Selective laser trabeculoplasty as replacement therapy

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Selective laser trabeculoplasty as replacement therapy in controlled glaucoma patients

Selectieve laser trabeculoplastie als vervangtherapie bij gecontroleerde glaucoompatiënten

Proefschrift voorgelegd tot het behalen van de graad
Doctor in de Geneeskunde en Gezondheidswetenschappen
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Abbreviations

ALT	argon laser trabeculoplasty
CCP	clear corneal phacoemulsification
CCT	central corneal thickness
IOP	intraocular pressure
OCT	optical coherence tomography
OHT	ocular hypertension
POAG	primary open angle glaucoma
SLT	selective laser trabeculoplasty
TM	trabecular meshwork
TSS-IOP	treatment satisfaction survey- intraocular pressure

Poweranalysis

Power analysis was conducted in G*Power. Running a power analysis on a repeated measures ANOVA (group: two patiëntgroups x time: 7 time points) with two measurements, a power of 0.80, an alpha level of 0.05.
Using: Rosenfeld E, Shemesh, Kurtz. The efficacy of selective laser trabeculoplasty versus argon laser trabeculoplasty in pseudophakic glaucoma patients. Clin Ophthalmol. 2012;6:1935-40.

For a small effect size (f= 0.10), in groups with high correlation, the minimum required sample size is 48.
For a large effect size (f= 0.50), in groups with low correlation, the required sample size is 30.

In all of our chapters, these minimum sample sizes were exceeded at baseline, after 1 hour, 1 week, 1, 3 and 6 months. Most of the groups had enough eyes after 12 months, however not in the group of normal tension glaucoma (NTG) patients, chapter 8.
After 18 months (chapters 6 and 8), most groups became smaller than the minimum sample size of 48 eyes. A study involving more eyes on longer follow up will be necessary in these cases.

Acknowledgements

Starting a PhD study at my age was a challenge. The incentive was given 30 years ago by my original professor of ophthalmology, professor Neetens, who saw the scientist in me and helped me publish two articles in Neuro-Ophthalmology. Then my daughter was born and life took over. The dream to study things more profoundly remained however. Seeing my children work on their thesis brought back old memories and revived the old dream.

My husband Frank encouraged me to pick up where I left and pursue a PhD. The first hurdles to take were finding a promotor and designing a study protocol. Secondly, I had to pass the Ethical Committee with that protocol. However, Frank helped me and showed me the way. As the study advanced, he kept me going when disappointment and desperation about the slow acceptance process for the articles was knocking me down. Thank you, Frank! This would never have worked without you.

Professor Veva De Groot of the department of Ophthalmology at the Antwerp University Hospital had enough faith in me to start a thesis project. She gave me the freedom to do it my way, but bothered me enough to set off with the right premises. Without her, the aspect of quality of life would not have been so broadly investigated. Throughout the publication process, she continued to review texts and slowed me down every time I wanted to go too fast. This improved the overall quality of the work, and I am very grateful for her help and faith.

My most precious collaborator in this study was **my daughter Maya;** she made sure the patient trial was started in a professional and correctly randomized way. She kept an eye on dropouts and follow-up failures. She motivated me to maintain the most strict and scientific approach possible. She showed me how to prepare the patient data in a way that they could be analyzed. The burden of statistical analysis fell completely on her shoulders. Often she had a hard time to convince me that apparently significant results were in fact not statistically relevant. I was lucky that she was patient enough to calculate and recalculate data for me as the study developed from three to seven articles.

Thank you also to **my two sons, Simon and Jonas** for helping me cope with the website of the University and helping me to find the templates of the UA. They navigated me through Smart school and Blackboard, which were like black holes to me at first. Thanks also for reviewing my texts; your English was a lot better than mine.

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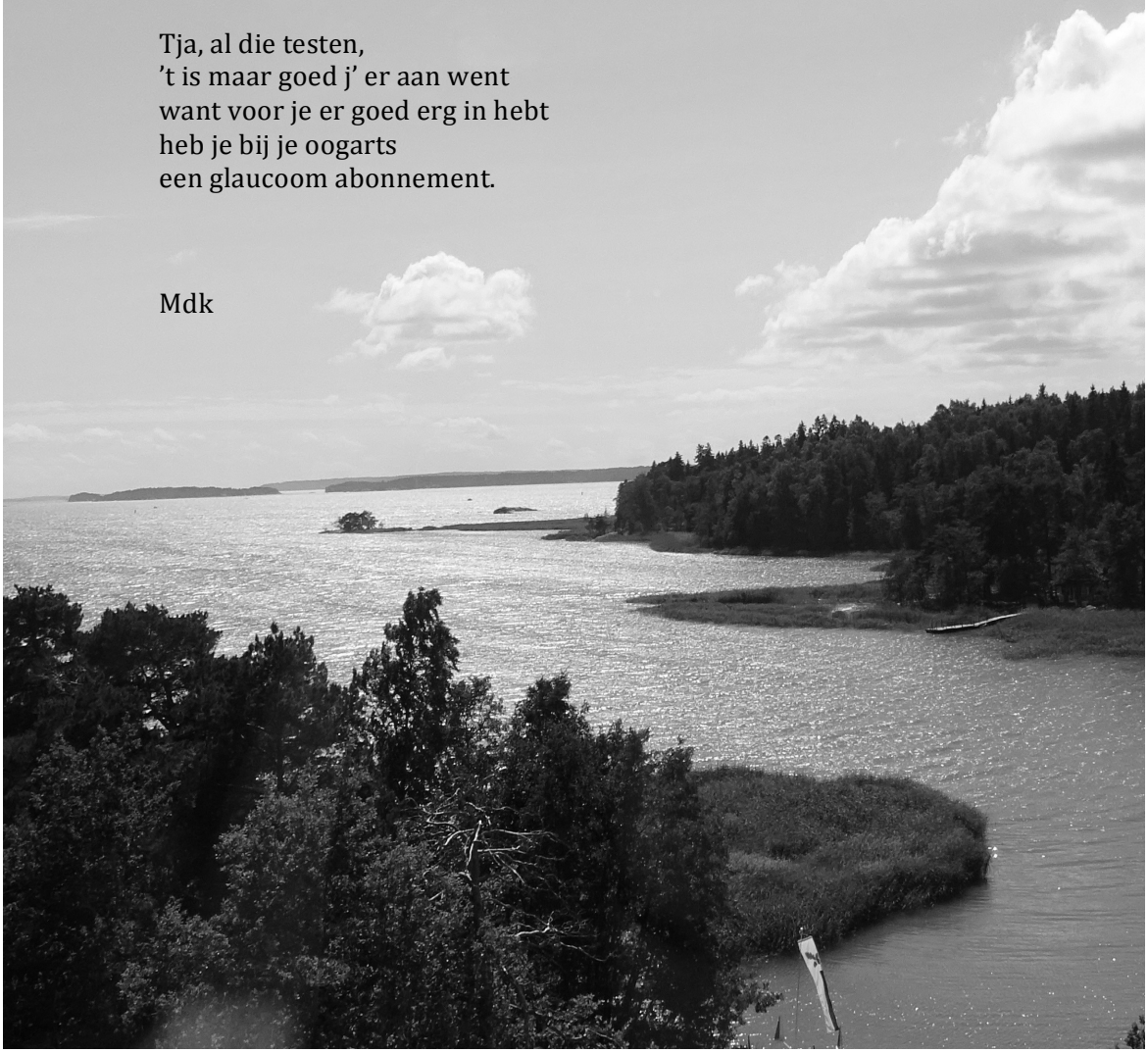
Abo

Glaucoom
is dat niet
grauwe staar
of grijze of zoiets.
Het heeft wat met de druk te maken
maar toch voelt je niets.

Soms geven ze je druppeltjes
of lasertherapie.
Er wordt ook wel geopereerd
maar dan is het al ver.
Er is zo'n test met lichtjes
en een pufje in je oog.

Tja, al die testen,
't is maar goed j' er aan went
want voor je er goed erg in hebt
heb je bij je oogarts
een glaucoom abonnement.

Mdk



CHAPTER 1. General introduction and aims of this study

Glaucoma is the second main leading cause of blindness in the world[1], and is a common disorder in the aging western population. Eye drops are typically the first line of therapy for glaucoma but they can produce systemic and local side effects. Compliance poses a problem. Not using the prescribed drops is a major cause of visual loss in patients with glaucoma.

Problems with topical medication

Therapy of glaucoma has the aim to maintain the patient's visual function and related quality of life, at an affordable cost [2]. Up to now, the only risk factor of glaucoma that can be influenced is intra ocular pressure (IOP). The Early Manifest Glaucoma Trial indicated that every mmHg of lowering the IOP means 10% less risk of disease progression[3]. IOP can be lowered through the use of local and systemic medications, laser treatment and surgery.

Topical medications can have significant systemic **side effects** like dyspnea, angina, bradycardia and hypoglycaemia[2] .They also have several local side effects like burning, stinging, itching and allergic blepharoconjunctivitis[4,5,6]. On top of this, most eye drops contain a preservative with known toxic effect on the eye surface[7]. Because glaucoma therapy represents a long term treatment, side effects of medication usually become worse during the course of treatment. This may eventually lead to a reduction in compliance or to discontinuation of drop application[5].

Glaucoma is predominantly present in the elderly women. Unfortunately, this is also the population with the highest frequency of keratoconjunctivitis sicca[8,9]. **Dry eye disease** affects functional visual acuity and the ability to work, read, use a computer and drive at night [8,10]. Topical medication can enhance the already present complaints of dry eyes[4].

As in all chronic diseases, **compliance** poses a problem in glaucoma treatment[11,12]. Any prescribed drop cannot work when the patient does not take it.

Polytherapy is very common in glaucoma. However, increasing the complexity of a medical regimen is associated with decreased patient adherence[13].

Quality of life can be reduced in glaucoma for a number of reasons: the distress of the diagnosis, loss of vision and independence and local discomfort[14,15]. Half of the patients undergoing laser or surgery for their glaucoma declared their situation had improved afterwards[14].

Why did we do this study?

In the public hospital where I worked we had a 'difficult' population; there was a tendency to irregular follow up examinations (no show), lac of means and of discipline to use glaucoma medication. This could lead to disease progression.

Laser, as a non-invasive treatment, could partly solve these problems. Initial work with selective laser trabeculoplasty (SLT) gave very good results. Eye pressure went down, medication was no longer needed, and side effects of the laser were few.

The IOP lowering effect of SLT has proven to be comparable to medication[16]. Still, SLT has difficulty to evolve to the first line of treatment in glaucoma. We decided to perform a clinical trial to find out if SLT could replace topical medication and whether the patient experienced an improvement in quality of life after laser treatment.

Set up of the study

We performed a prospective, randomized clinical trial at the glaucoma consultation of ZNA Jan Palfijn Hospital, Merksem. The trial was registered as NTR 5417. The Ethical Committee of ZNA hospitals gave its approval (4313 MEC).

We included all forms of open angle glaucoma or ocular hypertension patients. All patients were already on glaucoma medication and with a well controlled IOP. Previous glaucoma laser or surgery or any corneal disease that prevented visualization of the anterior angle were excluded.
At baseline, demographic and full ophthalmic parameters were recorded. Patients were also asked to fill out the Treatment Satisfaction Survey-IOP (TSS-IOP)[17,18].

Randomization was performed with a computer-generated allocation schedule. This only became apparent after demographic parameters were introduced.

When allocated to the SLT group, laser treatment was performed on both eyes. We used different post-laser medications in both eyes. The control group maintained their glaucoma medication. Patients were examined at 1 hour, 1 week and 1, 3, 6, 12 and 18 months after SLT. Glaucoma drops were continued until IOP was more than 2mmHg below target pressure. At that point they were stopped one by one.

Goals of this study

Primary question

Can SLT be used as a replacement therapy to medications in controlled glaucoma patients?

SLT has proven to be a valid alternative to medication as first line and as adjunctive therapy for glaucoma and ocular hypertension[16,19].
We hypothesized that treatment with SLT can replace topical medication while maintaining IOP control. This is the first prospective randomized clinical trial examining replacement of medication by SLT.

Secondary questions

1. **Does the use of anti-inflammatory drops after SLT influence the IOP lowering effect or the side effects after SLT?**

   After laser trabeculoplasty with older lasers, we were used to apply anti-inflammatory drops. This habit still remains after SLT[20]. However, the effect of this newer SLT relies on an inflammatory reaction of the trabecular meshwork (TM). Using anti-inflammatory products after SLT may be good to lower immediate side effects, but may meanwhile diminish the IOP lowering effect.

   We randomized patients to receive one of two possible anti-inflammatory eye drops (Indomethacin or Dexamethasone) in one eye and no anti-inflammatory drops in the other eye. Immediate side effects (redness, pain, cells in the anterior chamber, IOP peak) were recorded.
   Efficacy of the SLT was studied by comparing the evolution of IOP and number of medications needed between the two treated groups and the control group.

2. **Can structural variations of the eye, like corneal thickness, influence the outcome of SLT?**

   The thickness of the cornea (CCT) is an important parameter in the assessment of glaucoma[21,22]. It is also thought to reflect the biological properties of ocular tissues like the posterior sclera and the lamina cribrosa[23,24]. The TM is located between the junction of cornea and sclera. Since SLT relies on the reaction of the tissue, it is not unthinkable that CCT might influence the outcome of SLT.

We compared the effect of SLT in a group with low CCT (<550 µm) to a group with higher CCT (≥550 µm).

3. Does previous lens extraction influence the effect of SLT?

Lens extraction is associated with significant and sustained reduction in IOP[25-28]. Shazly et al.[29] described a delayed SLT response in patients with a lensimplant (pseudophakes). It was argued that lens extraction and SLT may share a common pathway which was depleted after surgery, thus slowing down the response to SLT [29].

We examined if there was a difference in effect of SLT in pseudophakic and phakic eyes (with their own lens) in terms of IOP lowering effect, speed of response and possibility to decrease medication.

4. Can SLT be used in normal tension glaucoma (NTG) or is it less effective in NTG than in other kinds of open angle glaucoma?

Normal tension glaucoma (NTG) is a progressive optic neuropathy like open angle glaucoma. Although the IOP in NTG never rises above 21 mmHg, optic nerve damage and visual field loss appear[30]. The Collaborative Normal Tension Glaucoma Study showed that a slower progression of visual field loss was recorded in NTG patients with ≥30% IOP lowering[31].
Pre-laser IOP is known to predict the effect of SLT. In a population with known low IOP, like NTG patients, SLT may be less effective.

We examined the effect of SLT in NTG patients and compared this to other open angle glaucoma patients.

5. Does SLT significantly improve quality of life?

Glaucoma patients use their drops for years on end. Local side effects of the active compound and toxic effect of the preservative become worse in the long run[5,7]. This can result in lower adherence[32,33] and can influence quality of life[14,15].
SLT reduces the number of medications needed, diminishing their side effects [34].

We examined whether SLT made a significant difference on several anterior segment signs and symptoms. We also investigated the patient's treatment satisfaction by a questionnaire (TSS-IOP).

