in the 90–150 ms post-stimulus interval to avoid contamination by non-nociceptive responses that can occur before (RII reflex) or after (e.g., startle responses, voluntary movements) the NFR. In this individual, the NFR emerges between 14 mA and 16 mA (NFR threshold) and the magnitude of the reflex increases with greater stimulus intensities. *Adapted from Rhudy et al., 2008*.[402]

Based on the observed EMG response (Figure B2), intensity of stimulation required to elicit the NFR is used as an objective index of nociceptive threshold.[304,403] Prior research has demonstrated that NFR threshold is often highly correlated with subjective pain threshold,[304,404,405] and the magnitude of the reflex response is related to intensity of perceived pain.[406] Results from the previous studies suggested that standardized peak (NFR Interval Peak *z* score) and mean (NFR Interval *z* score) biceps femoris EMG activity were accurate and reliable criteria for defining NFR threshold (Table 1).[304,407,408] Using these empirically-derived cut-points, it has been demonstrated that the resulting NFR threshold showed good test-retest reliabilities both within-session and across days.[409]

Table 1: NFR magnitude scoring methods and definitions after Rhudy et al. 2008[402].

Scoring method	Definition
Baseline adjusted NFR interval peak	NFR interval peak – baseline mean
NFR interval peak z-score [a]	(NFR interval peak – baseline mean) / baseline SD
Baseline adjusted NFR interval mean	NFR interval mean – baseline mean
NFR interval z-score [a]	(NFR interval mean – baseline mean) / baseline SD

NFR = nociceptive flexion reflex, SD = standard deviation
[a] refers to standardized criteria (z scores are standardized, SD in denominator)

The NFR circuitry integrates a central processing site of sensory information in the dorsal horn of the spinal cord and a central processing site for motor output in the ventral horn; therefore, its reduction is mediated by drug effects on either one or both of these sites. Many researchers compare NFR with the H reflex which is analogous to the mechanically induced spinal stretch reflex, generated 28-35 ms after the stimulus.[304,410]

Evidence demonstrated a stronger reduction of the H reflex by for example sevoflurane than by propofol, whereas both drugs suppress the nociceptive flexion reflex to a comparable degree.[411] The more profound H reflex reduction by sevoflurane directly indicates that sevoflurane has stronger suppressive effects on ventral horn excitability than propofol. In this context, the similar suppression of the nociceptive flexion reflex indirectly implies that propofol would have comparably stronger effects on the dorsal horn.[412] In addition, several analgesic drugs have been shown to significantly reduce the nociceptive RIII reflex.[413] Opioids (frequently used on the OR and ICU) have also been shown to significantly alter the NFR.[403,414,415]

Pupil Dilation Reflex

Since general anesthesia first became widely used in late 1846, assessment of anesthetic depth was a problem. To determine the depth of (exclusively ether) anesthesia, the anesthetist relies on a series of physical signs. It lasted until 1937, with the observations of Guedel that a general accepted classification system was performed. From then, physicians focused on the pupil for the determination of different sedations states; progressive dilation of the pupil indicated deepening levels and lowered the anesthetic exposure consequently. With the use of modern anesthetics including volatiles desflurane, sevoflurane and propofol, such major pupil responses are no longer seen.[416] Larson was one of the first investigators to conclude the presence of an absent sympathetic contribution of pupil size under general anesthesia.[417] This is in contrast to cardiovascular reflexes who are still sympathetically mediated. A possible explanation for this contradiction is found in a locational difference of both reflexes, i.e. upper mesencephalon for pupil reflex and lower brainstem for cardiac responses.[418] Previous described research showed an exclusive parasympathetically effect of pupil variations in anesthetized subjects. During anesthesia changes in pupil size are the result of alteration in the muscle tone of the pupillary sphincter and lack influences of circulating catecholamines. On the other hand, a correlation of PDR in response to a noxious stimulation is associated with local catecholamine release at the level of the brainstem, has it is demonstrated that dopamine-2 antagonists have a PDR depressant effect.[419]

