Influence of morphine and Naloxone on pain modulation in rheumatoid arthritis, chronic fatigue syndrome/fibromyalgia, and controls : a double-blind, randomized, placebo-controlled, cross-over study

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Influence of morphine and naloxone on pain modulation in Rheumatoid Arthritis, Chronic Fatigue Syndrome/Fibromyalgia and controls: a double blind randomized placebo-controlled cross-over study

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Abstract: Background

Impaired pain inhibitory and enhanced pain facilitatory mechanisms are repeatedly reported in patients with central sensitization pain. However, the exact effects of frequently prescribed opioids on central pain modulation are still unknown.

Methods

A randomized, double-blind, placebo-controlled cross-over trial was carried out. Ten CFS/FM patients, 11 RA patients and 20 controls were randomly allocated to the experimental (10 mg morphine or 0.2 mg/ml Naloxone) and placebo (2 ml Aqua) group. Pressure Pain Thresholds (PPTs) and temporal summation at the Trapezius and Quadriceps were assessed by algometry. Conditioned Pain Modulation (CPM) efficacy and Deep Tissue Pain pressure were assessed by adding ischemic occlusion at the opposite upper arm.

Results

Deep Tissue Pain pressure was lower and temporal summation higher in CFS/FM (p=0.002 respectively p=0.010) and RA patients (p=0.011 respectively p=0.047) compared to controls at baseline. Morphine had only a positive effect on PPTs in both patient groups (p time =0.034). Accordingly, PPTs increased after placebo, and no effects on the other pain parameters were objectified. There were no significant effects of naloxone nor nocebo on PPT, Deep Tissue Pain, temporal summation or CPM in the control group.

Conclusions

This study revealed anti-hyperalgesia effects of morphine in CFS/FM and RA patients. Nevertheless, these effects were comparable to placebo. Besides, neither morphine nor naloxone influenced Deep Tissue Pain, temporal summation or CPM. Therefore, these results suggest that the opioid system is not dominant in (enhanced) bottom-up sensitization (temporal summation) or (impaired) endogenous pain inhibition (CPM) in patients with CFS/FM or RA.

Introduction

Chronic pain is a highly disabling symptom affecting the quality of life in various medical conditions such as chronic fatigue syndrome (CFS)[1], fibromyalgia (FM)[2] and rheumatoid arthritis (RA)[3]. The sensitivity for pain in CFS and FM depends largely on the function of central pain mechanisms[4].

Changes in central pain mechanisms commonly lead to widespread hypersensitivity of the somatosensory system[5]. These malfunctions can be divided into: firstly, deficient descending inhibitory pathways, e.g. serotonin-norepinephrine or opioidergic[6, 7] neurotransmission; secondly, enhanced descending facilitator pathways; and thirdly, central sensitization at spinal cord level, which depends upon the release of glutamate and substance P. Excessive glutamate acts with the N-methyl-D-aspartate (NMDA) receptor, which in turn activates Ca^{2+} influx, resulting in extension of the pain response[6].

In a subgroup of RA patients altered pain modulation is assumed, as this subgroup may also present widespread pain[8, 9] wherein only a weak correlation between pain sensitivity and inflammation is reported[10]. Moreover, the review of Sarzi-Puttini et al.[11] stated that approximately 8% of the patients with RA may fulfill the criteria of FM.

The functioning of descending nociceptive modulatory pathways is currently indirectly assessed in research with the Conditioned Pain Modulation (CPM) paradigm also known as the pain-inhibits-pain procedure. The involvement of opioidergic mechanisms in CPM has been extensively reported in animals[12, 13] and also the contribution of opioids in high-order brain regions during CPM in healthy participants has been observed[14].

Another frequently used paradigm to assess the efficacy of endogenous nociceptive inhibition as well as bottom-up excitability at spinal cord level is the temporal summation procedure. This procedure measures the degree of wind-up of pain, which seems to be enhanced in patients with FM[12], CFS patients with comorbid FM[15] and RA[16]. It is believed that temporal summation is dampened by opioids in healthy people[17] and patients with FM[18].

In conclusion, CPM and temporal summation or wind-up of nociceptive stimuli are the two most frequently used models to study central sensitization. Whilst it is clear that patients with central sensitization display impaired pain inhibitory, increased wind-up and enhanced pain facilitatory pathways[19, 20], the precise mechanisms still remain to be determined. Otherwise, attempts to improve pain inhibition in clinical practice stay speculative. Peripheral acting pharmacological agents will not necessarily decrease the central sensitization pain[4]. Thus, continuing studies of centrally acting drugs in patients with central sensitization are warranted. To prove that a treatment is effective, it is necessary to include a placebo trial. Up until today only a few randomized placebo-controlled trails have investigated the effects of exogenous opioids on CPM[21] and temporal summation[22] in chronic pain patients.

The chronic pain population is highly diverse and the effects of pain modulation differs between sufferers. Whilst a body of literature on chronic pain is currently available, few of the studies have made direct comparisons between different chronic pain conditions. The comparison of various chronic pain disorders is crucial for understanding the differences and similarities of the nature of chronic pain, especially with respect to providing the correct treatment in each case.