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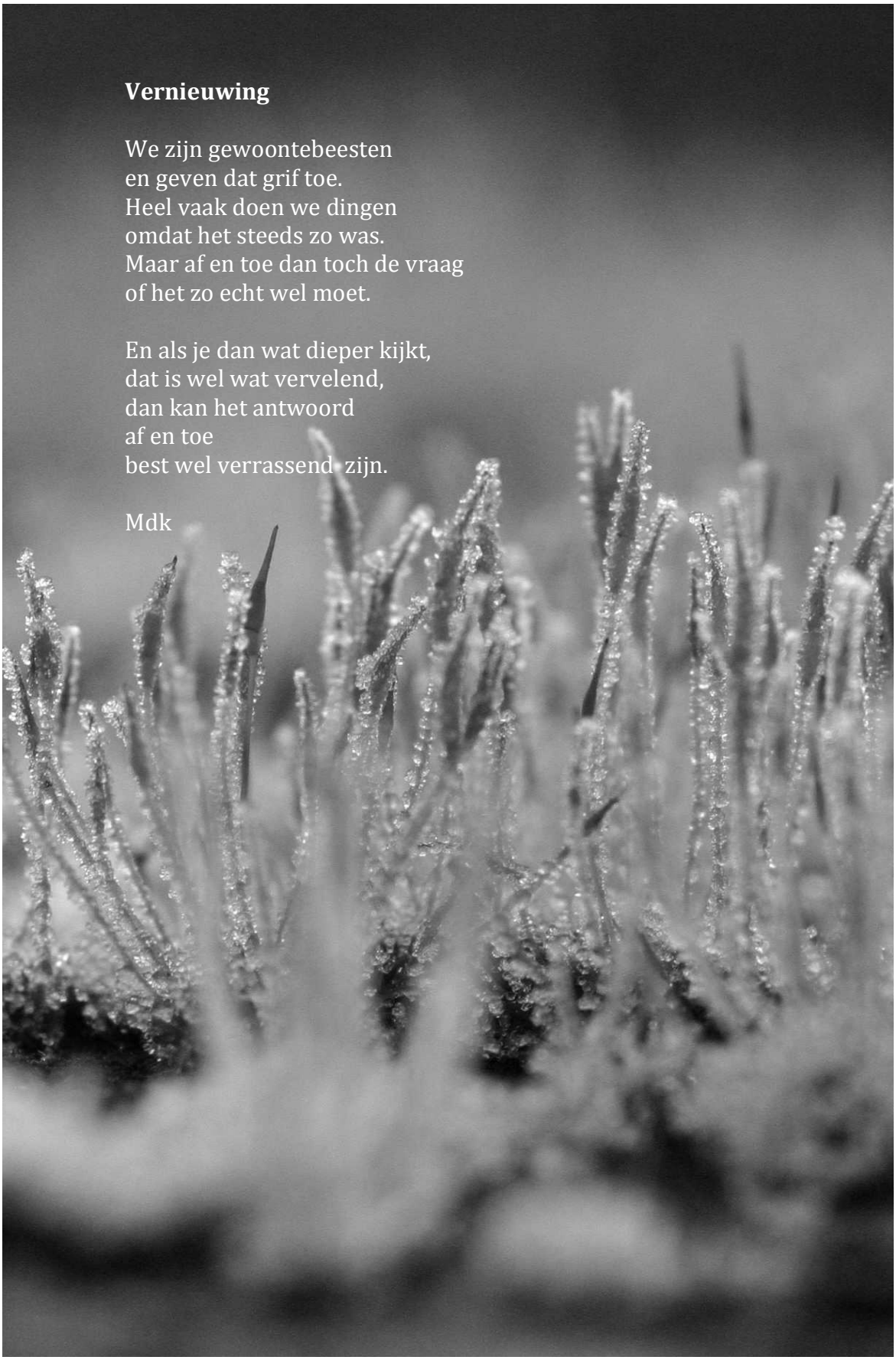

Vernieuwing

We zijn gewoontebeesten
en geven dat grif toe.
Heel vaak doen we dingen
omdat het steeds zo was.
Maar af en toe dan toch de vraag
of het zo echt wel moet.

En als je dan wat dieper kijkt,
dat is wel wat vervelend,
dan kan het antwoord
af en toe
best wel verrassend zijn.

Mdk

CHAPTER 2. Glaucoma and its impact on quality of life

Chronic open angle glaucoma is very common in the elderly western population and throughout the world. Topical medication remains the first choice of therapy. However, chronic instillation of drops leads to local and systemic side effects. It is often associated with loss of compliance.

Definitions

Glaucoma is a multifactorial disease[1] characterized by damage to the optic nerve. It is often caused by an elevated intraocular pressure (IOP) but not always. Worldwide it is the second leading cause of blindness, following cataract[2]. The prevalence is 2-3%, predominantly in the elderly population[3]. It occurs more often in women than in men, with ratios ranging from 1,5 to 2,2[2]. Open angle glaucoma takes up 74% of the glaucoma group [4].

The aim of glaucoma treatment is to maintain the patient's visual function and related quality of life, at an affordable cost [3]. The evolution of the disease is determined by either visual field loss or changes in optic nerve head or retinal nerve fibre layer morphology.
Variables enhancing glaucomatous visual field progression are: higher IOP, abnormal baseline anti cardiolipin antibody, higher baseline age, higher mean follow-up IOP, female gender[1]. Exfoliating glaucoma, having both eyes attained by glaucoma and showing disc haemorrhages also means a greater risk of glaucoma progression [5].

Of all of the factors, only IOP can be influenced. Every millimetre of mercury of lowering the IOP means 10% less risk of progression of the disease[4]. Thus, lowering IOP with a minimum of side effects and a maximum of quality of life stays the main goal of therapy[3].

Treatment options in glaucoma

IOP can be lowered through the use of local and systemic medications, through laser treatment and by surgery. We will only discuss the most frequently used treatment options for open angle glaucoma.

.1. Medications

Four classes of medication are mostly used for chronic open angle glaucoma:

A. Beta-blocker drops

Since its introduction in 1978, topical timolol has rapidly become the most widely used agent for the treatment of glaucoma. Beta-blockers decrease the production of aqueous humour in the eye through beta-receptor blockade. In general, these drops are applied twice daily[5].

Product names: Timolol, Levobunolol, Metipranolol, Carteolol, Befunolol, Betaxolol

B. Prostaglandin analogues

The introduction of the prostaglandin analogue Latanoprost in the mid 1990s was greeted with enthusiasm. Latanoprost had a superior IOP lowering efficacy and a near absence of systemic side effects.

Prostaglandin analogues have rapidly replaced beta-blockers as first choice therapy[5]. Their once-daily administration was a definite advantage. Prostaglandin analogues primarily increase uveoscleral outflow. They have been reported to lower diurnal IOP fluctuation [7].

Product names: Latanoprost, Travoprost, Bimatoprost, Tafluprost

C. Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors have been used perorally to treat glaucoma since the sixties. Their application was mostly as an adjunctive treatment of refractory primary open angle glaucoma and to lower intraocular pressure in acute angle closure glaucoma.

The carbonic anhydrase inhibitors lower intraocular pressure by suppressing the production of aqueous humour in the eye. However, these agents also inhibit carbonic anhydrase in the kidney and other tissues and cause a mild diuresis, a systemic acidosis and alkalization of the urine[6].

Carbonic anhydrase inhibitors have also been developed in collyre. In general, these are applied twice daily.

Product names: Brinzolamide, Dorzolamide, Diamox

D. Alpha-adrenergic agonists

Also considered as first line drugs are the alpha-2 selective adrenergic agonists. They decrease aqueous humour production and increase uveo-scleral outflow[5].

Product names: Apraclonidine, Brimonidine, Clonidine

.2. Laser treatment

Argon laser trabeculoplasty

As an alternative to eye drops, argon laser trabeculoplasty (ALT)[8,9] has proven to be a useful instrument. Using an Argon laser, non-overlapping spots are made on the trabecular meshwork (TM) in the anterior angle. At the coagulation site the TM shrinks and opens up the adjacent parts of the TM. ALT produces much coagulative damage on bio microscopy[10]. Bylsma et al. showed that ALT also activates a cellular mechanism that stimulates TM cell division. This would rejuvenate the meshwork[11].

Long-term follow-up showed that after a few years 68-95% of patients returned to a higher IOP. Retreatment with ALT was found to be ineffective[12,13].

Selective laser trabeculoplasty

Selective laser trabeculoplasty (SLT) was launched in 1998 by Latina et al.[14]. A frequency-doubled, Q-switched, 532nm Nd:YAG laser is used. Pulse duration is 3nsec and the spot size 400µm. The used pulse duration is too short for melanin to convert the electromagnetic energy to thermal energy. This means that no heat is generated. The total energy flux (energy per unit area) of the SLT is some 6500 times lower than that of the ALT. This provides a theoretical basis to consider SLT as a repeatable treatment for lowering IOP.

.3. Surgery

Filtering surgery procedures remain the most efficient pressure lowering interventions. Trabeculectomy is still the gold standard for glaucoma surgery[5]. It produces a 'guarded' fistula between the anterior chamber and the subconjunctival space.
Many complications are possible, including vision decrease. This illustrates that the ideal surgical procedure has not been found yet.

Problems with medication in glaucoma

.1. Side effects of active component

Effective medical treatment for glaucoma was first introduced in the later part of the nineteenth century. In recent years, increased numbers of drugs have been developed for the treatment of glaucoma. However, the issue of safety of glaucoma medication remains.

The systemic influence of eye medications may be easily overlooked when general practitioners evaluate patients. When drug history is taken, many patients do not mention their eye drops. They assume that this medication should not be considered in the same category as oral medicines. However, ophthalmic medications can have significant systemic side effects, see table A.

Entry of the topical medications into the systemic circulation occurs by drainage into the lacrimal ducts. The highly vascular nasal mucosa and conjunctival and episcleral vessels absorbe the substances and drain them into the ophthalmic and facial veins. The drugs thus avoid the first-pass hepatic metabolism that awaits oral medications.

It is important to maintain a high index of suspicion concerning systemic effects of glaucoma medications, particularly in elderly patients. Such effects may be overlooked, may present non-specifically, or can be misattributed to primary disease elsewhere[6].

Medications	% IOP red	Dyspnoea, asthma exacerbation	Angina	Bradycardia, arrhythmia	Hypo-glycemia	Depression, confusion	Impotency, decreased libido	Headache	Asthenia	Urticaria, paraesthesia	Intestinal cramps
Beta-blockers	20-25%	*		*	*	*	*				
Prostaglandin analogues	25-35%	*	*								
Carbonic anhydrase inhibitors	20%						*	*	*	*	*
Selective adrenergic agonists	25-35%			*					*		

Table A. Systemic side effects of anti-glaucoma medication[3]

Side effects of beta-blockers

The effect of rapid absorption through the nasal mucosa is especially relevant for the beta-blockers. When taken orally, these may be 90% metabolized on a first-pass effect[6]. All ophthalmic beta-blockers can be expected to affect the cardiovascular system through beta-1 receptor blockade. They may lower heart rate and blood pressure, slow cardiac conduction and decrease cardiac contractility.
They may also lead to decompensation of congestive heart failure.

Adequate beta-2 adrenergic tone is important for the maintenance of open airways in patients with reactive airway disease. Beta-2 blockade may cause constriction of pulmonary bronchi and of some arterial vasculature. Thus, ophthalmic beta-blocker drops may cause respiratory distress in some patients.
Beta-adrenergic neurotransmission plays a major role in many aspects of the central nervous system activity. Systemic beta-blockade has been linked with depression, impotency and other central nervous system dysfunctions. Hypoglycemia can occur after use of beta-blocker eye drops.

Beta-blockers are also known to provoke several local side effects like conjunctival hyperaemia, superficial punctate keratitis, dry eye syndrome, corneal anaesthesia and allergic blepharo-conjunctivitis, see table B. The burning and stinging of the eye is more pronounced using selective beta-blockers[15].

Medications	Allergic blepharo-conjunctivitis	Darkening iris and skin / dermatitis	Eyelash changes	Conjunctival hyperaemia	Burning, irritation	Reactivation herpes	Superficial keratitis	Precipitates angle closure	Cystoid macular oedema	Uveitis
Beta-blockers	*			*	*					
Prostaglandin analogues		*	*	*	*	*			*	*
Carbonic anhydrase inhibitors				*	*		*	*		
Selective adrenergic agonists	*	*								

Table B. Local side effects of anti-glaucoma medication[3]

Side effects of prostaglandin analogues

Prostaglandin analogues rarely have system side effects. However, they do show several ocular side effects. Some of these have no apparent serious consequences other than cosmetic. These include conjunctival hyperaemia, elongation and darkening of eyelashes, iris darkening and peri-ocular skin pigmentation[16].

Other possible side effects are potentially sight threatening such as iris cysts, cystoid macular oedema, anterior uveitis and reactivation of herpes simplex keratitis. Fortunately, these effects are relatively rare[16].

.2. Side effects of preservatives

Regular eye drop bottles contain preservatives. The benefits of reducing microbial contamination through use of preservatives are offset by their known toxic effects[17,18].

The most common preservative in anti-glaucoma medication and other topical ophthalmic preparations is benzalkonium chloride (BAK). It is commonly used at concentrations of 0.004%-0.025%. Baudouin et al. showed the toxicity of BAK. It creates adverse reactions on various surface and deep ocular tissues (conjunctiva, trabecular meshwork, lens, retina)[19]. BAK also induces a loss of the protective tear film of the eye, causing dry eye symptoms and corneal damage. Treatment with glaucoma medications that contained higher levels of BAK resulted in higher damage to the cornea and conjunctiva[19].

Long-term anti-glaucoma therapy with preservatives induced adverse effects such as inflammation of the conjunctiva. This related to a lower success rate for filtration surgery[19].

.3. Compliance

A problem with any kind of chronic medication, is compliance[20]. The latest diagnostic techniques and treatment advances are of no benefit if the patient is noncompliant. At best, treatment adherence in chronic diseases is estimated to be 75%[21]. Even in symptomatic diseases where lapses in therapy may result in clinically significant symptoms (e.g. epilepsy and oncology), treatment adherence remains a problem. In glaucoma, the lack of overt symptoms may tend to decrease the adherence of the patient.

Robin et al. did al large study in 2007 using a medication-monitoring device to record the time and date of each opening of a bottle of a hypotensive medication that had to be taken twice daily. Even in this study, with patients very aware of the fact that their compliance was being monitored, the amount of dosing errors with the second drop was significant. Another observation was the fact that the second drop was frequently taken at less than a 10-hour interval. This is a major safety concern, given that systemic effects may occur if beta-blocker drops are taken too fast one after the other.

Increasing the complexity of the medical regimen was associated with decreased patient adherence**[22].** With every additional medication used, compliance diminished. As soon as three or four medications need to be used to get the IOP down, alternatives should be looked for[4,21].

Also, the economic implications of managing glaucoma are big. In every stage of the disease, medication has a 42-56% part in the costs. Continuing on medication that does not work is useless.
Lee et al demonstrated in a study of 2006 that costs could be cut and better results can be obtained by using laser therapy earlier in the therapeutic scheme[23].

.4. Dry eye syndrome

Keratoconjunctivitis sicca or dry eye syndrome is a common complaint among middle-aged and older adults. The symptoms are always the same
– a sandy, gritty, burning feeling. Other complaints are soreness, tiredness, dryness, photosensitivity, foreign body sensation, irritation and discomfort[24].
Deficiencies in tear quantity or quality can be caused by low tear production or excessive tear evaporation. This results in an unstable tear film and dry eye symptoms[25,26].

There is no known cure for dry eye syndrome. It remains one of the leading causes of patient visits to ophthalmologists and optometrists in the western world[26]. Dry eye syndrome has been demonstrated to affect functional visual acuity and impact the ability to work, read, use a computer or bank machine, and drive at night[27,28]. In addition, the disease leads to increased risk of infection[26,]. Dry eyes can also reduce the resistance of the cornea and conjunctiva to the presence of toxic or irritant compounds[19].

The prevalence of dry eye disease varies depending the definition used and varies from 11% [29] to 28,7% [24,30]. This last number means that approximately 1 in 4 patients in the population can be symptomatic for some degree of dry eye symptoms [24], and at least 1 in 10 patients has severe complaints of dry eye [26,29].

The disease is not sex-indifferent: women are up to twice as likely as men to have dry eyes. The dry eye is also age-dependent. It shows a bimodal distribution with a notable proportion (38%) of younger patients (21 to 30 years) and 34 to 41% of symptomatic patients over 70 years old [24]. This association between older age and an increase in dry eye symptoms is likely a result of normal changes in tear production and characteristics associated with advancing age[27].

This means that dry eye disease typically affects the population that is also at risk for glaucoma: the elderly women. Complaints caused by medications can superimpose on the very common dry eye symptoms.

.5. Quality of life

Quality of life in glaucoma patients can be lost for a number of reasons: the distress of the diagnosis, the insidious loss of vision and independence, the problems with frequent treatment and regular outpatient appointments.
For instance, in a large study on QoL by Odberg et al.[32], more than 80% of patients reported negative emotions like anxiety, fear of blindness, depression and shock, when they were informed about their glaucoma diagnosis. Merely giving the diagnosis of glaucoma affected quality of life .

Nearly half of the patients examined in the same study had no visual problems. In the ones who did report everyday activities being influenced by decreased vision, the most frequent complaints were problems reading, walking on stairs and recognizing a person outdoors. The Salisbury Eye Evaluation reported glaucoma to be associated with slower walking, worse performance on a mobility course, falling, and more avoidance of difficult driving situations. These limitations can profoundly impact a person's quality of life [31].

Quality of life is also influenced by local discomfort. In a large prospective epidemiological study of 4107 patients, Pisella et al.[18] examined the side effects of topical beta-blockers in terms of symptoms and ocular signs of irritation. 57% of their patients reported at least one symptom some time after instillation.
Discomfort on instillation (40%) was the most commonly reported symptom followed by symptoms between instillations – burning and stinging (37%), foreign body sensation (28%), dry eye sensation (22%), tearing (20%) and eyelid itching (17%). There were also objective signs of ocular irritation such as conjunctival hyperaemia (38%), conjunctival follicles (20%) and superficial punctate keratitis (18%).

All symptoms occurred more frequently in patients treated with preserved eye drops than in those receiving preservative free drops. Discomfort upon instillation was up to 2,5 times more prevalent in those using preserved eye drops: 43% versus 17%.