For interpreting pupil measurements in anesthetized patients, one have to know that even a pupil dilation in a dark environment does not occur as a result of disinhibiting by various midbrain centers.[420] EW cells are therefore allowed to fire at their rapid intrinsic, pacemaker-like firing rate. Furthermore, with the induction of general anesthesia, loss of consciousness is induced and thereby the pupil size decrease as EW cell inhibition decreases. In the literature this phenomenon is called as anesthetic-induced miosis. In was in the late 20th century researchers described a 10 minute stabilization period for this response to a mean pupil size of 1-3 mm within those anesthetized subjects.[421]

In the circumstances of a general anesthesia, noxious stimulation (laryngoscopy or skin incision) still can elicit pupil dilation as surgery reestablish inhibitory control of the EW cells. The peroperative pupil dilation can again be blocked by opioid administration. There are many proposals on how opioids exactly effect the pupil. [422-424422-424] The hypothesis that increased activity in the pupilloconstrictor nucleus by the administration of fentanyl, similar to the addition of ambient light, constricts the pupil of anesthetized patients can not be confirmed in repetitive studies.

During laparoscopy, installing a pneumoperitoneum may produce a pupil dilation, with no decreasing effect after opioid administration. Other examined the pupil during cardiopulmonary bypass, observing the same small dilation.[425] However, more research is necessary to distinguish all surgical and drug effects on the site of the pupil. Even the choice of a sedative drug has a potential influence on the pupil response. Although research has been done in small patient groups, a decrease in PLR amplitude is seen after volatile anesthetics or propofol. Moreover, ketamine and nitrous oxide decrease the PLR. PDR during general anesthesia is slow and relatively prolonged in contrast to the PLR. One speaks about 800 milliseconds latency in comparison to <300 milliseconds for PLR.[421] However, a few studies described a greater amplitude of PDR at high volatile concentrations and the authors suggesting an involvement of GABA chloride currents in generating PDR.[358,386,417,421,426-428] Contributing, opioids depress PRD in a dose-related fashion and interfere with GABA in the midbrain.[429]

Automated portable pupillometry

Measurement of the human eye was first referred to as “the windows to the soul” by a French poet in the 16th century. Yet, it lasted until the 20th century for the discovery of nociceptive influences on the pupil. There are two major stimulations for elicitation of pupillary reflexes: the pupillary light reflex (PLR) and the pupil dilation reflex (PDR). The first occurs when a light stimulus is presented to the eye, the second occurs after noxious stimulation. Different variables from those analyses include baseline pupil amplitude, maximum pupil size, latency, and duration of the reflex. Numerous studies have extracted information about the eye, with relevance for different specialities as neurosurgery, ophthalmology, pharmacology, intensive care, and anaesthesiology. Modern pupillometers use an infra-red camera for pupil visualization. By this evolution, pupil measurements are possible in a dark environment bypassing the influence of the consensual light response.

Despite many new insights and device adjustments in the past ten years, measurement of pupil reflexes remains challenging and result interpretation needs further research because pupil reactions are not fully understood. Therefore, up to now, physicians do not use the modern automated infra-red pupillometry on a routine basis.

Mechanism of action

We can divide two divisions of the autonomic nervous system that control pupil responses; the sympathetically innervated radial muscle of the iris and the parasympathetically innervated sphincter muscle (after Loewenfeld 1999)[430] (see Figure B3).