It is essential to determine whether impaired pain pathways in patients with chronic pain is due to malfunctioning of opioid-mediated pain inhibition. In the present study, a chronic pain condition with a joint pathology (RA) was compared with chronic pain patients without peripheral abnormalities but with clear evidence for central sensitization (CFS/FM). This study compared the acute effects of morphine and a placebo on the pressure pain threshold (PPT), Deep Tissue Pain, temporal summation and CPM in patients with CFS with comorbid FM and RA.

Healthy volunteers underwent the same procedure, but with naloxone instead of morphine. It has been shown that naloxone hydrochloride, a non-selective opioid receptor antagonist, inhibits the endogenous pain inhibitory systems activated by the CPM model[23]. This implies that CPM systems are opioid-mediated[23]. The hypothesis was that there are significant improvements in PPTs, Deep Tissue Pain, temporal summation and CPM-effect after morphine compared to placebo in patients with FM and RA. Conversely, the administration of naloxone was expected to provoke a negative effect on all four parameters in healthy controls and this effect was predicted to be significantly different from nocebo.

Methods

In this study a randomized, double blind, 2-sequence, 2-period, 2-treatment crossover design was used. The study took place at the Research Unit of the Antwerp University Hospital (Belgium) and was approved by the ethical committee of the University Hospital of Antwerp and the Federal Agency for Medicines and Health Products and is registered by Clinical-Trials.gov (EUDRA CT 2010-020498-17).

Subjects

Two chronic pain populations were included in the present study: RA patients and patients fulfilling the criteria for both CFS and primary FM. Healthy pain-free sedentary subjects were included as controls. Only females were recruited and all participants were aged between 18 and 65 years.

CFS/FM patients met the diagnostic criteria for FM and CFS as defined by the 2010 American College of Rheumatology (ACR) criteria[24] and the Centre of Disease Control criteria[25] respectively, implying no other medical illnesses could explain their pain and fatigue conditions. RA patients were diagnosed by the department of Rheumatology of the Antwerp University Hospital, following the 2010 ACR/EULAR criteria for RA[26].

Healthy control subjects who did not display any pain complaints and having a sedentary lifestyle were included. Sedentary lifestyle was defined as having a sedentary job and performing less than 3 hours of moderate physical activity a week. Moderate physical activity was defined as an activity demanding at least the threefold of the energy spent passively[27]. Pregnant females or females who gave birth less than a year ago / up to one year postnatal females were not included. Participants were not permitted to undertake physical exertion and to refrain from consuming alcohol, caffeine or nicotine on the day of the experiment. A steady state treatment for at least 4 weeks prior to the test was demanded. On the day of the experiment a complete medication stop (except NSAID's and acetaminophen for ethical reasons) was requested. Patients taking anti-IL6, MAO-inhibitors, triptans, opioids and rifampicin were excluded.

An increase in 20% of the endogenous pain inhibition in case of opioid receptor stimulation and a reduction of 20% in pain inhibition in case of opioid receptor blockage were anticipated. Subsequently, a priori sample size estimations for cross-over trial indicated that 13 patients were needed to detect a difference in temporal summation of 3,60 ∑temporal summation, assuming a within subject standard deviation of 2,921 ∑temporal summation, and corresponding with a power of 0.8, a Cohens' dz effect size of 0.87 and significance level of 5%. These calculations were based on a study of temporal summation in FM-patients[28], a previous in-house study on spatial summation[29] and unpublished data of temporal summation in FM-patients. Calculations were obtained in G*Power 3.1.9.2[30]. This final sample size was set at 19 to adjust for a drop-out rate of 30%.

Procedure

Prior to the experiment participants were provided with an information leaflet and requested to sign an informed consent form. The flow chart of the double-blind randomized controlled trial (RCT) with cross-over design is detailed in figure 1. The current study examined whether opioids alter PPT, Deep Tissue Pain, temporal summation and CPM by injecting subcutaneous morphine or naloxone to respectively patients and controls versus a placebo injection. A study nurse randomly executed the order of the different allocations, for which the simple randomization protocol procedure was used on the first day of assessment. Both evaluator and participant were blinded for substance.

The pain protocol consisted of PPT measurements and the manifestation of temporal summation with and without a conditioning stimulus (CPM). Intersession-period was at least one week.

Morphine, Naloxone and Placebo, Nocebo

All three variables; morphine (10 mg morphine in 0.5 ml + 1,5 ml sodium chloride 0,9%), naloxone (0.2 mg/ml Naloxone diluted to 2ml) and placebo respectively nocebo (2 ml Aqua) were injected intramuscular in to the deltoid muscle directly after the baseline pain measurements. Injections were followed by a thirty minute rest period in supine position under medical supervision. During this period participants filled out questionnaires and heart rate and blood pressure were monitored. Because maximum analgesic response after intramuscular morphine injection occurs after thirty to sixty minutes, a rest period of thirty minutes was chosen. To eliminate carry-over effects, a one-week wash-out period was respected between sessions.

Pain Measurement

First, PPT locations were marked at right-side M. Trapezius (middle of C7 and acromion) and M. Quadriceps rectus femoris (middle SIAI and upper border patella).

Secondly, PPT was measured twice by Fisher manual algometry (Force Dial model FDK 5 and 20, Wagner instruments, Greenwich) at the M. Trapezius with a 30 seconds interval. After 2 minutes, temporal summation was evaluated by pressing the previously defined average PPT pressure ten times, asking the participants to rate first, fifth and tenth pulse intuitively on a verbal numeric rating scale (VNRS) regarding unpleasantness (0= no pain to 10= worst possible pain). In the same manner PPT and temporal summation were executed for the M. Quadriceps rectus femoris.