In Odbergs study, half of the patients undergoing laser or surgery told that their situation had improved afterwards. Possibly because of the relief related to a lowering of the IOP and/or less need of medication. A satisfactory regulation of the IOP without the use of topical therapy can improve the perceived quality of life[32].

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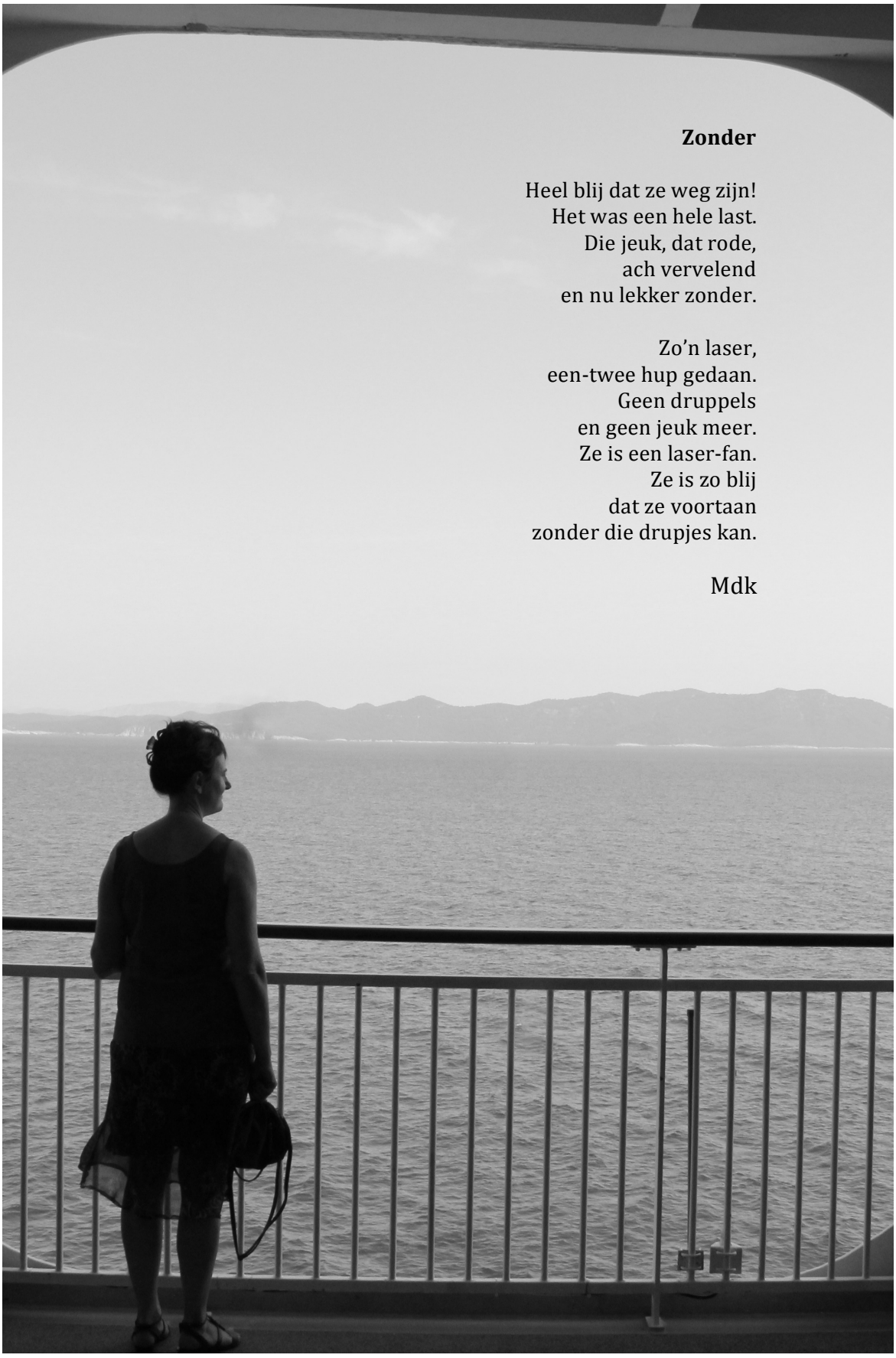

Zonder

Heel blij dat ze weg zijn!
Het was een hele last.
Die jeuk, dat rode,
ach vervelend
en nu lekker zonder.

Zo'n laser,
een-twee hup gedaan.
Geen druppels
en geen jeuk meer.
Ze is een laser-fan.
Ze is zo blij
dat ze voortaan
zonder die drupjes kan.

Mdk

CHAPTER 3. Introduction to laser trabeculoplasty

Argon laser trabeculoplasty (ALT) is effective as primary and as secondary treatment of glaucoma. However, its effect diminishes in time and ALT is not repeatable.

Selective laser trabeculoplasty (SLT) uses a short pulse of very low energy. Heat is contained in the pigmented endothelium cells of the TM and produces minimal tissue damage. SLT appears to be repeatable.

Two meta-analyses have proven SLT to be as effective as ALT and as effective as medication in the treatment of glaucoma.

Argon laser trabeculoplasty

Ever since its development in 1979[1] argon laser trabeculoplasty (ALT) has proven to be a useful instrument for the treatment of open angle glaucoma. It is effective as primary treatment and can be used as a secondary treatment. For instance in uncontrolled glaucoma after maximum topical therapy or as the last step before surgical intervention[2].

The laser spots are focused on the inner surface of the TM using a gonioscope, a special lens with one mirror, placed against the cornea. In ALT we generally treat 180° of the TM, using 50 applications of 50 µm spot size, 0,1 sec duration and an average power ranging from 400 to 600mW. This produces a blanching in the anterior TM[3].

Argon laser improves the outflow of aqueous humour. Several theories have been proposed to explain the mechanism by which this functions. The most widely accepted are the mechanical and the cellular theory.

The mechanical theory states that ALT causes coagulation damage to the trabecular meshwork with shrinking of the collagen and scarring of the TM. This narrows the network on the spot of the laser burn but opens up the adjacent, untreated intertrabecular spaces.

The cellular theory proposes migration of macrophages responding to coagulation necrosis induced by the laser. These macrophages phagocyte the debris and clean up the TM[3,4].
Whether ALT works through a mechanical or a cellular reaction or a combination of both, it results in an increased outflow of the anterior chamber humour at the level of the TM and thus diminishes IOP[5].

ALT produces an IOP lowering up to 35% compared to baseline IOP. The effect diminishes in time. Ten year follow up showed that 68-95% of patients returned to a higher IOP and retreatment with ALT was found to be ineffective[4]. Failure in the long run could probably be explained by the damage done to the microstructure of the trabecular meshwork, the anterior chamber reaction and the formation of anterior synechiae that can occur after ALT.

Histopathological studies showed serious damage to the uveoscleral network after ALT treatment. There was coagulation tissue necrosis and fragmented cells, formation of craters, collagen fibres damaged by heat and formation of membranes around the laser points formed by migrated endothelial cells. It is suspected that these membranes cover the TM and diminish the outflow, which later leads to failure of the therapy.
The disruption of the TM and accumulation of debris are probably the cause of the acute rise of the IOP that also occurs immediately after ALT[4].
To lower the tissue damage, several laser settings were tried. The same IOP lowering effect could be acquired by using a smaller number of laser points, with less energy and by treating half or less of the TM[6].

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Selective laser trabeculoplasty

Where does selective laser trabeculoplasty stand now?

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Abstract

Purpose
Chronic treatment of glaucoma can present a challenge in patients who lack the means and/or the discipline to use daily glaucoma medication. We wondered if selective laser trabeculoplasty (SLT) could be a useful alternative.

Methods
Inclusion criteria: controlled trials comparing efficacy of SLT in adult patients with any form of open angle glaucoma or ocular hypertension and case reports on side effects of SLT. Two recent meta-analyses identified eight randomized clinical trials (RCTs) comparing the effect of SLT with medication (prostaglandin analogues) and with argon laser trabeculoplasty (ALT). We took these eight RCTs as reference base and calculated their success rates where they were not given. Other articles were added to elaborate on technique and side effects.

Results
Mean intraocular pressure (IOP) reduction after SLT was 3.8-8.0 mmHg after 6 months to one year. Mean success rate of SLT at 6 months to one year is 55-82%. Higher IOP before laser predicts a higher IOP-lowering effect. In terms of mean IOP reduction, reduction in number of medications and treatment success, the effect of SLT was found to show no clinically relevant difference from that of contemporary medication (prostaglandin analogues) and from ALT.

Conclusions
The evidence indicates that SLT is an efficacious treatment to use as a primary or adjunctive therapy for treating glaucoma.

Background

Selective laser trabeculoplasty (SLT) was launched in 1998 by Latina et al. [20]. A frequency-doubled, Q-switched, 532 nm Nd:YAG laser is used with pulse duration of 3 nanosec and a spot size of 400 µm. This pulse duration is too short for melanin to convert the electromagnetic energy to thermal energy, which means that no heat is generated. The total energy per µm of spot size in SLT is much lower than in ALT, which provides a theoretical basis to consider SLT as a repeatable treatment for lowering IOP.

In our public hospital, we have a 'difficult' population, there is a tendency for irregular follow up examinations (no show) because of lack of means and mostly of discipline to use glaucoma medication, which compromises therapy. Laser could be a non-invasive treatment that can partly solve these problems. The question our patients always ask when we try to motivate them to have SLT done is: 'What are my chances that this laser will work and what problems can I expect from this laser?' This article sets out to answer those questions in terms of success rate and side effects of SLT.

Methods

Literature search and trial selection

Studies were identified and retrieved through a systematic search of PubMed, Web of Science and Google Scholar. Keywords used in identifying relevant research included 'selective laser trabeculoplasty', 'SLT', 'glaucoma treatment', 'ocular hypertension' and 'side effects of selective laser trabeculoplasty'.
Inclusion criteria: retrospective and prospective comparative controlled trials studying the effect of SLT in adult patients with any form of open angle glaucoma (OAG) or ocular hypertension (OHT), with or without medication. We also included case-reports on side effects of SLT.
Exclusion criteria: studies in which SLT was used as adjunct for glaucoma operations.

Recently, two meta-analyses were published on SLT. A meta-analysis by Li et al.[8] identified four randomized clinical trials (RCTs) comparing the effect of SLT with medication[21 -24.] The meta-analysis of Wong et al.[25] included these four RCTs and four additional RCTs, that compared SLT to ALT[26-29]. These eight RCTs were taken as reference base for our calculations. Other articles were used to elaborate on technique and side effects.

The information on author, mean age, sample size, type of glaucoma, and study design were extracted. We calculated the success rate if it was not given in the article and when enough data were present to make this calculation[21, 22, 26]. Definition of success was a 20% lowering of IOP compared to baseline IOP. Where mentioned, the incidence of transient post-laser IOP spikes, redness, anterior chamber reaction, discomfort or other side effects were recorded.

Review

Mechanism

Cvenkel et al. applied ALT to a part of the eye, and SLT to another part of the same eye in three patients that were planned to get an enucleation[15]. After the enucleation, the anterior segments of the eyes were dissected and examined. Light microscopy and transmission electron microscopy showed much less structural changes after SLT than after ALT.

Damaging the pigmented cells of the TM without mechanical or thermic effect by SLT seemed to be enough to enhance the outflow through the TM. This may be a sign that SLT works more at a cellular level, through stimulation of the formation of healthy TM tissue, like ALT[16, 17, 30.]

Detorakis et al. also found arguments for a biochemical mechanism with release of cytokines after laser that possibly attract macrophages and stimulate phagocytosis of debris in the TM[31]. Both cellular and biomechanical mechanisms can enhance the outflow capacity of the TM with minimal damage to the tissue[15, 32].

Characteristics of intervention

In the eight reference RCTs of Wong et al.[25] and Li et al.[8], 45-102 SLT applications were applied, with a spot size of 400 µm and power between 0.47 and 1.7 mJ, with each spot lasting 3 nanosecond. See also Table 1.

In the 2005 study, Nagar et al.[23] randomized patients to 90, 180 and 360 degrees treatment. The 90° had a very low success rate at a mean of 10.3 months (34%). Although there was no statistically significant difference in outcome after 180° or 360° of SLT treatment, success rates were better with 360°. In their trial, Bovell et al. [26], Liu et al.[27], Rosenfeld et al.[28,] and Kent et al.[29] chose to treat 180° of the TM. Lai et al.[22], Nagar et al.[23], and Katz et al.[21] treated 360°. Katz et al. started by treating 360° and performed a 180° treatment when a second SLT was needed during follow up.

The energy level used is titrated to the degree of trabecular pigmentation. The greater the pigmentation, the less energy is required. To determine the optimal energy level, the power setting is initially set at 0.6-0.9 mJ and the energy level is increased by 0.1 mJ until bubble formation (champagne bubbles) is observed. If bubble formation is already noted at the initial energy level, the laser energy is reduced by 0.1 mJ[20]. An energy level just below that of bubble formation is then maintained.

In their population of pseudo-exfoliative syndrome (PEX) patients, Kent et al. used a mean energy level of 0.6 mJ[29]. Ayala et al.[33] found that higher energy creates a longer IOP lowering effect after SLT and Lee et al.[34] also suggested using a higher energy density (number of spots multiplied by mean energy) to improve SLT outcome. On

the other hand, more energy and more spots may be associated with more side effects[23] and an increased risk of corneal oedema[35], so caution has to be taken.

It may be important to bring in mind that the energy used in SLT is much lower than in ALT. SLT classically uses around 0,9 mJ of energy[23-25], whereas ALT uses around 50mJ (500 mW for 0.1sec)[26-28]. This makes the energy used by SLT 55 times smaller than in ALT. The laser spot used in SLT has a diameter of 400 µm[23-25] or an area of 0.13 mm^2. ALT uses a spot of 50 µm[26-28] or an area of 0.002 mm^2. The energy in ALT is thus aimed at an area 64 times smaller than in SLT. This means that the energy per mm^2 of tissue is 3520 times smaller in SLT than in ALT.

Comparison of SLT to medication

The effectiveness of SLT compared to contemporary medication (prostaglandin analogues) was investigated in a large meta-analysis by Li et al.[8]. Five prospective studies were included in their study, four randomized and one non-randomized. Wong et al. identified the same four randomized RCTs. We included these four studies, one published by Lai et al.[22], two by Nagar et al.[23, 24], and one by Katz et al.[21]. Two of them were single centre, while the others were multicentre trials, see Table 1.
The number of patients treated with SLT ranged from 20 to 67, the largest trial by Nagar et al. included 128 eyes[23]. Mean follow up time was short: 4 to 12 months. Lai[22] and Bovell[26] had a follow up time of 5 years.

The study of Nagar (2005) mentioned a range of follow up from 1 to 12 months. In this study, patients were randomized to medication and 90°, 180° and 360° of SLT. The second trial of Nagar et al.(2009) was designed to compare the effect of reduction of IOP fluctuation between SLT and Latanoprost, with a mean follow up of 4 to 6 months.

This study showed a significantly higher baseline IOP in the Latanoprost group, which was adjusted for calculation of the IOP fluctuation. Baseline IOP was above 24.5 mmHg in three of the four RCTs (not available in Nagar 2005).
No significant differences in IOP lowering effect could be found between the medication and the SLT groups.

Comparison of SLT to ALT

Wong et al.[25] conducted a meta-analysis involving all studies on SLT effect in patients with OAG or OHT. They included primary open angle glaucoma (POAG), pseudo exfoliation syndrome (PEX), pigment dispersion syndrome (PDS), uveitis glaucoma, juvenile glaucoma, steroid-induced glaucoma, and normal tension glaucoma. Four RCTs comparing the efficacy of SLT and ALT were identified. These studies were conducted between 2011 and 2013, and included one multicentre and 3 single centre trials. Baseline characteristics are shown in Table 1.
The number of patients treated was mostly limited (20-37) with one larger study (89 patients) by Bovell et al.[26]. Liu et al. focused on younger patients, with a mean age of 48.7 years and a significantly lower baseline IOP (19.1 mmHg).