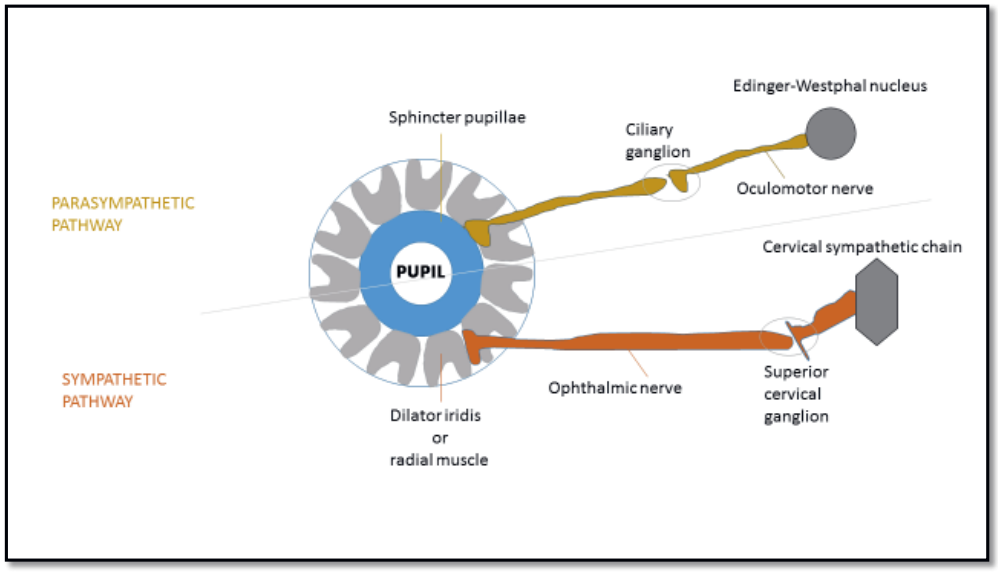


Figure B3. Overview of autonomic nervous system control of the pupil response.

In awake subjects, the PDR is sympathetically mediated transmitting signals via the cervical sympathetic chain up to the ophthalmic nerve (part of the trigeminal nerve) to the dilator iris. The neuromuscular synapse at the level of the iris is an α1-adrenergic junction. Stimulation by relevant agonists (phenylephrine, norepinephrine, ephedrine) administrated topically activate the radial muscle resulting in mydriasis. Previous research by Larson et al. revealed however no pupil dilation by circulating catecholamines during anesthesia.[417] Apparently, plasma levels aren't high enough to reach the threshold for dilation. An exception is the production of remarkably high levels of endogenous catecholamines by pheochromocytomas as investigated by Cryer in 1980.[431] Otherwise, when suppressing the cervical sympathetic chain by example a high epidural block or cervical sympathectomy, Horner's syndrome occurs (ptosis, miosis, anhydrosis). Moreover, the radial muscle is the weakest of the two muscles (in comparison with the sphincter muscle), meaning that when anisocoria appear by sympathetic deficit and pupil evaluation is made in ambient light levels, the deficit will be less obvious because of overruling pupil size by the stronger sphincter pupil muscle.[432]

On the other hand, in anesthetized patients, PDR is parasympathetically mediated. The sympathetic pathway is suppressed by the use of sedatives and indirectly a parasympathetic overbalance occurs. Further, the Edinger-Westphal nucleus have intrinsic pacemaker activity cells that are firing in the absence of synaptic input. Pupil dilation results passively as the sphincter relaxes when inhibitory neurons are thought to depress the nucleus.[433] Those inhibitory neurons play an important role in pupil response, as they are activated by nociception and blocked by opioids. Therefore, pupillometry can be used to detect noxious procedures in non-communicating patients in the OR or ICU as an alerting stimulus with sufficient intensity elicits a PDR. Moreover, the administration of analgesics,

which are mainly opioids, theoretically depress the reflex. Research is necessary to determine dose-response relations, pupil reflex alterations by different opioids and central-acting drugs.

Common preoperatively used sphincter pupillae antagonist are scopolamine and glycopyrolate (Figure B4). The first acts as a strong pupil constrictor with weak effects at the sinoatrial node, the latter is a strong drug at the sinoatrial node but has only weak effects on the pupil.[434] Opioids increase the activity of the Edinger-Westphal nucleus by disinhibition, stress decreases activity via inhibition resulting in mydriasis.

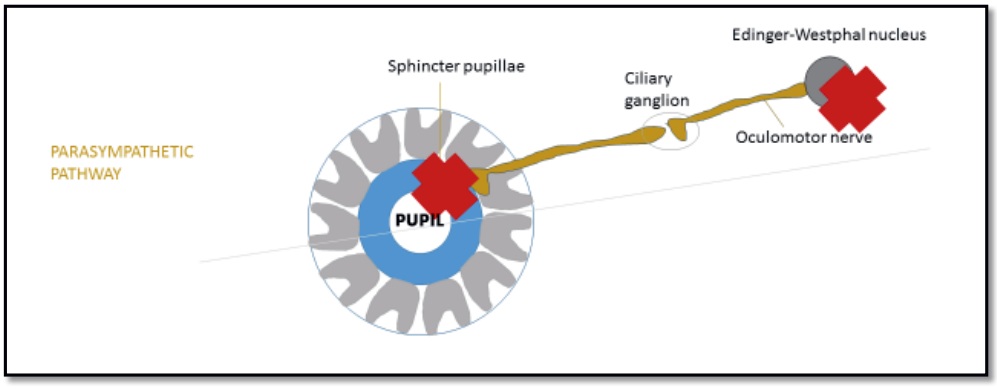


Figure B4. Pupil effects by parasympathetic pathway involvement.