Thirdly, Deep Tissue Pain was assessed by an occlusion cuff at the left upper arm, inflated to an individualized unpleasant level and after 30 seconds the cuff was inflated or deflated to a VNRS-score of 3/10 (Deep Tissue Pain pressure VNRS-3).

Lastly, repeating the temporal summation assessment associated with a conditioning stimulus assessed CPM. The conditioning stimulus was the Deep Tissue Pain assessment, subsequently this occlusion level at VNRS-3 was held during temporal summation assessment of the M. Trapezius directly followed by temporal summation of the M. Quadriceps. The effectiveness of this CPM method has been proved by several studies[31, 32]. Additionally, the test has a good reliability[33] and all

tests were performed by the same evaluator not permitted to have knowledge of the allocation to the respective participants. In the healthy population a conditioning stimulus is able to reduce the temporal summation[32, 34], while equal or increased temporal summation are revealed during conditioning stimulation in patients with central sensitization[32].

Temporal summation was calculated as the sum of the VNRS-scores of the first, fifth and tenth pulse. For CPM evaluation VNRS-score of the tenth pulse of the temporal summation assessment with cuff occlusion was subtracted from VNRS-score of the tenth pulse of temporal summation without cuff occlusion.

Statistical Analysis

All data was analyzed using the IBM Statistical Package for Social Sciences for Windows version 23.0 (IBM Corp., Armonk, N.Y., USA). Normality of data distribution was assessed with the Shapiro-Wilk test and additionally subjected to a qualitative quality control. Descriptives are presented as means with standard deviations.

Groups were compared for age with a Mann Whitney U test (2 group comparison) and a Kruskal Wallis test (3 groups comparison), because of the non-parametric distribution of age in the RA and control group. Baseline PPTs, Deep Tissue Pain and CPM were compared between groups with a Kruskal-Wallis test and additionally with a Mann-Whitney U-tests. In-between groups comparison of baseline temporal summation was completed with a one-way ANOVA and Tukey HSD post hoc analysis.

The effect of morphine and placebo on PPTs, Deep Tissue Pain, temporal summation and CPM were compared between the CFS group and RA group with repeated measures ANOVAS. The effect of naloxone and nocebo in controls was likewise measured with repeated measures ANOVAS. Correspondingly, changes in PPTs, Deep Tissue Pain, temporal summation and CPM between placebo and medication (morphine/naloxone) within groups were evaluated with repeated measures ANOVAS.

Effect sizes were calculated with (partial) eta-squared for each intervention and subsequently Cohens'd for pairwise comparisons at baseline. Eta-squared effect sizes can be interpret as 0.02 representing small effects (2% of the variance in the dependent variable is attributable to the model), 0.10 representing medium effects and 0.25 representing large effects[35]. Cohens'd represents

small (0.20 = groups' means differ 0.2 standard deviations), medium (0.50), large (0.80) up to huge (2.0) effects[35]. Significance level was set at 0.05 for all tests.

Results

Forty-one volunteers participated in the study (10 CFS/FM patients, 11 RA patients and 20 healthy controls), all women between 22 and 65 years old (mean age 39,8 ± 13,2). Six volunteers did not complete the whole trial. Two patients had an allergic reaction to the morphine (1 CFS/FM patient, 1 RA patient), one CFS/FM patient became sick after the first day and withdrew, one control showed abnormalities on the electrocardiogram in rest and during submaximal exercise and was therefore referred to a cardiologist and excluded for the second appointment and two volunteers (1 CFS/FM patient and 1 RA patient) withdrew after the first day without giving a reason. A schematic overview is shown in the consort flow diagram in figure 2.

All available data was used in the analyses. Sensitivity analyses of the results with the last observation carried forward procedure did not reveal any significant differences.

1. Comparison of baseline characteristics

There was no significant difference for PPT between CFS/FM patients, RA patients and controls (p=0.076 ES=0.129). Although Deep Tissue Pain pressure at a VNRS-score of 3 (the proposed intensity of the conditioning stimulus defined by Cathcart et al.[33]) was significantly lower in the CFS/FM (p=0.002 ES=1.421) and RA group (p=0.011 ES=1.019) compared to the control group.

A higher temporal summation score was observed in the CFS/FM (p=0.010 ES=1.112) and the RA group (p=0.047 ES=1.123) compared to the control group.

For CPM the three groups did not show any significant differences at baseline (p=0.096 ES=0.117), although CPM was almost nearly absent in patients with CFS/FM.

Mean baseline results for PPT, Deep Tissue Pain at VNRS-score 3, temporal summation and CPM for the three groups is shown in figure 3.

2. Influence of morphine/naloxone and placebo/nocebo on pain

Means and standard deviations are presented in table 1.

a. Effect of morphine on pain scores (patient groups)

Morphine had a significant positive effect on the PPT in both patient groups (p time=0.034 ES=0.267). The increase was not significantly influenced by diagnosis (p time*diagnosis=0.791 ES=0.005), which is shown in the graphs in figure 4a. No difference in Deep Tissue Pain pressure at VNRS-score 3 after morphine was observed in both patient groups (p time=0.338 ES=0.061).

The effect of morphine on temporal summation was significantly different between the two patient groups (p time*group=0.034 ES=0.266). This is shown in figure 4c. In advance anticipated decreases of 20% were not reached.