Table 1. Baseline characteristics of randomized clinical trials using SLT

Author, year, ref	Design location	Type of glaucoma	# eyes after SLT	Treatment in control arm	Mean follow-up (months)	Mean age (years)	SLT group baseline IOP (mmHg)	Control group baseline IOP (mmHg)	Characteristics SLT (extent, number spots, power)
Lai, 2004 [22]	SC, China	POAG, OHT	29	medication (?)	60	51.9 ± 14.7	26.8 ± 5.6	26.2 ± 4.2	360°, 100, 1.0 ± 0.1 mJ
Nagar, 2005 [23]	MC, UK	POAG, OHT, PEX, PDS	128	medication (lat)	10.3	63	NA	NA	90°, 25-30 180°, 48-53 360°, 93-102 0.8-1.7 mJ
Nagar, 2009 [24]	SC, UK	POAG, OHT	20	medication (lat)	4-6	66.4	26.1 ± 4.0	22.8 ± 4.5	360°, 100 ± 5, 0.8-1.4 mJ
Katz, 2012 [21]	MC, USA	POAG, OHT	67	medication (prost)	6-12	NA	25.0 ± 2.2 (4-6 m) 24.5 ±2.1 (9-12 m)	24.5 ± 2.2 (4-6 m) 24.7 ± 2.4 (9-12 m)	360°, 100, 0.8-1.2 mJ
Bovell, 2011 [26]	SC, Canada	POAG, PEX, PDS, mix mech, others	89	ALT	60	69.7 ± 10.52	23.8 ± 4.9	23.48 ± 4.21	180°, 50, 0.47-1.5 mJ
Liu, 2012 [27]	SC, Canada	POAG, OHT, PEX, PDS, NTG, juv OAG, mix mech	20	ALT	37	48.7 ± 9.4	19.1 ± 4.5	21.9 ± 4.4	180°, 45-55, 0.7-0.8 mJ
Rosenfeld 2012 [28]	SC, Israel	POAG, OHT, PEX, PDS	22	ALT	12	71.95	25.36 ± 1.83	25.11 ± 2.16	180°, 50-70, 0.8-1.2mJ
Kent, 2013 [29]	MC, Canada	PEX	37	ALT	6	72.9 ± 9.86	23.1 ± 4.22	25.2 ± 4.87	180°, 53 ± 3.75, 0.6 mJ

Abbreviations: SC= single centre; MC= multicentre; NA= not available; POAG= primary open angle glaucoma; OHT= ocular hypertension; PDS= pigment dispersion syndrome; PEX= pseudo-exfoliation syndrome; NTG= normal tension glaucoma; juv= juvenile glaucoma; mix mech= mixed mechanism glaucoma; ?= not specified; lat=latanoprost; prost=prostaglandin analog

Rosenfeld et al.[28] recruited patients that underwent successful cataract extraction 3-6 months before the study commenced. Kent et al.[29] limited their study to patients with PEX.

All studies concluded that the IOP-lowering effect of SLT was comparable to ALT.

Success rate

The IOP reduction varied from 3.8 to 8.0 mmHg at 6 months to 1 year after SLT (see Table 2). The lowest reduction of 3.8 mmHg was found in the population of Liu et al.[27]. This group started with a low mean baseline IOP (19.1 mmHg). As a higher baseline IOP is predictive of a greater IOP decrease, a lower response could be expected.

Five studies used 'more than 20% reduction of the IOP compared to baseline IOP' as their definition of success (Lai et al.[22], Nagar et al.[23, 24], Bovell et al.[26], Kent et al.[29]). Their success rates at 6 months to one year varied from 55 to 82%. Again, Liu et al. reported the lowest success rate. This result is in line with trials that claim SLT can be used to lower IOP in normal tension glaucoma, but rarely (in 22% of patients) creates an IOP reduction of more than 20%[36].

The success rate of the group that was treated over 90° of TM by Nagar was the lowest recorded, this treatment was considered as insufficient[23]. Lai[22], Katz[21] and Rosenfeld [28] reported success rates ranging from 75 to 97% after 6 months to one year, but used criteria of success that deviated from the others and appeared less stringent (IOP less than 21 mmHg[22], IOP less than 2 mmHg above target IOP[21] or more than 15% IOP reduction[28]).

Prediction of success of SLT was examined in several trials and proved indifferent to: gender, race[23], family history, other glaucoma risk factors, type and severity of OAG, TM pigmentation[19,37], pseudo-exfoliation[18], number and type of anti-glaucoma medications[22, 38], previous laser[26, 39], phakic or pseudophakic eyes[40], patent iridotomy[41], presence of systemic hypertension or diabetes mellitus mellitus[9, 42].

The only variable that predicts a better IOP-lowering effect after SLT is a higher IOP prior to laser[5, 18, 43, 44]. One study found shortened time to failure with increasing age33, but this was not confirmed by others. Lee et al.[34] also found a significant correlation between both eyes. In almost 80% of treated OAG subjects, success after SLT in one eye correlated with a higher chance of success in the other. This was confirmed by Shazly et al.[45]. Thinner corneas (CCT <555µm) also seemed to give better IOP reduction after SLT[46, 47].

Table 2. Results of randomized clinical trials using SLT

Author, year, ref	SLT IOP red (mmHg) 6m–1 y	SLT IOP red (mmHg) end of study	Control group IOP red (mmHg) 6m- 1 y	Control group IOP red (mmHg) end of study	SLT definition of success	SLT success rate 6m- 1 y (%)	SLT success rate end of study
Lai, 2004 [22]	8.0 (12m)	8.6 ± 6.7 (60m)	7.0 (12m)	8.7 ± 6.6 (60m)	IOP<21mmHg	97 (12m)	72 (60m)
Nagar, 2005 [23]	NA	NA	NA	NA	>20% IOP red	90°=34 180°=65 360°=82 (10m)	90°=34 180°=65 360°=82 (10m)
Nagar, 2009 [24]	6.2 ± 0.8 (4-6m)	6.2 ± 0.8 (4-6m)	7.8 ± 0.8 (4-6m)	7.8 ± 0.8 (4-6m)	>20% IOP red	75 (4-6m)	75 (4-6m)
Katz, 2012 [21]	6.3 ± 2.7 (12m)	6.3 ± 2.7 (12m)	7.0 ± 1.8 (12m)	7.0 ± 1.8 (12m)	IOP ≤ 2 mmHg above target IOP + no VF loss ≥3 unit	80 (12m)	80 (12m)
Bovell, 2011 [26]	6.0 ± 6.1 (12m)	7.4 ± 7.3 (60m)	6.0 ± 4.8 (12m)	6.7 ± 6.6 (60m)	>20% IOP red	71 (12m)	25 (60m)
Liu, 2012 [27]	3.8 (12m)	1.8 (24m)	2.7 (12m)	2.8 (24m)	def 1. > 20% IOP red def 2. IOP<targetIOP	55 (12m)	def 1.40 (24m)* def 2. 75 (24m)*
Rosenfeld, 2012 [28]	4.3 (12m)	4.3 (12m)	3.23 (12m)	3.23 (12m)	≥15% % IOP red	75 (12m)	75 (12m)
Kent, 2013 [29]	6.8 (6m)	6.8 (6m)	7.0 (6m)	7.0 (6m)	>20% IOP red	73 (6m)	73 (6m)

Abbreviations: IOP red= IOP reduction; m= months; y= year; NA= not available; VF= visual field; def= definition; end of study= when study was longer than 12 months
*Results of Liu et al. [27] at end of study, 37 months, were not available

Long term effect

The effect of ALT diminishes over time and the 5-year success rate is reported to be about 50%[26]. Long-term effectiveness of SLT seems to show similar results. Bovell et al.[26] started with a 71% success rate at 1 year, which decreased to 52% at 2 years, 44% at 3 years, 38% at 4 years, and 25% at 5 years. Lai et al.[22] reported a success rate of 97% one year after SLT and 72% 5 years after SLT, but as noted, their definition of success was less stringent (IOP below 21 mmHg).

The usefulness of SLT and its possible cost-efficient character[12, 48] thus relies upon its repeatability. Hong et al.[39] published one of the first studies on repeat SLT. They examined the effect of a second SLT over 360° in patients who underwent an initial 360° SLT that was successful for more than 6 months but eventually lost efficacy. They recorded no significant difference between treatments and equal success rates after the first and the second SLT. They also compared the group of patients who had a second SLT after 6 months with a group that only needed a second SLT after 12 months and found no differences. They concluded a repeat SLT could be performed as soon as 6 months after a successful first SLT.

Ayala et al.[42] treated only 180° of the TM and examined if repeat SLT had better results when it was performed in another area as the first SLT. After a failed SLT, they randomized patients to receive a second SLT in the same or in a different area than the first SLT. This made no difference, which supports the minimal damage theory.

Table 3. Side effects mentioned in the randomized clinical trials using SLT								
Author, year, ref	Drops before SLT	Drops after SLT	Redness first week	Discomfort first week	Anterior chamber reaction first week	Definition IOP spike	IOP spike (%)	Other side-effects
Lai, 2004 [22]	apra	apra 1x+ pred 4x, 7d	yes	NA	yes	> 5mmHg	10.34	no
Nagar, 2005 [23]	ameth	dex or keto 4x, 5d	NA	90°=6% 180°=20% 360°=39%	90°=31% 180°=41% 360°=50%	≥ 5mmHg	90°=9% 180°=16% 360°=27%	no
Nagar, 2009 [24]	ameth	keto 4x, 5d	NA	NA	NA	NA	NA	NA
Katz, 2012 [21]	NA	NA	NA	NA	NA	NA	NA	no
Bovell, 2011 [26]	apra or brim	pred 4 x, 5d	NA	NA	NA	≥6mmHg	4.5	NA
Liu, 2012 [27]	brim	fluoro 4x, 5d	NA	NA	NA	NA	no	no
Rosenfeld, 2012 [28]	apra	dex 3x, 7d	NA	NA	NA	NA	NA	no
Kent, 2013 [29]	brim + pilo	keto 4x, 5d	NA	NA	NA	> 6mmHg	NA	NA

Abbreviations: NA= not available; apra=1% apraclonidine; pred=1% presnisolone acetate; ameth= 1% amethocaine; dex=0.1% dexamethasone; keto=ketorolac; brim= 0.2 or .15% brimonidine; fluoro=0.1% fluoromethalone; pilo= 1% pilocarpine; 4x= 4 times daily, 5d= for 5 days

Side effects of SLT

Redness, discomfort and anterior chamber reaction in the first week after SLT are very common. Nagar et al.[23] recorded discomfort and pain in the first week in 6% of the patients that underwent 90° SLT, 20% after 180°, and 39% after 360°. Anterior chamber reaction/uveitis was present in 31% of patients after 90° SLT, 41% after 180°, and 50% after 360° treatment. These adverse effects were common but much less pronounced than after ALT[49].

Seven of the RCTs used steroids or non-steroidal anti-inflammatory drops after SLT to diminish the side effects (see Table 3). Katz et al.[21] did not mention the use of pre- or post laser drops. Other short lived side effects include headache, photophobia, corneal abrasion, pigment dispersion and subconjunctival haemorrhage[25].

IOP spike

The transient IOP spike after laser trabeculoplasty is supposed to be dependent upon the energy used per pulse and the total energy administered[50]. Since SLT uses much less energy than ALT (0.9 mJ compared to 50 mJ per pulse) the IOP-rise is much less common and less pronounced[26-28, 49]. Still, a short increase of more than 5 mmHg above baseline IOP was recorded in 4.5-27% of patients in three of the RCTs (Lai et al.[22], Nagar et al.[23] and Bovell et al.[26]).

As in ALT[50], a drop of apraclonidine[22, 33, 39, 51-53] or brimonidine[54-56] before and immediately after SLT can be used to prevent the IOP spike. Seven of the RCTs mentioned the use of apraclonidine, amethocaine, or brimonidine prior to SLT. If IOP elevation did occur, it was treated with anti-glaucoma medication.

Corneal changes

Transient corneal thinning and changes in endothelial cell count seem common after SLT, with recovery to normal after one month[57, 58]. In the eight RCTs, no other complications after SLT were noticed. Other studies reported on some rare corneal changes: two cases of transient corneal oedema[59] and one case of corneal decompensation[60] after SLT have been described.

Knickelbein et al.[35] reported 4 cases of corneal hydrops, a condition characterized by acute corneal oedema followed by stromal thinning. Their findings suggest that SLT induces cytokine production and activation of matrix metalloproteinase, which are also involved in destructive inflammatory responses and can enhance collagen degeneration by corneal fibroblasts.

Cystoid macular oedema

Two cases of cystoid macular oedema[61, 62] have been reported, but it is suggested that this kind of complication is related to previous complicated lens-surgery. Caution would be needed in patients after compromised cataract surgery. Other very rare complications that have been reported include one case of iritis and choroidal effusion[63] and two cases of hyphema[64] after SLT.

Conclusions

Robust evidence was presented that there is no significant difference in IOP lowering effect between medication and SLT or between ALT and SLT. At 6 months to 1 year, the success rate of SLT varied between 55 and 82%. Higher baseline IOP is correlated to higher IOP lowering effect of SLT.

Side effects of SLT are minor. A transient IOP spike one hour after laser is common. Apraclonidine, amethocaine, or brimonidine drops can be administered before and immediately after SLT to counter this IOP rise. More severe side effects like corneal or macular oedema, peripheral anterior synechiae, hyphema, severe uveitis or persistent IOP rise are very rare.

Topics to be addressed in the future:
Further investigation is needed to demonstrate if SLT can be repeated enough to maintain IOP under control for decades on end. Possibly, the future of SLT lies in a yearly application of a smaller number of spots, as is currently under investigation by Gandolfi et al. (Vienna, SOE meeting, 2015).

In conclusion:
SLT may be introduced into glaucoma management algorithms in two ways. First, as a primary treatment to patients with OAG, comparable in efficacy to medication. Second, as a treatment alternative for patients not controlled with maximally tolerated medication, before invasive surgery.

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Power is not energy

ALT is often expressed in power (mW), while SLT is often expressed in energy (mJ). These entities should not be compared, since they are quite different.

Letter to the Editor: Power is not energy

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Letter to the Editor:

In an article comparing selective laser trabeculoplasty (SLT) to argon laser trabeculoplasty (ALT), Kent et al. [1] made a very common mistake of comparing power to energy.

Very often, ALT is expressed in power (500-800 mW), while SLT is expressed in energy (0.8-1.2 mJ). To compare the two, it is better to use the same measure, energy.
Since an ALT spot lasts 0.1 sec, ALT produces an energy of 50-80mJ. However, the habbit of comparing different measures is widespread.
Kent et al. use the term 'total energy used': this would normally express the sum of energy used for all spots together. This was expressed in mW (power) for ALT, and in mJ (energy) for SLT. This is a comparison of two different things.

The article recorded a total energy of 31.9 mJ for the SLT. For a mean of 53 spots, this gave 0.6 mJ per spot, which is a normal amount of energy.
For ALT, the group recorded a 'total energy' of 632.2 mW or more correctly 63.22 mJ. For a mean of 51 spots, this gave 1.239 mJ for each spot (12.39 mW), which is a totally unrealistic amount of energy for ALT.
There must have been some mistake in the calculation of 'total energy used', but please note that energy should always be expressed in Joules or mJ and not Watt or mW.

Reference

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Response to Reader's Comment on "Power is Not Energy"

*Francie Fengqin Si, MD, MSc**
and Cindy Hutnik, MD, PhD, FRCSC†*

We thank you for the enquiry about our published paper in JOG-D-16-002 and appreciate the comment from Dr Myrjam De Keyser.

It is a standard protocol in most clinical settings for the argon laser trabeculoplasty (ALT) power to be set between 500 and 800 mW per 50 micron spot for ALT. Similarly it is standard for the frequency-doubled neodymium: YAG laser to be set between 0.8 and 1.2 mJ per spot for selective laser trabeculoplasty (SLT).

We agree with Dr De Keyser that the table in which we compared the 2 was confusing. It is absolutely correct that power and energy have different units and hence, although related, are not equivalent.

The power of a laser is measured in Watts or mW, whereas the energy is in Joules or mJ. The energy of a laser typically refers to the output of a pulsed laser and is related to the power output,[1] where the energy (E) is the laser's peak power (P_{peak}) multiplied by the laser pulse duration (t):

$$E = P_{peak} \times t.$$

The value 632.2 mW in Table 1 that we quoted indicates the average power range per spot that was used for ALT. Herein we have converted this value to energy per spot of 63.22 mJ. The spot duration was 0.1 second. As we conducted 51 spots per ALT session, the total energy per ALT session was 63.22 times 51, which totals 3224.22 mJ. Thus, Table 1 shall be modified as below.

TABLE 1. Baseline Clinical and Surgical Parameters Comparisons [mean (SD)]

	ALT	SLT	*P*
Age	73.0 (8.09)	72.9 (9.86)	0.97
Sex (F) (%)	64	68	0.77
logMAR BCVA	0.24 (0.36)	0.27 (0.45)	0.78
Angle grade*	11% grade 2	23% grade 2	0.36
Meshwork pigmentation†	45% grade 2	67% grade 2	0.13
Maximum recorded preoperative IOP	27.3 (4.84)	25.9 (7.42)	0.04
Preoperative baseline IOP	25.2 (4.87)	23.1 (4.22)	0.03
Total energy used (mJ)/session	3224.22 (817.02)	31.9 (29.41)	NA
No. spots	51 (3.86)	53 (3.75)	0.03

*Gonioscopic grading system.
†Trabecular meshwork pigmentation grading: 0 = none, 1 = light, 2 = medium, 3 = dark brown, 4 = almost black.
ALT indicates argon laser trabeculoplasty; BCVA, best corrected visual acuity; IOP, intraocular pressure; NA, not available; SLT, selective laser trabeculoplasty.