Lesions of the cervical sympathetic chain induce Horner's syndrome resulting in miosis (see Figure B5). The same is true for high thoracic epidural analgesia. At the pupil site, the radial muscle activity augments with phenylephrine.

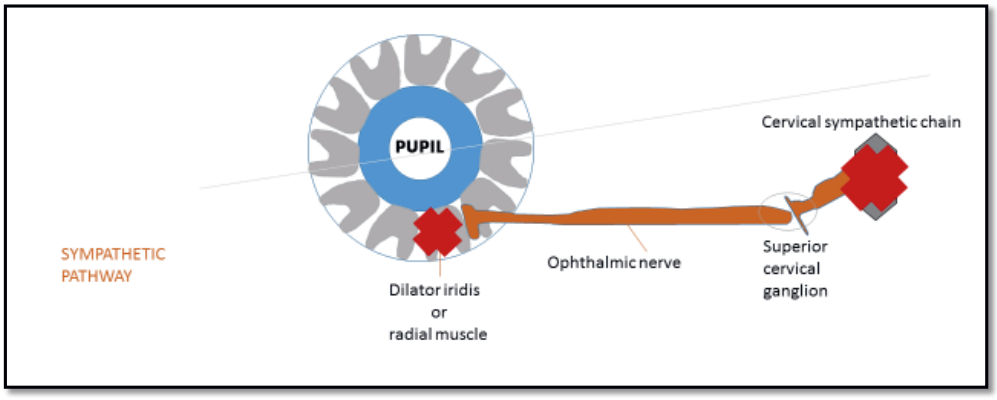


Figure B5. Pupil effects by sympathetic pathway involvement.

Pupillary light reflex versus pupillary dilation reflex

When using pupil reflexes, one has to consider two different responses. The PLR as a consequence of a flash of light offered to the eye and causing pupil diameter to decrease. Pupil characteristics as reflex amplitude and latency are easy to obtain in a few seconds. Presence of a normal PLR implies an intact optical and oculomotor cranial nerves. Although many clinicians from different specialities use the PLR for diverse reasons, up to now, not all involved neurotransmitters and reflex pathways are known. PLR is mainly used in awake subjects, by ethical considerations of noxious stimulation and a rapid onset. It was Loewenfeld and colleagues who were one of the first in 1958 to review neural pathways and transmitters in PDR generation.[435] One of the most logical reasons for this gap in knowledge may be the longer onset time of the PDR and there need for a high enough elicitation stimulus.

One has to take into account that each commercially available device has his own specifications and evaluation criteria, therefore pupil response has to be interpreted with caution. Furthermore, animal studies are not completely comparable with humans as regard pupil reflexes. Many mammalians have light-sensitive contractile elements within the iris muscles, making a full working brainstem unnecessary.

Pharmacodynamics of opioids and mechanisms of pupil alterations

Opioids act as agonists at stereospecific opioid receptors at presynaptic and postsynaptic sites in the central nervous system and peripherally. Opioids exert their major influence at the brainstem and spinal cord as a part of the central nervous system. Mu-opioid receptors are found in different areas of the nervous system. Presynaptic, they act on voltage-gated calcium channels by inhibition and therefore blocking neurotransmitter release. Postsynaptic, opioid administration results in blocking potassium channels causing a potassium influx, resulting in hyperpolarization and therefore decreasing impulse transmission. Moreover, the information transfer from nociceptor and the spinal cord to cortex by myelinated (fast transmission) A-δ – and non-myelinated (slow) C fibers is blocked. Larson and colleagues studied the latency of pupillary reflex dilation during general anesthesia. The researchers hypothesized that the reflex was generated by slowly conducted C nociceptive fibers and would therefore by significantly delayed if a distal dermatome was stimulated compared with a proximal dermatome. They found no difference between latencies of reflex dilation after the noxious stimulations and concluded that there is no evidence for selective C fiber activation that initiated PDR.[421]

The desired effect of opioid administration is caused by activation of central μ-receptors. In contrast to many undesired side effects as nausea and vomiting (by activation of the chemoreceptor trigger zone at the 4th ventricle), gastrointestinal constipation and sphincter spasms, pruritus or urine retention, which are the result of peripherally located receptor activation.