Morphine had no effect on CPM (p time=0.934 ES=0.000). In addition, no significant interaction of diagnosis could be determined (p diagnosis*time=0.189 ES=0.112).

b. Effect of placebo on pain scores (patient groups)

The PPT in both patient groups slightly increased after placebo (p time=0.015 ES=0.302). No significant change over time in Deep Tissue Pain pressure was found (p time=0.682 ES=0.010). Accordingly, temporal summation did not change in response to placebo administration (p time=0.583 ES=0.018) and there was no difference between the patient groups (p diagnosis*time=0.071 ES=0.179). For the CPM-effect, no significant effects of placebo could be detected (p time=0.165 ES=0.110, p diagnosis*time=0.621 ES=0.015).

c. Comparison Morphine versus Placebo condition

PPTs increased over time after morphine as well as placebo (PPT p time=0.017 ES=0.343 in CFS and PPT p time=0.022 ES=0.260 in RA), although Deep Tissue Pain remained the same. These effects were not influenced by the type of substance (p time*substance varying between 0.499 and 0.993).

With regard to temporal summation only a significant increase in temporal summation after administrations was found in RA patients (p time=0.036 ES=0.222). Again the type of substance did not have any influence (p time*substance varying between 0.545 and 0.751).

The CPM-effect remained quite stable in both patient groups after both substances. No significant time or time*substance effects were found, as reported in Table 1.

d. Effect naloxone and nocebo on pain scores (healthy controls)

There was no significant effect from neither naloxone nor nocebo on PPT (p=0.890 ES=0.001 respectively p=0.896 ES=0.001), Deep Tissue Pain at VNRS-score 3 (p=0.331 ES=0.053 respectively p=0.119 ES=0.123), temporal summation (p=0.222 ES=0.082 respectively p=0.585 ES=0.016) and CPM (p=0.575 ES=0.018 respectively p=0.184 ES=0.091). Neither could a significant difference be demonstrated between the effect of naloxone nor nocebo on PPT (p time*substance =0.993 ES=0.000), Deep Tissue at VNRS-score 3 (p time*substance =0.067 ES=0.088), temporal summation (p time*substance =0.182 ES=0.048) or CPM (p time*substance =0.180 ES=0.048) over time.

Discussion

This study showed significantly lower Deep Tissue Pain pressure thresholds and considerably higher temporal summation in CFS/FM and RA patients compared to healthy controls, suggestive for central sensitization in both patient groups. Although significantly lower PPTs as well as CPM were also expected, this was not observed in this study. These results suggest that a subgroup of RA patients may display signs of central sensitization. Moreover, the malfunctioning pain modulation of this subgroup is probably attributable to enhanced bottom up excitability rather than to failing top down mechanisms. The administration of morphine and placebo in the patient groups induced a positive effect on the PPTs. Additionally, a discrepancy in the effect of morphine on the temporal summation was found between CFS/FM and RA patients. Neither morphine nor placebo had an impact on Deep Tissue Pain pressure or CPM. An unforeseen aspect was that naloxone did not significantly affect any of the parameters in the healthy controls.

Baseline comparison

The low Deep Tissue Pain pressure at VNRS-3 in both CFS/FM and RA, and high temporal summation in both patient groups is in accordance with the systematic review of Lee et al.[6] about the role of the central nervous system in the chronic pain of RA and FM patients. Therefore, central sensitization is presumable in a subgroup of RA patients, as assumed in the reviews of Meeus et al.[9] and Sarzi-Puttini et al[11]. The enhanced temporal summation in the CFS/FM group is in accordance with earlier studies[15, 36].

This study did not reveal a significant difference in CPM between groups. However, inferior CPM in CFS/FM had been described in several earlier studies[19, 37]. The hypersensitivity (displayed by higher temporal summation) and the lack of other signs of central sensitization in RA, underlines the hypothesis that the central sensitization possibly present in a subgroup of RA is peripherally driven, as increased temporal summation reflects increased bottom-up excitability. These peripherally induced changes of the central nervous system are similarly reported in patients with osteoarthritis[38].

It is possible that the small sample sizes of the two patient groups accounts for some non-significant results that are found. Larger sample sizes would be needed to confirm or reject this hypothesis. However, these results suggest two different types of dysfunctional pain mechanisms in terms of peripherally driven central sensitization in a subgroup of RA versus impaired pain modulation in CFS/FM.

Morphine and Naloxone

Morphine only had a beneficial effect on PPTs. These results may raise the suggestion that morphine acts in the first phase as an antihyperalgesic drug and possibly has a secondary effect on descending pain inhibition. The activation of descending inhibition via OFF cells in the rostral ventromedial medulla[4, 21] and the release of noradrenaline in the spinal cord[21] requires more time to develop as well as further periods of treatment rather than one injection[39]. Nonetheless, this notion requires further exploration. Another possibility is that opioids act upon the spine rather than supraspinal level as assumed in the study of Suzan et al.[17], based upon the fact that no effect was found of oxycodone, a synthetic opioid, in CPM in healthy participants. However, this latter study[17] did reveal a significant reduction of temporal summation from oxycodone. In contrast, the study of Arendt-Nielsen et al.[40] reported potentiation of CPM by buprenorphine and fentanyl compared to placebo with no significant difference between placebo and the buprenorphine and fentanyl treatment on pressure pain tolerance threshold in healthy volunteers. Since fentanyl is also a strong μ-opioid