It has been suggested that the SLT treatment delivers a fraction of the laser energy (< 1%) compared with ALT.[2] Our modified result shows that the energy used in SLT is about 1% of the energy used in ALT per laser session, which is consistent with the literature.[2]

Please let us know if you have any more questions.

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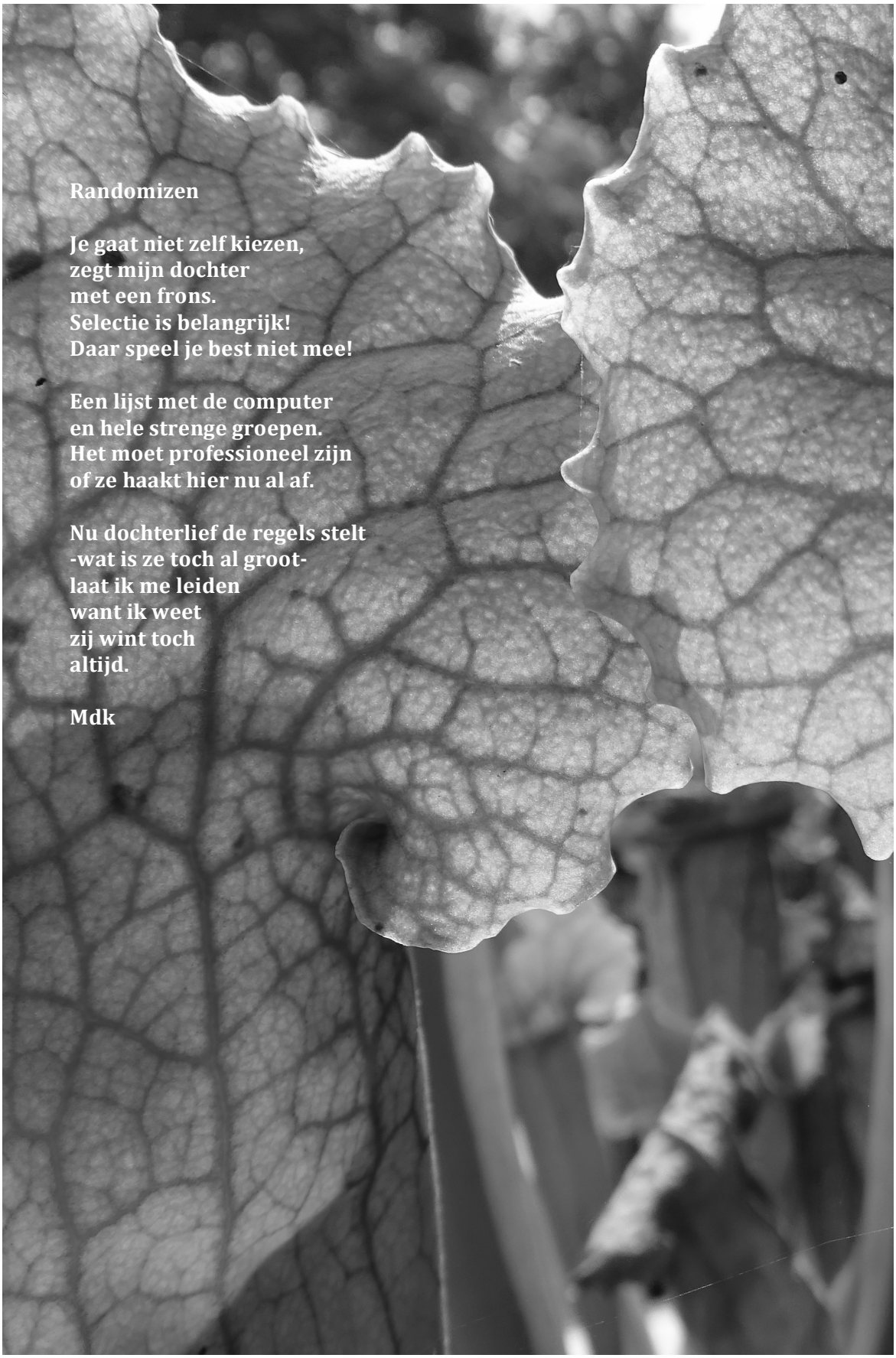

Randomizen

Je gaat niet zelf kiezen,
zegt mijn dochter
met een frons.
Selectie is belangrijk!
Daar speel je best niet mee!

Een lijst met de computer
en hele strenge groepen.
Het moet professioneel zijn
of ze haakt hier nu al af.

Nu dochterlief de regels stelt
-wat is ze toch al groot-
laat ik me leiden
want ik weet
zij wint toch
altijd.

Mdk

CHAPTER 4. General set of the thesis: methods, assessment and aims

The study was designed as a randomized prospective clinical trial. In this chapter we go through the study protocol in detail. We explain our primary goal and all secondary targets.

PURPOSE

In our public hospital we had a 'difficult' population. There was a tendency to irregular follow up examinations (no show), lac of means and discipline to use glaucoma medication. This compromised therapy. Laser could be a non-invasive treatment to partly solve these problems.
There were only eight randomized clinical trials (RCT) on the efficiency of SLT. No RCTs investigated the possibility to replace medication with SLT. So we decided to perform a clinical study to evaluate whether SLT could replace medical therapy.

STUDY PROTOCOL

Prospective, randomized clinical trial at the glaucoma consultation of ZNA Jan Palfijn Hospital, Merksem. Trial registration NTR5417.
Approval of the ethics committee of the clinic was obtained (4313 MEC).

Patient recruitment

Inclusion criteria: any form of open angle glaucoma or ocular hypertension, already medically treated and with IOP under control. Patients had to agree to sign an informed consent form.
Exclusion criteria: any other kind of glaucoma than open angle glaucoma. Previous laser trabeculoplasty or glaucoma surgery. Corneal disease that prevents visualisation of the anterior angle. Use of systemic or topical steroids.

Baseline examinations

Demographic data were recorded: sex, age, risk factors for glaucoma (myopia, arterial hypertension, diabetes mellitus, migraine, vascular problems, family history of glaucoma), previous ocular problems, type of glaucoma.

At baseline a **full ophthalmological examination** of each study participant was conducted, including a medical history review, best-corrected visual acuity measurement, IOP measurement using Goldmann applanation tonometry (mean of two measurements was taken), slit lamp examination of the anterior segment (conjunctival injection, tear break up time, cornea, iris, lens appearance, gonioscopy), central corneal thickness (CCT)

measurement, dilated fundus examination, visual field examination by computerized perimetry (program 24-2, Humphrey Field Analyzer 745i, Zeiss, Jena, Germany), Optical Coherence Tomography (OCT) of the optic nerve head and recording of glaucoma medications and artificial tears used prior to SLT.
All OCT scans were performed with the spectral-domain OCT RTVue (Optovue, Fremont, USA). We used focal loss of volume (FLV) as determinant for the OCT (Zhang, American Glaucoma Society, Washington, March 1, 2014).

Maximal IOP before treatment was calculated as the mean of three measurements taken before starting glaucoma medication at three different days, at least 3 to 6 months apart. IOP at baseline was calculated as the mean of the Goldmann measurements made on the three last examinations before laser treatment, while on the same medication.
Clinical evaluation of inflammation/cells in the anterior chamber was carried out with a slit lamp. The beam of the slit lamp microscope projected at 45 degrees transverses the cornea and shows light scattering in the anterior chamber and cellular inflammatory cells in the aqueous humor. The light intensity and magnification of the slit lamp were put maximal; the beam 3 mm long and 1 mm wide.[1]
The same examiner performed all examinations.
Patients were also asked to fill out the **TSS-IOP questionnaire** after the baseline examination.

Randomization

Randomization was performed with a computer-generated allocation schedule that assigned patients to six possible groups:

1. get SLT done in both eyes, with Dexamethasone in the right eye and no drops in the left eye after SLT
2. get SLT done in both eyes, with no drops in the right eye and Dexamethasone in the left eye after SLT
3. get SLT done in both eyes, with Indomethacin in the right eye and no drops in the left eye after SLT
4. get SLT done in both eyes, with no drops in the right eye and Indomethacin in the left eye after SLT
5. continue on medication
6. continue on medication

Post laser treatment consisted of one drop of Dexamethasone or Indomethacin, three times a day for a week or no drops.

Laser technique

A frequency doubled, Q-switched Nd:YAG laser was used, coupled to a slit lamp delivery system (Selecta Duet 5 ™, Lumenis, Tel Aviv, Israel). This emitted a wavelength of 532 nm. We used single pulses with a pulse duration of 3 nsec and spot size of 400µm. Laser

energy was initially set at 0.9 mJ and increased in steps of 0.1 mJ until minimal bubble formation was observed. We aimed to achieve minimal bubble formation at each laser point. All patients received 360° treatment of the TM. The same experienced surgeon (MDK) applied all treatments.

Immediately before the laser procedure a drop op pilocarpine 1% and apraclonidine 0.5% were instilled into the treated eye. After the laser treatment, a drop of apraclonidine 0.5% was instilled in the treated eye. As further postoperative treatment Indomethacin or Dexamethasone drops were given 3 times daily for one week. The first drop was administered immediately after laser. The other eye of the same patient received no drops. Depending on study protocol this could be the right or the left eye. The second eye (always left) was treated one week later.
All patients continued with the same anti-glaucomatous medical treatment after SLT.

Postoperative management
Patients were examined at 1 hour, 1 week and 1, 3, 6, 12 and 18 months after SLT. They were encouraged to report any discomfort or change in vision. IOP was measured; pain sensation, conjunctival injection and cells/pigmentation in the anterior chamber were registered. These last three were assessed on a scale of 0-4 (4= most pain or highest inflammation) according to the Standardization of Uveitis Nomenclature.[2] These clinical parameters of inflammation were chosen because of their clinical significance.[3] A slit lamp examination of anterior and posterior segment was performed at each visit. At 6 months and every six months thereafter, the same parameters as at baseline were assessed, including the TSS-IOP questionnaire.

Anti-glaucoma drops were continued until IOP was more than 2 mmHg below target pressure. At this point they were stopped one by one. For example a Latanoprost-Timolol combination was considered as a combination of two separate medications. The first step entailed a switch to Latanoprost. If possible, the second step involved the discontinuation of Latanoprost at the next check up.

Assessment of QoL
QoL scales can be complicated, not user-friendly and contain a myriad of complex mathematics. In a review of 2008, Severn et al. tried to highlight the strengths and weaknesses of several QoL-tests on the market[4]. Many questionnaires capture the influence of vision related problems in glaucoma patients (NEI-VFQ 25, COMTOL)[4]. Jowever, within the time period of this study we did not expect major changes in vision.

Atkinson et al.[5,6] examined patient's satisfaction with their glaucoma therapy using a new test, the Treatment Satisfaction Survey for Intraocular Pressure (TSS-IOP). The questionnaire was designed to assess patient satisfaction with various elements

associated with topical medications to control intraocular pressure. We were given kind permission by Pfizer to use this survey for the duration of our study.

QUESTIONS/AIMS

Primary question:

Can SLT be used as a replacement therapy to medication in well controlled glaucoma?

Secondary questions:

1. The effect of SLT relies on an inflammatory reaction. Anti-inflammatory therapy is often used immediately following SLT. Does this influence the IOP lowering effect or the side effects after SLT?
2. Does pseudophakia influence the IOP lowering effect of SLT?
3. Can structural variations of the eye, as corneal thickness, influence the outcome of SLT?
4. Is there a significant difference in IOP lowering effect of SLT in normal or high tension glaucoma?
5. Anti-glaucoma eye drops have a lot of side effects. Does SLT improve quality of life by reducing the side effects and number of eye medications?

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CHAPTER 5. Impact of anti-inflammatory drops

After ALT, we were used to apply anti-inflammatory drops. This habit still remains after SLT[29]. But the effect of SLT relies on an inflammatory reaction of the TM and using anti-inflammatory products after SLT may diminish the IOP lowering effect.

We randomized patients to receive one of two possible anti-inflammatory eye drops (Indomethacin or Dexamethasone) in one eye and nothing in the other eye. Immediate side effects (redness, pain, cells in the anterior chamber, IOP peak), evolution of IOP and number of medications needed were recorded.

Randomized prospective study of the use of anti-inflammatory drops after selective laser trabeculoplasty.

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This subject was presented at:
European Society of Ophthalmology, June 2015, Vienna, Austria

Abstract

Purpose
Evaluating the use of Indomethacin, Dexamethasone and no anti-inflammatory treatment immediately after selective laser trabeculoplasty.

Materials and Methods
Prospective randomized clinical trial of 132 eyes. Both eyes of the patient underwent SLT. One of the eyes was treated with Indomethacin 0.1% or Dexamethasone 0.1% 3 times daily for 1 week, the other eye did not receive any anti-inflammatory treatment. IOP and inflammatory parameters were recorded at 1 hour, 1 week, 1, 3 and 6 months.

Results
Cells in the anterior chamber were present in 57-71% of the patients after one hour. 16-37% of the patients reported pain/discomfort after one hour. Redness was present before SLT in 29-34% of the patients, probably due to anti-glaucoma medication. After one hour, the amount of redness recorded raised to 32-42%, but the amount of patients with redness returned to pre-treatment levels after one week. An IOP peak of more than 5mmHg above baseline IOP one hour after laser was present in 3-9% of the patients. IOP lowered 11-21% compared to IOP at baseline. The number of medications needed changed from 1.45-1.49 before, to 0.23-0.45 six months after SLT.
No differential effects based on the kind of anti-inflammatory treatment or no treatment were found for any of the parameters.

Conclusions
SLT induces little inflammation: anti-inflammatory drops do not make a significant difference in pain, redness, cells in anterior chamber or peak IOP following SLT.
The IOP lowering effect of the SLT is not influenced by the use of Indomethacin or Dexamethasone.

Introduction

Laser trabeculoplasty is widely accepted as a valuable tool for the treatment of glaucoma[1]. After argon laser trabeculoplasty (ALT), side effects like transient tension rise[2,3], peripheral anterior synechiae[3], cystoid macular oedema[4], refractive changes[4] and iritis[5] have been described. To diminish the immediate inflammatory reactions of the eye, anti-inflammatory drops are often prescribed[1,5,6].

Selective laser trabeculoplasty (SLT) is a more recent technique[7] with less side effects [8], but the habit of using anti-inflammatory drops after laser has persisted[8-12]. Postoperative medication after SLT consists of non-steroidal anti-inflammatory drops (NSAID)[9,13-17] or steroid drops three or four times a day for three to seven days[10,12,18-23]. In order to reduce the postoperative intra ocular pressure (IOP) spikes, amethocaine[9,20], brimonidine [13,14,19,23] or apraclonidine drops[12,16,18,19] are often given prior to and/or immediately after[10,12,16,18] laser treatment. Some of the more recent studies only use pilocarpine before SLT[24] and/or no other drops after the laser[24,25].

The functional mechanism of SLT remains unclear, but microscopy shows minimal tissue damage to the trabecular meshwork (TM), so a cellular or biochemical pathway is more likely than a mechanical one[26]. These pathways have been demonstrated in ALT[27,28]. In ALT, Mermoud et al. [5] recorded larger decreases in pressure for those eyes that had significant anterior chamber inflammation. This latter finding suggests that prostaglandin release by the TM may increase inflammation but also improves IOP lowering effect. Since SLT relies more on the inflammatory reaction of the eye than ALT does, it is possible that the use of anti-inflammatory post-laser drops may be counterproductive.

To the best of our knowledge, this is the first prospective randomized study investigating anterior chamber inflammation after SLT treatment while comparing the use of different anti-inflammatory drops.
We aim to determine whether the anti-inflammatory effect of Indomethacin or Dexamethasone drops immediately used after SLT makes a significant difference in observed inflammation of the anterior segment, IOP spike and/or the IOP lowering effect of the laser.

Materials and Methods

Study design and subjects

A prospective, randomized clinical trial including 66 consecutive patients, 132 eyes at the glaucoma consultation at ZNA Jan Palfijn Hospital, Merksem, Belgium. Enrolment occurred from January 2014 to July 2015. Recruitment finished after the admission of 140 patients, a goal set before study commencement. The main goal of the study focused on the use of SLT in order to lower the amount of prescribed anti-glaucoma medication and examine effects of SLT on the quality of life.