Opioids exert an excitatory action on the autonomic nerve system. The parasympathetic nervous system influences pupillary tone controlled by the Edinger-Westphal nucleus, oculomotor nerve and ganglion ciliary respectively. In the absence of opioid administration, various (not all specified) centers in the brain cause inhibition of the automatically firing (pacemaker) EW cells, resulting in an inhibiting of impulse transmission towards the oculomotor nerve. When administrating opioids, via disinhibiting, finally pupil constriction occurs. Tolerance to the miotic effect is not seen in patients on chronic opioid usage.

In clinically practice, infrared pupillometry is already used for nociceptive evaluation to assess the quality of performed local anesthesia with or without general anesthesia.[436,437] The PDR is a supraspinal parasympathetic reflex during general anesthesia. By local anesthetic techniques nerve blocks are performed in such way that transmission of noxious stimulation to the brain is stopped. Hence, the PDR on noxious stimulation remains intact in the presence of general anesthesia and administration of sympatholytic drugs. Blocking preganglionic sympathetic fibers during epidural does not block the PDR.[438]

Furthermore, opioids depress PDR during general anesthesia in a dose-dependent fashion and total blockade of PDR requires relatively large opioid dosages.[439] Moreover, as investigated in 2003 by Barvais and colleagues in healthy patients during propofol anesthesia, the decrease in pupil response to a noxious stimulation is a better measurement of progressive remifentanil increase than haemodynamic or BIS monitoring.[358]

Figure B6 shows the raw data obtained from the pupillometer while running the inbuilt stimulation protocol. The first part (Figure B6-1) illustrates the pupil response under general anesthesia *without* opioid administration. X-axis represent a timeline in seconds, Y-axis pupil dilation. Blue and red lines represent minimum and maximum pupil size. Pupil diameter is represented in mm by the green line. The purple lines define the beginning and end of the stimulation. The dark grey line determines when a stimulation was given. As baseline pupil diameter is measured, dilation percentages are showed as well (8 vs 56%). Figure B6-2 shows the pupil response in the same patient *after* administration of remifentanil using Minto's model for pharmacokinetics, 5 µg/l. One can observe the necessity of multiple, and higher stimulation intensity to dilate the pupil. Even after administration of the maximum stimulation impulse (i.e., 60mA), no dilation of 13% is accomplished (0 vs 0 vs 0 vs 1 vs 3 vs 7 vs 7 vs 7%).