agonist[41] and buprenorphine is an agonist as well as an antagonist with μ, δ and κ- opioid receptor affinity[42], the application of the drugs (transdermal patches with wash out period 10 days[40], versus acute oral administration[17] and injection in our study) had an influential effect next to the receptor affinity and the methodological differences in pain assessment. Also oxycodone and morphine indicate partial interaction with a different population of opioid receptors[43]. Based upon the study of Olesen et al.[43] different opioid derivates have different effects on experimental pain measures, this is because of subtle differences in analgesic potencies (eg. interactions with different opioid receptors). Furthermore, the study of Harris et al.[7] displayed a reduction of supraspinal μ-opioid binding potential in FM-patients. In line with this, research for the μ-opioid binding potential at spinal level in central sensitization patients is warranted. Besides, studies examining pain processing by administrating κ- and δ-opioid agonists are currently lacking. Given the differences in methodology (pain measures, administration, etc.) and given the differences between different opioids, it is not yet possible to draw any conclusion concerning opioid involvement in specific aspects of central pain processing.

The systematic review of Werner et al.[44] investigated the effect of opioid antagonism on experimental pain models and this extensive review concluded that naloxone does not have a significant influence on experimental pain. This is in accordance with the results of this investigation that naloxone did not affect any of the pain parameters in the healthy participants, which gives indications that μ-opioid receptors are not primarily involved in temporal summation and CPM. Other non-opioid mediated mechanisms are in all probability involved in mainly CPM. For example, two studies[31, 45] reported improved CPM by reinforcing serotonergic pathways, which is in accordance with the animal study of Chitour et al.[46]

Placebo and Nocebo

No significant differences between placebo and nocebo effect were observed as compared to morphine and naloxone on any of the pain parameters. This is partially in accordance with the results of Suzan et al.[17]. Although this study found a reduction in temporal summation after oxycodone but not after a placebo, in healthy participants. This reinforces the indications for opioid mediated placebo analgesia by activating the top down pathways[47] in at least CPM assessment. However, the present study only revealed anti-hyperalgesia effects, so the μ-opioid system is unlikely to be dominant in either bottom-up or top-down pathways.

In their systematic review Hermans et al.[48] reported a positive correlation between expectations and CPM effect. However, even though placebo analgesia and the hypoalgesic expectancy of CPM effect both presume pain relief, the recent study of France et al.[49] noted a difference between placebo analgesia and hypoalgesic expectancy effects of CPM. Only an association between expectancy and CPM-effect was found in the group that reported hypoalgesic expectancies and not in the groups that previously reported no change or pain increase expectancies. These hypoalgesic expectancies were neither mediated by naloxone nor morphine. This indicates a probability that the same opioid pathways are not involved, and CPM expectancies are possibly mediated by other kinds of analgesia than placebo analgesia. Hence, the present study did not take CPM expectancy into account, which could have influenced the results. It is recommended to include this CPM expectancy factor also in placebo studies in future research.

Clinical implications

Several studies[14, 17, 21, 22, 39, 40] have investigated the effect of opioids on pain processing. Currently no consensus exists, but as earlier mentioned, indications point in the direction of more μ-opioidergic involvement at spinal level. It is important to note that opioids-induced sensitivity including decreased pain thresholds, enhanced temporal summation and reduced CPM was reported in

chronic patients under chronic opioid treatment[50]. Therefore, the involvement of serotonergic pathways in descending tracts and the effects of serotonin-norepinephrine reuptake inhibitors (SNRIs) in central sensitization patients are of special interest. SNRIs show significant improvements in pain thresholds in FM patients[51, 52]. Currently, one study[45] investigated the effect on descending inhibition in FM and the results are promising since an increased CPM-effect was observed. It is not known whether other studies have examined the effect of SNRIs on pain in RA. Because increased glutamate and substance-P are important factors in the occurrence of central sensitization, treatment options inhibiting these neurotransmitters, for example pregabalin, could be a possibility. Especially since the central sensitization in RA consists of predominantly hypersensitivity and enhanced temporal summation, the inhibitory effect of $A_2\delta$ ligands on neurotransmitters including glutamate and substance-P seems colorable. However, the results of a systematic review[53] about the effect of pregabalin on pain in FM patients were moderate. Currently, no studies have yet investigated this treatment in RA.

Chronic pain can be approached as a continuum with on the one hand a purely peripherally driven painful condition and on the other hand total central sensitization[54]. A long duration of (neuropathic) pain may result in long lasting structural changes in the central sensitization process and thence a further point in this continuum. No drug will solely help when patients are approaching total central sensitization. Treatment of these latter patients requires an individualized multidisciplinary approach that takes into account the multifactorial aspects of the pain as well as the multiple pathways involved. This implies that treatment of central sensitization may necessitate a combination of different acting pharmacological and non-pharmacological treatments[6, 54] together with other therapies targeting comorbid symptoms such as pain education[55].

Limitations and suggestions

The sample size of the control group was sufficient, as previously determined in an a priori analysis. Nonetheless the patient samples were too small because of the recruitment difficulties due to the perceptions about morphine and the strict inclusion criteria regarding medication intake. This is probably why several results show a trend but with no significant results. Nevertheless, caution is needed when interpreting the results. Still, the very strict inclusion criteria strengthened the methodological quality by reducing the influence of confounders.