Approval of the ethics committee was obtained (EC 4313), we followed the guidelines of the Helsinki Declaration. The trial was registered by the Dutch Trial Register: NTR 5417. Data were recorded at baseline, at one hour, one week, one, three and six months post-SLT.

Inclusion criteria concerned primary open angle glaucoma (POAG), normal tension glaucoma (NTG) or ocular hypertension (OHT) controlled with medical therapy. Only patients with recording of all data at all time points were included. Patients had to agree to sign an informed consent form.
Exclusion criteria were other types of glaucoma than open angle glaucoma, previous trabeculectomy or laser trabeculoplasty treatment. Patients with corneal disease that inhibited good visualization of the TM and those taking systemic steroids were also excluded from the study.

POAG was defined as IOP above 21 mmHg on two separate occasions, open angle on gonioscopy and either glaucomatous visual field defects on Humphrey visual field analyser, optic disc changes on funduscopy and/or loss of retinal nerve fibre layer on Optical Coherence Tomography (OCT). NTG was defined as analogue changes in visual field, optic disc and/or retinal nerve fibre layer but with a Goldmann applanation measured IOP ≤ 21 mmHg [10]. The diagnosis of OHT was made when an IOP higher than 21 mmHg was measured on two separate occasions in the absence of field or disc changes or defects in retinal nerve fibre layer.

Randomization of patient allocation was performed with a computer-generated allocation schedule using a blocked allocation sequence of 6 possibilities per block. Patients were consecutively introduced into the study, only after introduction of the personal patient data, the allocated group became clear to patient and observer. No further masking was executed.

Both eyes received SLT, the right eye was treated first, the second eye was treated one week later. While one eye was treated with Indomethacin 0.1% (Indocollyre®, Bausch & Lomb, Montpellier, France) or Dexamethasone 0.1% (Maxidex®, Alcon, Puurs, Belgium) drops three times a day for one week, the other eye received no anti-inflammatory drops. Randomization scheduled patients to receive either Indomethacin or Dexamethasone in the computer assigned eye.
Any difference in inflammatory parameters after (non) treatment with anti-inflammatory medication is likely to occur within the first week after SLT [7]. Even if the anti-inflammatory medication would influence the contralateral eye, the drops used for the first eye are unlikely to have any effect on the second eye since this was treated one week later.

This study was not designed to create an additional IOP lowering effect, because IOP was already controlled with medication before treatment with SLT. The main goal of this study involved the maintenance of the same low IOP after SLT with reduced medication use.

Baseline examinations

At baseline a full ophthalmological examination of each study participant was conducted, including a medical history review, best-corrected visual acuity measurement, IOP measurement using Goldmann applanation tonometry (mean of two measurements was taken), slit lamp examination of the anterior segment (conjunctival injection, tear break up time, cornea, iris, lens appearance, gonioscopy), central corneal thickness (CCT) measurement, dilated fundus examination, visual field examination by computerized perimetry (program 24-2, Humphrey Field Analyser 745i, Zeiss, Jena, Germany), Optical Coherence Tomography (OCT) of the optic nerve head and recording of glaucoma medications and artificial tears used prior to SLT (Table 1).
All OCT scans were performed with the spectral-domain OCT RTVue (Optovue, Fremont, USA). We used focal loss of volume (FLV) as determinant for the OCT (Zhang, American Glaucoma Society, Washington, March 1, 2014).

IOP before treatment was calculated as the mean of three measurements taken before starting anti-glaucoma medication. IOP at baseline was calculated as the mean of the Goldmann measurements made on the three last examinations before laser treatment, while on the same medication.

Clinical evaluation of inflammation/cells in the anterior chamber was carried out with a slit lamp. The beam of the slit lamp microscope projected at 45 degrees transverses the cornea and shows light scattering in the anterior chamber and cellular inflammatory cells in the aqueous humour. The light intensity and magnification of the slit lamp are put maximal, the beam 3 mm long and 1 mm wide.[24]
The same examiner performed all examinations.

Laser technique

A frequency doubled, Q-switched Nd:YAG laser was used, emitting a wavelength of 532 nm, coupled to a slit lamp delivery system (Selecta Duet 5 ™, Lumenis, Tel Aviv, Israel). We used single pulses with a pulse duration of 3 nanosec and spot size of 400µm. Laser energy was initially set at 0.9 mJ and increased in steps of 0.1 mJ until minimal bubble formation was observed. We aimed to achieve minimal bubble formation at each laser point. All patients received 360° treatment of the TM. The same experienced surgeon (MDK) applied all treatments.

Immediately before the laser procedure a drop op pilocarpine 1% and apraclonidine 0.5% were instilled into the treated eye. After the laser treatment, a drop of apraclonidine 0.5% was instilled in the treated eye. As further postoperative treatment Indomethacin or Dexamethasone drops were given 3 times daily for one week. The first drop was administered immediately after laser. The other eye of the same patient received no drops, depending on study protocol this could be the right or the left eye. The second eye (always left) was treated one week later.
All patients continued with the same anti-glaucomatous medical treatment after SLT.

Postoperative management

Patients were examined at 1 hour, 1 week and 1, 3 and 6 months after SLT. They were encouraged to report any discomfort or change in vision. IOP was measured, pain sensation, conjunctival injection and cells/pigmentation in the anterior chamber were registered. These last three were assessed on a scale of 0-4 (4= most pain or highest inflammation) according to the Standardization of Uveitis Nomenclature[29]. These clinical parameters of inflammation were chosen because of their clinical significance[25]. A slit lamp examination of anterior and posterior segment was performed at each visit.

At 6 months the same parameters as at baseline were assessed. Anti-glaucoma drops were continued until IOP was more than 2 mmHg below target pressure, at which point they were stopped one by one. For example a Latanoprost-timolol combination was considered as a combination of two separate medications, the first step entailed a switch to Latanoprost, if possible, the second step involved the discontinuation of the use of Latanoprost at the next check up.

Statistical methods

In order to calculate sample size, the expected difference between the two groups and an acceptable error must be known. Since no clinical trial previously examined the effect of NSAID or steroids on SLT side effects or IOP lowering effect, the expected difference was unknown. Hence a priori it was decided to enrol 35 patients into each group in this trial.

The baseline comparability of both patient groups was tested by performing a Student's t-test on paired data to compare difference between age, laser specifications (i.e. energy and number of points), IOP at medical baseline, MD, vision, central corneal thickness, visual field, cup-disc ratio, OCT, focal loss of volume and the maximum observed IOP before treatment. A Wald chi-square test was performed on gender, type of glaucoma, number of risk factors, number of medications taken at baseline.

Further analyses were executed to compare differences between four groups: Indomethacin and Dexamethasone groups and their respective control groups. A repeated measures ANOVA was executed to investigate the differences in evolution of mean IOP for all groups at all time points. The same time-evolution on number of used medications was tested using a Poisson log linear model (i.e. suited for nominal data). The results of the Wald chi-squared analysis are reported. Furthermore, the evolution of rating on cells anterior chamber, pain/discomfort and redness and the presence of a pressure peak over time were also tested using an ordinal logistic modelling approach (i.e. analyses suited for ordinal data). The Wald chi-squared tests results are reported.
Results of statistical analysis with p-values < 0.05 were considered to be significant.

Results

Table 1. Baseline characteristics

	Indo group N=35	Dexa group N=31	*p*-value
Demographics			
Age (years)	67.94 ± 10.99	68.32 ± 16.07	0.97
Sex (M/F) (%)	54.29/45.71	51.61/48.39	0.83
Risk factors*	1.49 ± 0.98	1.45 ± 0.93	0.87
Glaucoma parameters			
IOP baseline with medication (mmHg)	14.50 ± 3.81	13.45 ± 3.40	0.18
POAG/NTG/OHT (%)	63/28.5/8.5	48/42/10	0.48
Vision	0.85 ± 0.22	0.74 ± 0.29	0.02**
CCT (µm)	551.06 ± 35.94	541.18 ± 44.39	0.29
Cup disc ratio	0.77 ± 0.19	0.69 ± 0.25	0.06
Visual field MD	5.14 ± 6.78	5.47 ± 6.66	0.95
Visual field PSD	4.08 ± 3.44	4.63 ± 3.51	0.56
OCT FLV	4.73 ± 4.35	4.18 ± 4.59	0.59
IOP before medication (mmHg)	23.98 ± 6.00	22.02 ± 4.81	0.05
Medication at start			
Total number (mean)	1.40 ± 0.88	1.4 ± 0.91	0.39
Prostaglandin analogs (%)	85.71	87.10	
Betablocker (%)	34.29	35.48	
Carbo anhydrase inhibitor (%)	14.29	16.13	
Alphamimetics (%)	8.57	6.45	

Abbreviations: IOP, intraocular pressure; POAG, primary open angle glaucoma; OHT, ocular hypertension; BCVA, best-corrected visual acuity; CCT, central corneal thickness; MD, mean deviation; PSD, pattern standard deviation; OCT, optical coherence tomography; FLV, focal loss of volume in %

* Risk factor: myopia, arterial hypertension, diabetes, migraine, vascular problems, family history of glaucoma ** Statistically significant difference at $p<0.05$

Baseline characteristics

35 patients were given Indomethacin, 17 received it in the right eye, 18 in the left eye. All completed the entire follow up schedule. 35 patients received Dexamethasone in one eye, 17 in the right eye, 14 in the left eye. 31 of the patients in the Dexamethasone group completed a six months follow up. No severe complications were recorded, drop out was solely the result of patients not showing up at arranged follow up test moments. In total, 132 eyes of 66 patients were followed for six months. Demographic and baseline characteristics see Table 1.

Best-corrected visual acuity on Snellen chart was better in the Indomethacin group (0.85) compared to 0.74 in the Dexamethasone group. A trend was observed towards a slightly higher IOP before start of medication in the Indomethacin group (23.98 mmHg, opposed to 22.02 in the Dexamethasone group). No other significant differences were found between the two groups in terms of age, sex, presence of risk factors, severity of glaucoma and medication taken at baseline.

Laser technique

We used between 101.26 and 103.29 (t=1.14, p=0.26) of non-overlapping spots of SLT with a mean energy between 1.07 and 1.12 mJ (t=60, p=0.95). See Table 2. There were no significant differences in treatment modalities between the groups ($p > 0.05$).

Table 2. Laser specifications of SLT

Parameters	Indo group	Indo control group	Dexa group	Dexa control group	*p**
Energy (mJ)	1.07 ± 0.30	1.09 ± 0.28	1.11 ± 0.35	1.12 ± 0.32	0.26
Points	101.60 ± 6.05	102.71 ± 9.55	101.26 ± 9.70	103.29 ± 10.79	0.95

*Statistically significant difference at $p < 0.05$

Anterior segment reaction

Cells in the anterior chamber

The inflammatory reaction was always minimal (1+ cells) but very common. More than half of the patients showed presence of cells in the anterior chamber, 57.14% of patients in both the Indomethacin and its control group, compared to 70.97% in the Dexamethasone group and 64.52% in the Dexamethasone control group at the one hour check up.

After one week, no more cells were found in both of the Dexamethasone groups, only one patient still showed some reaction in the Indomethacin group, two in the Indomethacin control group (Table 3).
At no time point, there was a statistically significant difference between the treated groups and their control groups, nor between the two treatment groups (all $p > 0.05$).

Pain/discomfort

No patient gave his/her pain a value of more than 1 on a scale of 0 to 4. Around one third of the patients in the Indomethacin (34.29%) and Indomethacin control group (37.14%) complained of mild discomfort immediately after the treatment. With a significance of 0.005 the Indomethacin group showed more pain than the Dexamethasone group one hour after laser.
After one week, four patients who did not receive Indomethacin still complained of discomfort (11.43%) and five patients in the Dexamethasone control group (16.13%). However, the differences between the treated groups and their control groups, or between the two treatment groups did not reach a level of significance at any time point (all $p > 0.05$).

Table 3. Inflammatory parameters after SLT

	Time	Indo group (%)	Indo control group (%)	Dexa group (%)	Dexa control group (%)	*P**
Cells anterior chamber	1 hour	57.14	57.14	70.97	64.52	0.08
	1 week	2.86	5.71	0	0	1
	1 month	0	0	0	0	1
Pain/ discomfort	1 hour	34.29	37.14	25.81	16.13	0.005*
	1 week	0	11.43	3.23	16.13	1
	1 month	0	0	0	0	1
Redness	Before SLT	28.57	34.29	32.26	32.26	0.82
	1 hour	42.86	42.86	32.26	41.94	0.98
	1 week	28.57	37.14	9.68	29.03	0.66
	1 month	17.14	17.14	12.90	16.13	1
	3 months	5.71	5.71	3.23	3.23	0.73
	6 months	5.71	5.71	3.23	6.45	1
IOP peak	1 hour	5.71	2.86	8.57	8.57	0.07

*Statistically significant difference at $p < 0.05$

Conjunctival redness

A lot of patients already had light redness of the eyes before treatment with SLT (29-34%). This is probably due to the fact that they had been using several anti-glaucoma drops. The amount of patients with redness enhanced to 43% in both the Indomethacin and the Indomethacin control group one hour after laser (a raise of resp. 14.29% and 8.57%, Wald chi-square = 5.96, p = 0.02). After one week, the amount of patients with redness returned to pre-treatment levels in both groups (Wald chi-square = 17.02, p = 0.008). After 3 months, only 2 patients still had one red eye in the Indomethacin groups. The use of Indomethacin made no difference in redness after SLT.

In the Dexamethasone groups 32% of patients showed redness before treatment (32%). Redness occurred in 32% of patients on Dexamethasone compared to 42% of the patients without treatment after one hour (Wald chi-square = 7.02, p = 0.008) and resp. 9% of patients with Dexamethasone compared to 29% of patients without anti-inflammatory treatment after one week (Wald chi-square = 5.01, p = 0.02). Using a % gives the impression that this last difference (9.28% compared to 29.03) might be significant.
We acknowledge this but confirm that explicit statistical testing showed no difference on the raw data. In the Dexamethasone groups, one patient continued to have redness in both eyes after 3 months, a second one had two red eyes after six months.
However, at no time point there was a statistically significant difference between the treated groups and their control groups, nor between the two treatment groups (all p > 0.05).

IOP spike at one hour

A sudden rise in IOP of more than 5 mmHg one hour after SLT occurred in between 3-8.5% of the patients. The use of Indomethacin or Dexamethasone made no significant difference in the IOP spike (p > 0.05) (Table 3). No persistent IOP rise, cystoid macular oedema or other significant complications occurred.

Effect on efficacy

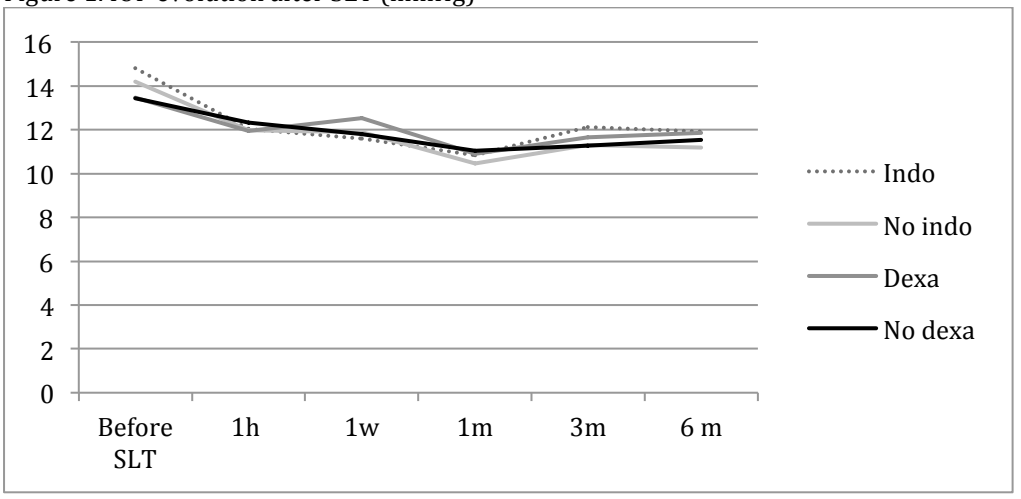
Table 4 and figure 1 show the evolution of the IOP after SLT.