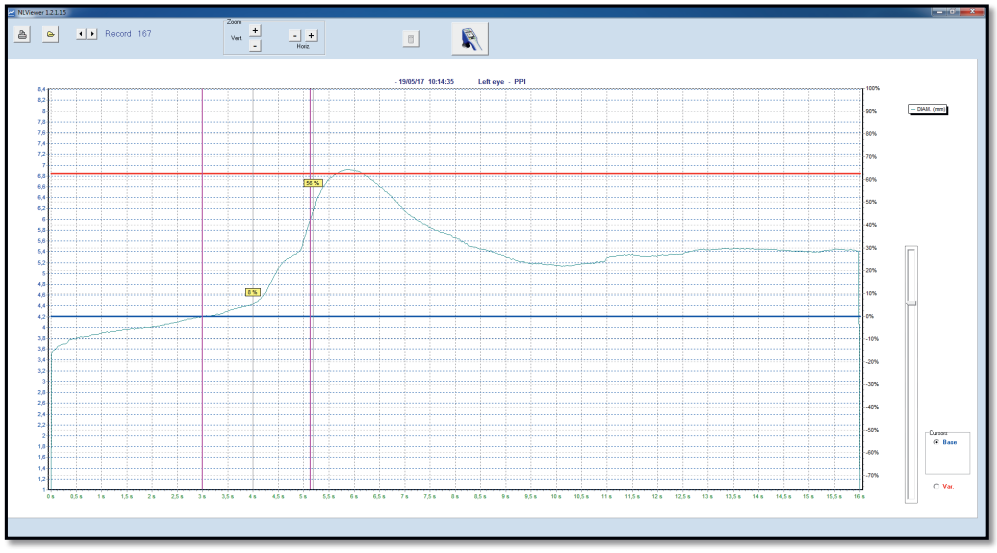


Figure B6-1. Screenshot from the pupillometry before opioid administration

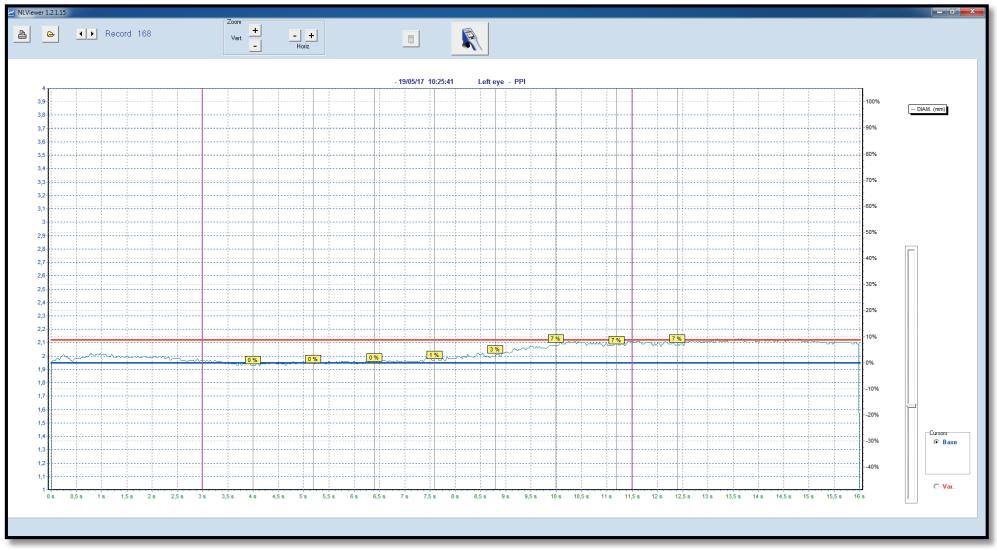


Figure B6-2. Screenshot from the pupillometry after opioid administration

Pupillary pain index: a novel pupillometric index

For pupil analysis, the commercially available, CE-marked, AlgiScan® (Figure B7) was used in the projects of this PhD-thesis. An advantage of this infrared pupillometry device is the ability to deliver an automated standardized noxious stimulation during pupil measurements. The pupillary pain index (PPI) is a novel pupillometric index, designed to assess intraoperative analgesia. This is an advantage when investigating the peroperative level of analgesia. Although results have to be interpreted by caution when translating analgesia level into pain sensation.

Figure B7. NeuroLight Algiscan® (IDMed, Marseille, France), distributed in Belgium by Draeger Medical.

IDMed has developed a PPI stimulation protocol, which not only assess pupil basic characteristics (baseline diameter, latency, variation) but calculated a PPI score (Figure B8). Therefore, the device uses an inbuilt algorithm based upon necessary stimulation intensity for pupil size enlargement. The more intense the potential noxious stimulation must be to accomplish a pupil dilation of 13%, the lower the PPI score. When there is an *overshooting* by pupil dilation above 20% during stimulation, the algorithm decides to increase the score by one point. By device algorithm convention, the cut off value of 13% dilation relative to the baseline pupil measurement to stop further increasing tetanic stimulation, has been incorporated to minimize the effect of a more noxious stimulation on a patients' vital parameters, with a still measureable PDR.

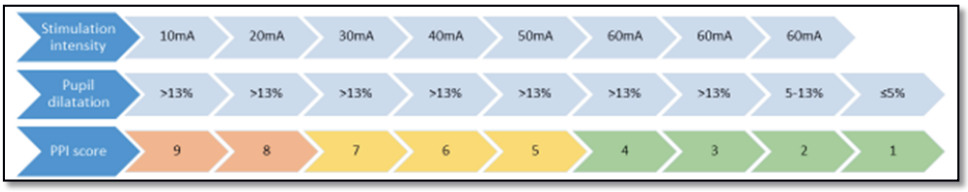


Figure B8. Pupillary Pain Index (PPI) stimulation protocol, generated automatic electric pattern with PPI score depending on necessary stimulation intensity. When pupil size exceeds 13% increase from baseline measurement the stimulation is stopped and the NeuroLight AlgiScan® calculates the PPI score, corresponding with a theoretical level of analgesia. Note: If the pupil dilatation is over 20% during the stimulation the PPI score is increased by one point.