Intramuscular morphine has a half-life of 3 hours and Baftiu et al.[56] previously reported a duration of 4 hours analgesia induced by intramuscular morphine. Hence, a one-week wash-out period may well be appropriate to eliminate carry-over effects.

Next to the previously mentioned age and CPM expectancies, other personal factors could possibly be influencing pain assessment, for example attention and menstrual cycle phase in CPM[48]. These personal factors should be taken into account in future research. Additionally, the stage in the earlier explained chronic pain continuum may affect the reversibility. Therefore, it could be considered an important factor to take into account in pharmacological pain assessment.

Conclusion

This study revealed lower Deep Tissue Pain thresholds and increased temporal summation in CFS/FM as well as RA patients. The effect of morphine in central sensitization patients appears limited and could have more effect on a peripheral level. Nevertheless, the morphine effect on experimental pain measures was comparable to the effect of placebo. Finally, naloxone did not significantly affect nociceptive modulation in the healthy participants. These results suggest that temporal summation and conditioned pain modulation are not primarily mediated by opioid mechanisms.

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Legends

Table 1.

(Sub.: type of substance; T: Time-effect; I: Interaction-effect; * significance p<0.05)

Figure 1.

(PPT: Pressure Pain Threshold; TS: Temporal Summation; CPM: Conditioned Pain Modulation)

Figure 2.

No legend

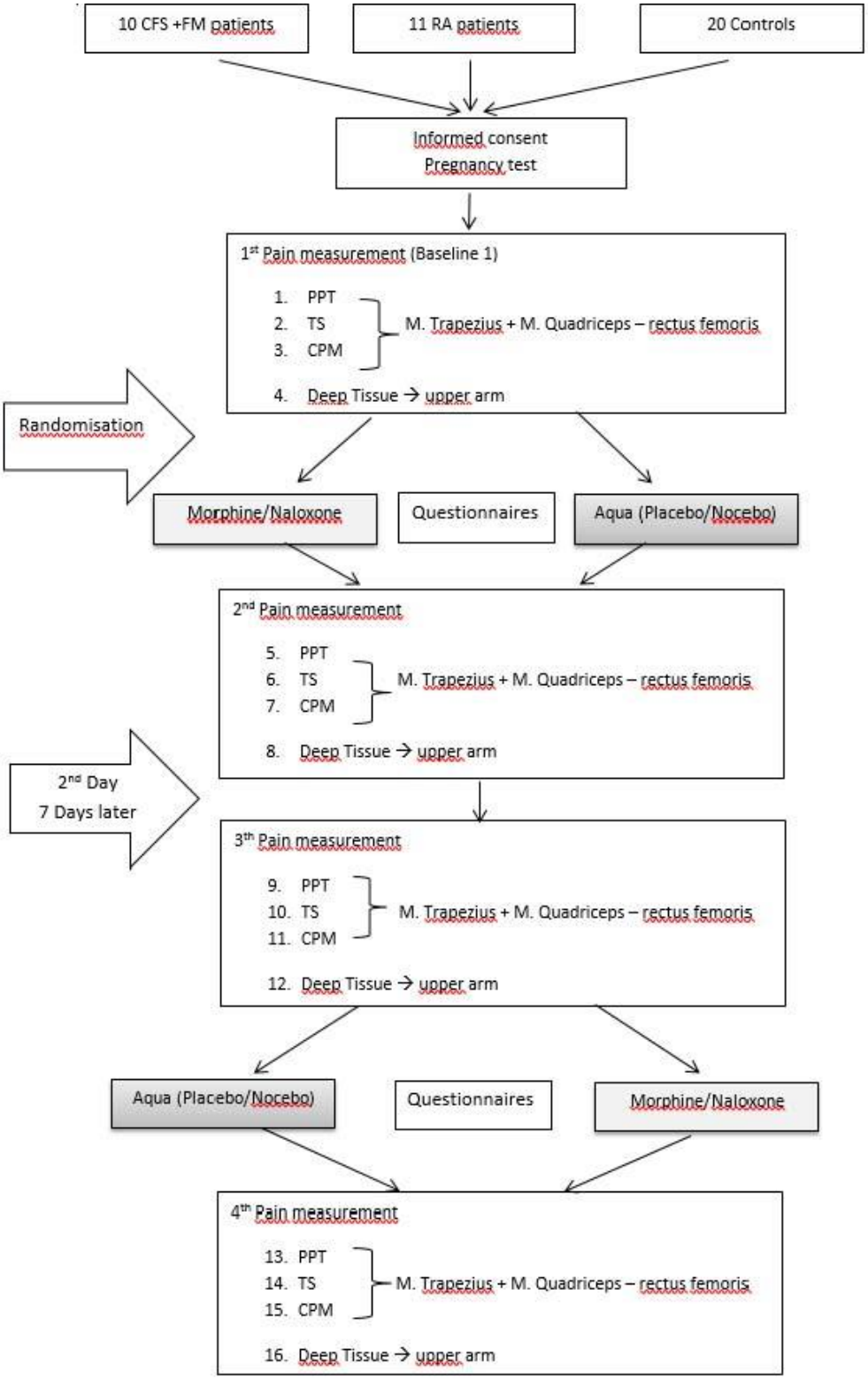
Figure 3.