Table 4. IOP evolution after SLT (mmHg) *

	Indo group	Indo control group	Dexa group	Dexa control group
Before SLT	14.82 ± 3.91	14.18 ± 3.73	13.46 ± 3.44	13.43 ± 3.41
1 hour	12.03 ± 4.95	11.97 ± 4.42	11.94 ± 3.66	12.32 ± 4.39
1 week	11.60 ± 4.23	11.89 ± 4.78	12.52 ± 3.64	11.79 ± 3.66
1 month	10.83 ± 4.22	10.46 ± 3.97	10.90 ± 2.97	11.03 ± 3.26
3 months	12.11 ± 5.14	11.31 ± 4.53	11.65 ± 3.07	11.26 ± 3.19
6 months	11.91 ± 4.25	11.20 ± 3.60	11.87 ± 2.97	11.54 ± 3.63

* Statistical analysis showed no interaction between time and group. No post-hoc t-test was performed, since the groups did not differ. IOP lowers in time for all groups.

Figure 1. IOP evolution after SLT (mmHg)



There was no significant difference in IOP lowering effect between the Indomethacin group and its control group, neither between the Dexamethasone group and its control population, nor between Indomethacin and Dexamethasone groups. Since the groups did not differ, no post-hoc t-test could be performed. There was no interaction between time and group. IOP decreased in time in all groups.
Since this was a population with controlled IOP, the main aim was to keep a low IOP while medication could be lowered. This was achieved in all groups.

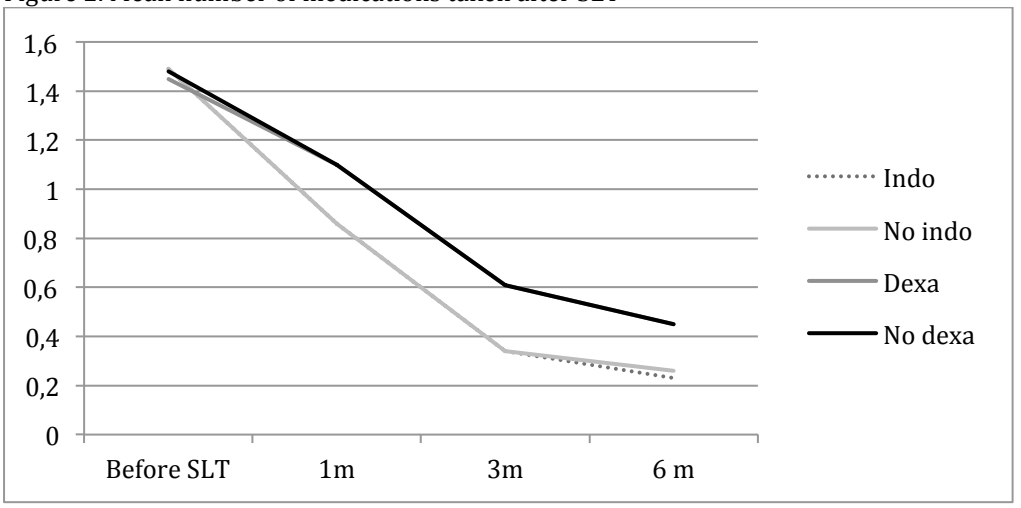
Medication was discontinued at 1 and 3 months if IOP was 2 mmHg lower than target IOP. The mean number of medications lowered from 1.49 to 0.23-0.26 in the Indomethacin groups and from 1.45-1.48 to 0.45 in the Dexamethasone groups (Table 5 and figure 2).

Table 5. Mean number of medications taken after SLT*

	Indo group	Indo control group	Dexa group	Dexa control group
Before SLT	1.49 ± 0.85	1.49 ± 0.85	1.45 ± 0.89	1.48 ± 0.85
1 month	0.86 ± 0.91	0.86 ± 0.91	1.10 ± 0.94	1.10 ± 0.94
3 months	0.34 ± 0.54	0.34 ± 0.54	0.61 ± 0.92	0.61 ± 0.92
6 months	0.23 ± 0.49	0.26 ± 0.51	0.45 ± 0.72	0.45 ± 0.72

- Statistical analysis showed no interaction between time and group. A post-hoc t-test was not performed, since the groups did not differ. No main effect is observed for applied treatment.

Figure 2. Mean number of medications taken after SLT



Number of medications after one hour and one week were the same as before SLT. After one month, there was a significant difference in number of medications taken compared to 'before SLT' ($p < 0.001$)
After 6 months 27-28 of the patients in both Indomethacin groups (77-80%) and 20 patients in both of the Dexamethasone groups (65%) no longer needed any medication. In the Dexamethasone groups, 9 patients (29%) still needed one medication after six months, in the Indomethacin groups only 6 and 7 patients (17-20%) were still on one anti-glaucoma drop (Table 6).
With significance values all above 0.05, there was no effect observed between applied treatment and no treatment.

Table 6. Medications needed after 6 months

	Indo group N=35	Indo control group N=35	Dexa group N=31	Dexa control group N=31	Indo/dexa comparison *p**
No medication	28	27	20	20	0.06
One	6	7	9	9	0.29
Two	1	1	1	1	0.92
Three	0	0	1	1	1

Abbreviations: Indo, Indomethacin; Dexa, Dexamethasone
*Statistically significant difference at $p < 0.05$

Discussion

ALT is a commonly used method to treat open angle glaucoma. The complications after ALT[2-5] seem to arise from introducing laser energy into the eye. Therefore the least amount of laser energy that achieves the desired effect is the appropriate amount to use [4, 22].
Selective laser trabeculoplasty (SLT) is an alternative laser treatment. It selectively affects pigmented TM cells that exhibit greater optical absorbance of the applied laser energy than the cells that surround them[30]. Histologic studies have shown that there is less coagulation damage after SLT compared to ALT[26]. SLT allows the use of lower energy levels than ALT (0,9 mJ compared to 50 mJ in ALT) in shorter pulses (3 nanosec) and spread over a larger spot size (400 µm compared to 50 µm)[7,31].

The total energy per µm of spot size in SLT is around 3500 times lower than that of ALT. This provides a theoretical basis for less irritation and less side effects after SLT, as was indeed recorded by Martinez et al.[15]. His group studied pain after laser and the presence of flare (laser flare meter) after SLT compared to ALT. At one hour after treatment, the anterior chamber flare was lower in SLT than in ALT[15]. Pain reported by the patients during treatment was also lower in the SLT group[15]. Damji reported more inflammation of the anterior segment after SLT than ALT, but this was never confirmed in another study[6].

Cells in the anterior chamber

In the initial study of 180° SLT by Latina et al., 83% of the eyes showed inflammation within one hour after treatment on split lamp examination, decreasing by 24 hours after treatment and completely resolving within 5 days of treatment[7,32]. This was confirmed by the work of Lai et al. who found no persistent anterior chamber reaction longer than one week after laser[12]. Other studies tried to record presence of cells on the second day instead of within the first hours and found no sign of anterior chamber inflammation[18,24].

In our study, the anterior chamber reaction occurred in every group (57-71%) one hour after SLT. Since we examined the anterior segment only with the slit lamp, it is very likely that we saw debris and pigment created by the treatment and not only an inflammatory reaction[15]. After one week, very few eyes still showed cells in the anterior chamber (one eye in the Indomethacin group, two in the Indomethacin control group). Nagar et al. noticed that anterior chamber reaction was dependent upon the amount of area treated. In their study, anterior chamber reaction occurred in 31% of patients after treating 90° of the TM, in 41% after 180° treatment and in 50% after 360° respectively[20]. The anterior chamber reactions in our study occurred in every group, independent of the type of treatment after SLT and also in the two groups of eyes without any anti-inflammatory treatment.

Discomfort

Latina et al. reported that 15% of eyes receiving SLT reported discomfort after the laser[7,32]. Nagar et al. noted complaints of discomfort in 6% of patients after 90° treatment by SLT, in 20% of patients after 180° and in 39% after 360°[20]. Martinez et al. recorded pain and presence of cells/flare in the anterior chamber after SLT and ALT and found both significantly less in the SLT-group[15]. Our study findings were consistent with the ones in Nagars study, in 16-37% of patients one hour after treatment, with very few patients complaining after one week.

Conjunctival redness

We recorded a high number of redness of the anterior segment (29-34%) before laser therapy in our patients. All were glaucoma patients who had been using several anti-glaucoma drops for a long time. Only 10 eyes (15%) used preservative free medication, as these have only recently been introduced. We assume the detrimental effect of preservatives in the anti-glaucoma medication has influenced the basic state of our patients. This concurs with Pisella et al. who reported a prevalence of 38% of conjunctival hyperaemia in a large epidemiological survey of 4107 patients using preserved glaucoma medication[33].

Baudouin et al. demonstrated that long term use of preservatives led to damage to the conjunctiva, the cornea and the eyelids[34]. The intensity of this inflammatory reaction seemed to be dose-dependent and related to both the number of anti-glaucomatous medications used and to the duration of the treatment[33]. Switching from a preservative-

containing to a preservative-free formulation led to significant reduction of complaints and objective clinical symptoms[33]. In our study the redness of the eyes dropped from 29-34% before the laser to 3-6% 3 months after the laser. We assume this is a positive result of the SLT since its use reduced the number of medications needed.

The laser treatment induced a short raise in the redness of the eyes within the first hour in all groups except the group treated with Dexamethasone. After one week this group had significantly less redness compared to before SLT. This suggests that the allergic/inflammatory reaction caused by the anti-glaucoma drops was suppressed by the use of Dexamethasone but differences were not significant. This concurs with McIlraith et al. who found comparable post laser inflammation in patients treated with NSAID after laser therapy to that in the patients treated with a steroid[35].

IOP spike

Sudden and short lived rising of the IOP has been described more often after iridotomy than after ALT[36]. One hour after laser, an IOP spike of 5 mmHg or more is also not uncommon in SLT. The reported incidence varies between 0-62%[8] but when prophylactic anti-glaucoma medication is used, the incidence lowers to 0-29%[12,19,23,37]. Occurrence of an IOP spike seems to be dependent upon the treated area of TM. Nagar et al. recorded 9% of patients with a IOP spike over 5 mmHg after 90° treatment of the TM, 16% after 180° and 27% after 360°[20]. This group did not use apraclonidine.
Shibata et al. instilled apraclonidine before and after laser and recorded 2% of patients with an IOP spike after 180° treatment and 3% after 360° treatment[16]. In our study, we applied apraclonidine before and immediately after SLT. We encountered an IOP spike of 5 mmHg or more in 3-8% of the patients, which is less than the 27% recorded by Nagar et al. [20] and close to the 9% of Shibata et al.[16].

Post-laser treatment with Indomethacin or Dexamethasone made no significant difference in the occurrence of a IOP spike. This concurs with the study of Robin et al., which demonstrated that apraclonidine lowers the frequency and the extent of the post laser IOP rises, whereas no other medication seemed to have any impact[36]. Since many glaucoma patients assigned to laser already show damage to the optic nerve, even a transient period of enhanced IOP can afflict further damage and may be sight threatening. Using prophylactic apraclonidine to lower the frequency of this complication, however seldom, seems good practice[36].

Harasymowycz reported four cases of persistently elevated IOP after SLT in highly pigmented anterior chamber angles[38], but several other studies reported no difference in IOP response independent of anterior angle pigmentation[20,21,35,39,40]. In general, it is suggested to use less energy for more heavily pigmented eyes or treat 180° instead of 360° of the TM[39].

Effect on efficacy

IOP at baseline (13.43-14.82 mmHg) was low in this population of medically controlled primary open angle glaucoma and ocular hypertension patients. Six months after SLT, the IOP was lowered by 19.64% in the Indomethacin group and 21.07% in its control group, in the Dexamethasone group the IOP lowered by 11.81% and 14.07% in its control group (Table 4). None of the differences were statistically significant.
Low baseline IOP was also reported by Lee et al. in two trials on normal tension glaucoma patients[10,41]. Mean pre-study IOP was 14.3 mmHg. A single session of SLT was able to achieve an additional 15% IOP reduction, while using 27% less medication at 1 year compared to pre-study levels.

The IOP lowering effect of SLT in our study was not influenced by the use of steroidal or NSAID therapy. Compared to no post laser anti-inflammatory treatment, there was no

statistically significant difference between either groups. This is in keeping with the study of McIlraith et al. who treated part of their patients after SLT with a NSAID and others with a steroid drop. There was no difference in the absolute IOP reduction between the two groups[35].

Reduction of medication

Very little studies start with medically controlled glaucoma patients in order to lower the number of medications needed. Francis et al.[23] started with a mean of 2.8 medications at baseline and reported a drop to 0.7 medications after 6 months. Reduction in medications was obtained in 97% of their eyes. In our study, we started with a lower amount of drops taken at baseline (1.43-1.45) that lowered to a mean of 0.23-0.45 medications needed after 6 months. Reduction in medications was attained in 100% of our eyes. The use of Indomethacin, Dexamethasone or no medication after laser made no difference.

Limitations of our study

Flare laser meter is a more precise manner to register anterior segment inflammation. We used clinical parameters of inflammation because of their clinical significance.

SLT seems to induce expression and secretion of interleukins, like ALT does[28]. Up regulating inflammatory pathways may trigger rare cases of corneal oedema, corneal decompensation[42,43,44] or macular oedema after SLT[45,46]. Our number of patients is too limited to exclude these complications. So it may still be prudent to use some mild anti-inflammatory medication after SLT in patients at risk or to monitor them closely and start medication in case of inflammation.

Eye drops are known to have systemic side effects[47]. It is also suggested that using eye drops in one eye induces an effect in the untreated fellow eye. E.g. a change in intraocular pressure has been demonstrated in the fellow eye after treatment of the contralateral eye with beta-blockers[48] and with prostaglandin analogues[49]. However, in our study it is unlikely that anti-inflammatory drops used in the first eye should have influenced the inflammation following treatment of the second eye since this was treated a week later.

Conclusions

SLT induces little and short-lived inflammation of the anterior segment. The use of NSAID or steroid drops after SLT makes no difference. The IOP lowering effect of the SLT is equally not influenced by the use of anti-inflammatory medication after laser.

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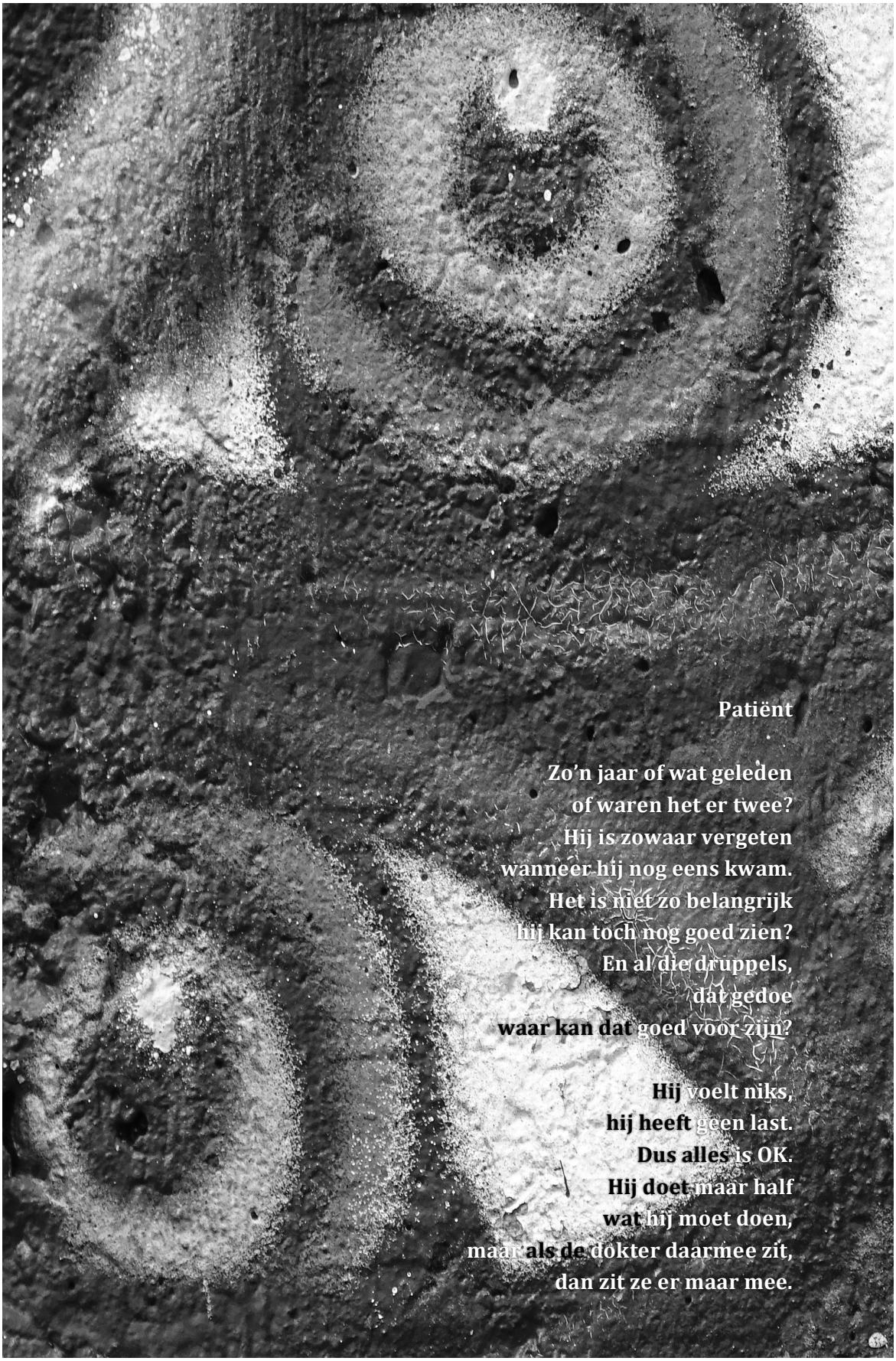

Patiënt

Zo'n jaar of wat geleden
of waren het er twee?
Hij is zowaar vergeten
wanneer hij nog eens kwam.
Het is niet zo belangrijk
hij kan toch nog goed zien?
En al die druppels,
dat gedoe
waar kan dat goed voor zijn?