For usage in daily practice, a portable easy to use device is of significant importance. PRD evaluation is different from other suggested nociceptive monitors by its short latency, independency of sympathetic influences and easy access (see Figure B9). Moreover, it is not blocked by the administration of β-adrenergic medication.

Figure B9. Electrodes (Ag-AgCl) at the skin innervated by the median nerve for nociceptive stimulation. The negative (black) electrode is placed distally from the positive (red) electrode.
Subject alignment for perioperative nociceptive testing; pupil analyses accompanied by sedation depth monitoring.

General considerations

There are some general considerations which the user of the pupillometry should take into account when using the device for pupil analysis.

Although in awake subjects, Watson and colleagues described **age** as a determining factor for pupil size. The size of the baseline (resting size) of the pupil decreases approximately 0.4mm for each decade of life after the age of 16.[440] Furthermore, age is a confounding factor as inhibition of PDR during skin incision in pre-pubertal children require a higher sevoflurane concentration compared with postpubertal subjects. Those results suggest that a relationship between the brain structure sensitivities may differ with brain maturation.[441]

Obviously, patients with a history of a **pupillary syndromes** (Adie pupil, Argyll Roberson pupil, senile miosis) are not good candidates for studying drug effects on pupil reflexes.

In contrast to modern infrared pupillometry devices, the older ones were more challenging for pupil measurements in **environmental darkness**. When the physician does not take those remarks into account, the direct and indirect (consensual) light responses disturb correct pupil information. Recently, most pupillometers are equipped with a rubber cup to place to the orbit for optimal dark measurement environment.[442] When interpreting pupil reflex results, one has to take into account that a full dark-adapted pupil requires approximately 6 minutes of total darkness, which is impractical for pupil reflex evaluation in daily practice.

The **effect of central acting and topical drugs** on the pupil reflex and size is mostly observed in awake subjects. Only a few investigated the effect on pupillometry preoperatively. Antiemetic's such as metoclopramide produces a small decrease in diameter and transiently depressed PDR whereas droperidol decrease pupil size only after ten minutes and depressed reflex dilation throughout the whole 40-minute study period. This supports the evidence that PDR after noxious stimulation is associated with the release of catecholamines at the level of the brainstem. As suspected the $5HT_3$ antagonist ondansetron revealed no effect on pupil size or PDR.[443]

muscle fibers. To find the lowest stimulation intensity for PDR elicitation without inducing tachycardia or blood pressure elevation remains challenging.

Even **temperature differences** may provide alterations in pupil reflexes. While mild hypothermia has no effect on PLR, hyperthermia dilates the pupil in anesthetized subjects.[448]

Neurological implications as brainstem lesions, alterations in cranial function by cardiac arrest, embolus, or stroke, or TBI can influence the pupil response as described above. Several authors describe the return of light reactive pupils as a valuable prognostic factor.[449-452]

Pupillometry in the postanesthesia ward can be used as a measure of pain, but only in controlled situations when confounding factors are well controlled. Moreover, it would be a mistake to conclude that pain dilates the pupil and opioids ablate pain, and therefore decrease dilation. We all observe patients who are in pain nonetheless with constricted pupils.[453] Although it provokes a variety of autonomic responses that are likely to be harmful, pain by definition is subjective. In conscious subjects, pain is thus best evaluated simply by asking, with visual analog scaler or numeric rating scale to guide therapy. However, Aissou et al. make the valid point that many patients in the immediate postoperative period have difficulty evaluating and/or communicating pain intensity.[454] In addition, some will relate pain scores that are inconsistent with their behavior. In response, they compared verbal pain scores with PDR in conscious communicative postoperative patients and found a relationship between the magnitude of PDR as a response to a controlled amount of pressure on the surgical wound and the patient his or her opioid requirements. Furthermore, the PDR magnitude was related to the patient's own verbal assessment.[454] In contrast, the population who will benefit the most from optimizing pain treatment or not able to communicate, as an effect of the peroperative used analgosedatives in the postanesthesia care unit. Validating this method in a targeted population is necessary.

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Benjamin Franklin

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Ralph Waldo Emerson

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