PPT: Pressure Pain Threshold; TS: Temporal Summation; CPM: Conditioned Pain Modulation; Δ VNRS; delta verbal numeric rating scale; * p<0.05; **p<0.01

Figure 4.

= CFS = RA *: p time<0.05 †: p diagnosis*time <0.05

Group		**Pressure Pain Threshold**				**Deep Tissue Pain**				**Temporal Summation**				**Conditioned Pain Modulation**			
	Sub.	Mean ± SD		P-Value T: Time I:Sub.*time	Effect size Partial eta2	Mean ± SD		P-Value T: Time I:Sub.*time	Effect size Partial eta2	Mean ± SD		P-Value T: Time I:Sub.*time	Effect size Partial eta2	Mean ± SD		P-Value T: Time I:Sub.*time	Effect size Partial eta2
		Pre	Post			Pre	Post			Pre	Post			Pre	Post		
CFS/FM	Morphine (n=8)	2.94 ± 1.66	3.47 ± 1.60	**T:.017*** I:.499	T:.343 I:.033	57.50 ± 39.91	66.25 ± 46.89	T:.367 I:.556	T:.058 I:.025	17.34 ± 5.18	15.69 ± 4.81	T:.064 I:.545	T:.224 I:.027	0.00 ± 0.71	0.34 ± 0.68	T:.800 I:.116	T:.005 I:.167
	Placebo (n=8)	4.58 ± 1.44	5.00 ± 1.78			71.25 ± 36.82	73.13 ± 23.14			16.16 ± 5.09	15.28 ± 5.54			0.22 ± 0.62	-0.25 ± 0.69		
RA	Morphine (n=9)	5.43 ± 2.09	5.45 ± 2.09	**T:.022*** I:.790	T:.260 I:.004	101.11 ± 48.85	110.00 ± 65.38	T:.518 I:.993	T:.024 I:.000	14.53 ± 3.60	15.72 ± 4.62	**T:.036*** I:.751	T:.222 I:.006	0.67 ± 0.90	0.28 ± 0.57	T:.240 I:.754	T:.076 I:.006
	Placebo (n=11)	3.49 ± 1.38	3.80 ± 1.53			111.36 ± 60.58	120.00 ± 89.44			12.36 ± 3.94	13.95 ± 5.80			1.05 ± 0.83	0.82 ± 1.08		
Controls	Naloxone (n=19)	4.28 ± 1.39	4.79 ± 1.60	T:.850 I:.993	T.001 I:.000	189.47 ± 64.50	183.68 ± 67.92	T:.537 I:.067	T:.010 I:.088	8.97 ± 3.26	9.72 ± 4.64	T:.485 I:.182	T:.013 I:.048	0.63 ± 0.50	0.72 ± 0.63	T:.593 I:.180	T:.008 I:.048
	Nocebo (n=20)	5.34 ± 2.13	5.36 ± 1.72			174.00 ± 83.44	185.50 ± 77.56			9.78 ± 4.45	9.54 ± 4.48			1.08 ± 0.84	0.86 ± 0.90		



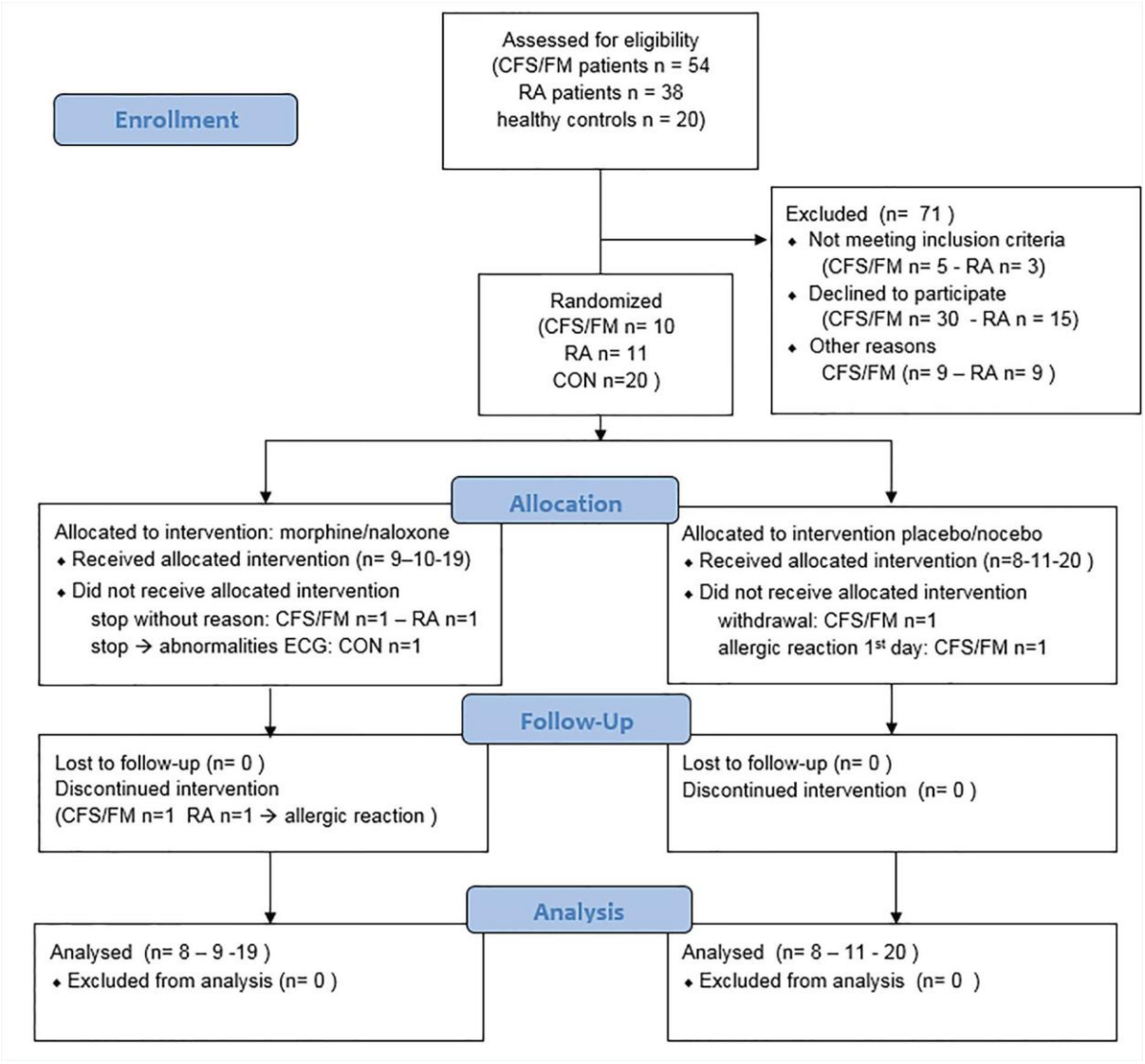


Figure 3. Baseline parameters

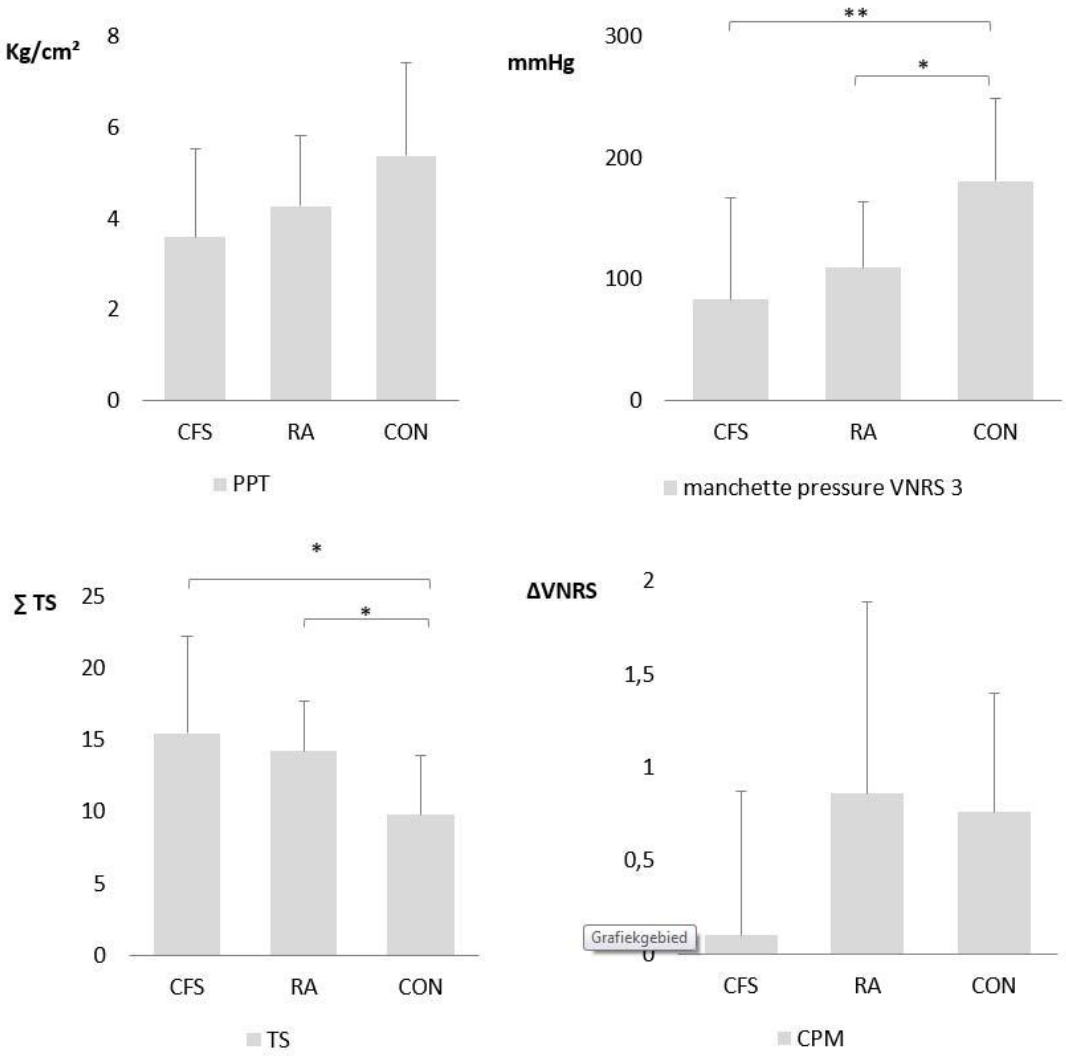


Figure 4. Effect morphine and placebo