Hij voelt niks,
hij heeft geen last.
Dus alles is OK.
Hij doet maar half
wat hij moet doen,
maar als de dokter daarmee zit,
dan zit ze er maar mee.

CHAPTER 6. Influence of corneal thickness

The thickness of the cornea (CCT) does not only influence IOP measurements, it is also thought to reflect the biological properties of ocular tissues, as cornea, sclera and lamina cribrosa. The trabecular meshwork is located between the junction of cornea and sclera.

Since SLT relies on the reaction of the tissue, it is not unthinkable that CCT might influence the overall outcome of SLT

We compared patients with a low CCT (<550 µm) to a group with higher CCT (≥550 µm).

Effect of selective laser trabeculoplasty in glaucoma patients with high or low corneal thickness.

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Abstract

Purpose
Comparison of the effect of selective laser trabeculoplasty (SLT) in glaucoma patients with high and low central corneal thickness (CCT).

Materials and Methods
Clinical trial on 72 glaucoma patients, controlled on medication that received SLT as replacement therapy. We compared the effect of SLT on patients with CCT ≥ 550 µm with patients having CCT < 550 µm. Primary end point was intraocular pressure and number of medications taken. Measures were made at 1 hour, 1 week, 1 month, 3, 6, 12 and 18 months after SLT.

Results
Mean IOP reduction after SLT was comparable between the low and the high CCT group at most time points ($p > 0.05$), only at 18 months after SLT, the low CCT group showed less IOP reduction compared to the high CCT group ($p = 0.04$).
The mean number of medications showed no significant differences between the high and the low CCT group at any point in time. In both groups, the mean number of medications lowered significantly, from 1.43 to 0.17 medications in the high CCT group and from 1.55 to 0.33 in the low CCT group.

Conclusion
CCT does not influence the outcome of SLT in terms of mean IOP reduction and number of medications needed.

Introduction

In 1997, Latina and co-workers launched selective laser trabeculoplasty (SLT) as a new treatment to lower intraocular pressure (IOP)[1]. Since then, SLT has proven to be efficient[2,3] and its use has become widespread. Several studies have been performed to investigate which factors influence the outcome of SLT. Up to now, only higher pre-laser IOP seems to be correlated to higher IOP lowering effect of the SLT[4-6]. Other factors like race[6], trabecular meshwork pigmentation[7,8], number and type of previously used anti-glaucoma medications[9,10], previous laser[11,12] and phakic or pseudophakic eyes[13] showed no impact on SLT efficiency. Shazly et al. examined whether central corneal thickness had influence on SLT outcome and suggested that thinner corneas gave better IOP reduction after SLT[14].

CCT is known to have an effect on IOP measurement[15] but some studies suggest that CCT may also give information about tissue properties of the eye that are otherwise difficult to measure[16,17].
The Ocular Hypertension Treatment Study[18] showed that CCT was a strong predictor for the development of open angle glaucoma in patients with ocular hypertension. This was confirmed by the European Glaucoma Prevention Study[19] and the Barbados Eye Studies[20]. Several studies have found that CCT is an important variable in patients with existing glaucoma[17,21-24].

The Early Manifest Glaucoma Trial however, reported that CCT was not a significant predictor of glaucoma progression [25]. Medeiros et al. did identify CCT as a risk factor for development of visual field loss among patients diagnosed with optic neuropathy[21].
The aim of this study is to examine the possible effect of CCT on SLT outcome.

Materials and Methods

Study design and subjects

This is a post hoc analysis of data collected in a randomized interventional clinical trial conducted to evaluate use of anti-inflammatory drops after SLT. The design of that study has been reported previously[21].

Inclusion criteria concerned primary open angle glaucoma (POAG) or ocular hypertension (OHT) controlled with medical therapy.
Exclusion criteria were other types of glaucoma than open angle glaucoma, previous glaucoma surgery or previous laser trabeculoplasty. Patients with corneal disease that inhibited good visualization of the trabecular meshwork and those taking systemic steroids were also excluded from the study.

POAG was defined as IOP above 21 mmHg on two separate occasions, open angle on gonioscopy and either glaucomatous visual field defects on Humphrey visual field analyser, optic disc changes on funduscopy and/or loss of retinal nerve fibre layer on Optical Coherence Tomography (OCT). The diagnosis of OHT was made when an IOP higher than 21 mmHg was measured on two separate occasions in the absence of field or disc changes or defects in retinal nerve fibre layer.

The study was not designed to create additional IOP lowering effect, because IOP was already controlled with medication before treatment with SLT. The main goal of this study was lowering the number of medications needed to maintain adequate IOP control and examine effect of CCT on SLT outcome.

Baseline examinations

At baseline a full ophthalmological examination of each study participant was conducted, including a medical history review, 5best-corrected visual acuity (BCVA) measurement, IOP measurement using Goldmann applanation tonometry (mean of two measurements was taken), slit lamp examination of the anterior segment, central corneal thickness (CCT) measurement, dilated fundus examination, visual field examination by computerized perimetry (program 24-2, Humphrey Field Analyser 745i, Zeiss, Jena, Germany), optical coherence tomography (OCT) of the optic nerve head and recording of glaucoma medications.

All OCT scans were performed with the spectral-domain OCT RTVue (Optovue, Fremont, USA). We used focal loss of volume (FLV) as determinant for the OCT[26]. CCT was measured at baseline using a handheld pachymeter (iPac Pachymeter, Reichert, Buffalo, NY, USA), the same pachymeter was used for every patient.
IOP before treatment was calculated as the mean of three measurements taken before starting glaucoma medication at three different days, at least 3 to 6 months apart. IOP at baseline was calculated as the mean of the Goldman measurements made on different time points on the three last examinations before laser treatment. The same examiner performed all examinations.

Patients were divided into a group with high CCT (≥ 550 µm) or low CCT (< 550 µm). Doughty et al. described a normal CCT in white adults could be expected to be 535 µm ± 2SD, i.e. 473-597 µm[15]. Shih et al. found a mean CCT of 544 ± 34 µm based on a large review[23]. The Ocular Hypertension Treatment Study Group (1636 subjects) arrived at a mean CCT of 573.0 ± 39.0 µm[24]. We took the mean of these three results to come to a cut-off value of 550 µm for the CCT in our study.

Laser technique

A frequency doubled, Q-switched Nd:YAG laser was used, emitting a wavelength of 532 nm, coupled to a slit lamp delivery system (Selecta Duet laser, Lumenis, Dreieich, Germany). We used single pulses with pulse duration of 3 nanosec and spot size of 400µm. The laser energy was initially set at 0,9 mJ and a single laser pulse was delivered at the 12 o'clock position. If a cavitation bubble appeared, the laser energy was reduced by 0,1 mJ increments until minimal bubble formation was observed. Treatment was then continued at this energy level. If no cavitation bubble was observed, the pulse energy was increased by steps of 0,1 mJ until bubble formation[1].

Immediately before the laser procedure a drop of pilocarpine 1% and apraclonidine 0.5% were instilled into the treated eye. After the laser treatment, Indomethacin 3 times daily, Dexamethasone 3 times daily for one week or no anti-inflammatory drops were administered, following study protocol. The observation that the use of anti-inflammatory drops did not influence SLT outcome was previously published[27].

Postoperative management

Patients were examined 1 hour, 1 week, 1, 3, 6,12 and 18 months after SLT. A full clinical examination, comparable to the examinations at baseline, was performed at 6 and at 12 months. After SLT, glaucoma drops were continued until IOP was more than 2 mmHg below target pressure, at which point they were stopped one by one. A fixed combination of drugs was considered as a combination of two medications, the first step entailed a switch to a single medication. The second drug was stopped if possible, after respecting a wash out period of three months. The number of applications daily was not changed during the study, medication was given at the normal frequency or stopped.
Target pressure was calculated using the formula proposed by H. Jampel (Target IOP= maximum IOP – maximum IOP% - z, where z is an optic nerve damage severity factor)[28].

Statistical methods

A paired samples *t*-test was performed to compare baseline differences between the low and the high CCT group for continuous variables (i.e. age, IOP at baseline with medication, BCVA, cup-disc ratio, CCT, visual field mean deficit, OCT FLV, IOPmax before treatment, number of medications at baseline). A χ 2-test was used to compare baseline differences in sex and type of glaucoma.
A second paired samples *t*-test was executed to investigate the difference in mean IOP reduction for both groups. A χ 2-test was performed to examine the difference in mean number of medications needed. Results of statistical analysis with *p*-values < 0.05 were considered to be significant.

Results

Population

Demographic and baseline characteristics are shown in Table 1.
135 eyes of 72 patients underwent SLT. We met no significant complications or side effects after SLT, data collection was stopped for practical reasons.
No significant differences were present between the high and the low CCT groups in terms of mean age, sex, BCVA, visual field deficits, OCT and medication taken at baseline. This excluded all these factors as possible confounders.

A significant difference was found in IOP before start of medication and IOP at baseline, patients with low CCT had significantly lower IOP at these two time points. Since a thin cornea leads to measuring a lower IOP than the 'true' IOP[15], this is not unexpected. There were significantly less patients in the low CCT group diagnosed with ocular hypertension.

A significant baseline difference was also present in the cup disc ratio of the two groups, optic discs were more excavated in the low CCT group. This concurs with other studies that showed glaucoma patients with thinner cornea have higher cups disc ratio[17,22,29]. However, the visual field and OCT examinations showed no significant difference between the two groups[17,30].

Laser technique

All patients received a 360° treatment of the trabecular meshwork. We used a mean number of 102.37 ± 9.34 non-overlapping spots with a mean energy of 1.09 ± 0.31 mJ. The same experienced practitioner (MDK) applied all treatments.

Table 1. Baseline characteristics of the population			
	High CCT group N=58	**Low CCT group N=77**	**t-test/ χ2 test *p*-value**
Demographics			
Age (years)	68.10 ± 13.10	68.53 ± 12.28	0.85
Sex (F/M)	27 (46.55%)/ 31 (53.45%)	40 (51.95%)/ 37 (48.05%)	0.54
Glaucoma parameters			
IOP baseline with medication (mmHg)	15.10 ± 3.89	13.07 ± 2.94	0.001*
POAG/OHT	43 (74.14%)/ 15 (25.86%)	72 (93.51%)/ 5 (6.49%)	0.002*
BCVA	0.83 ± 0.23	0.78 ± 0.28	0.24
CCT (µm)	584.05 ± 26.47	516.78 ± 28.02	<0.001*
Cup disc ratio	0.66 ± 0.25	0.80 ± 0.18	0.001*
Visual field MD	5.09 ± 7.38	5.73 ± 6.22	0.59
Visual field PSD	3.96 ± 3.48	4.95 ± 3.89	0.13
OCT FLV	4.31 ± 4.74	4.70 ± 4.16	0.61
Mean follow up (months)	13.45 ± 6.08	13.79 ± 5.31	0.72
IOPmax before medication (mmHg)	24.53 ± 5.91	22.30 ± 5.31	0.02*
Medication at start			
Total number (mean)	1.43 ± 0.70	1.55 ± 0.94	0.44
Prostaglandin analogs	49 (84.48%)	71 (92.21%)	0.09
Betablocker	23 (39.66%)	29 (37.66%)	0.54
Carbo anhydrase inhibitor	6 (10.34%)	14 (18.18%)	0.06
Alphamimetics	5 (8.62%)	5 (6.49%)	0.67

Abbreviations: F, female; M, male; IOP, intraocular pressure; POAG, primary open angle glaucoma; OHT, ocular hypertension; BCVA, best corrected visual acuity; CCT, central corneal thickness; MD, mean deviation; PSD, pattern standard deviation; OCT, optical coherence tomography; FLV, focal loss of volume

*Statistically significant difference ($p < 0.05$)

Evolution of IOP and medication

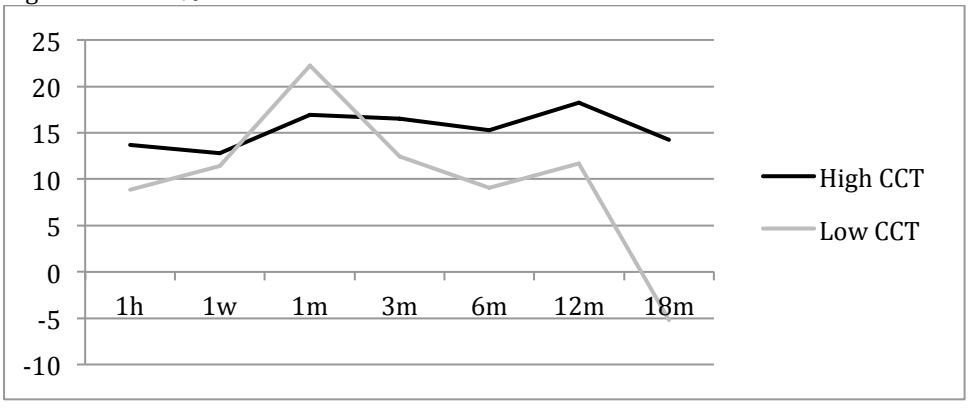
The mean percentage of IOP reduction in eyes with thinner corneas (CCT < 550 µm) showed no significant difference compared to the percentage of IOP reduction in thicker corneas at 1 hour, 1 week, 3, 6 and 12 months. At 18 months, there was a small rise in mean IOP in the low CCT group, resulting in a negative mean reduction percentage and a significant difference to the high CCT group, see table 2 and figure 1. The results at 18 months show a trend to less SLT effect in the low CCT group. We will check this in a follow up study that runs longer.

Table 2. Mean % of IOP reduction after SLT

	High CCT group	Low CCT group	t-test *p*-value
1 hour	13.67 (n=58)	8.88 (n=77)	0.40
1 week	12.80 (n=58)	11.40 (n=77)	0.80
1 month	16.92 (n=58)	22.23 (n= 77)	0.32
3 months	16.51 (n=58)	12.46 (n=77)	0.49
6 months	15.26 (n=58)	9.10 (n=77)	0.21
12 months	18.22 (n=41)	11.72 (n=60)	0.21
18 months	14.24 (n=24)	-5.19 (n=33)	0.04*

Abbreviations: n= number of patients
* Statistically significant difference ($p < 0.05$)

Figure 1. Mean % of IOP reduction after SLT.



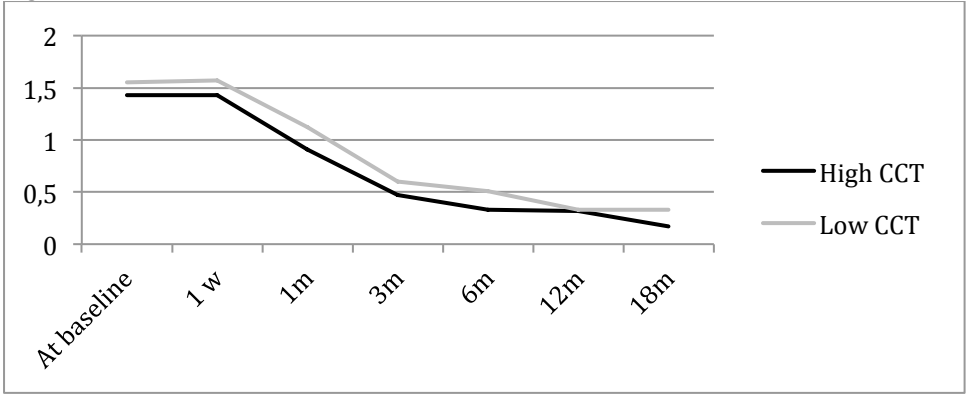
The mean number of medications showed no significant differences between the high and the low CCT group at all time points, see table 3, figure 2. In both groups, the mean number of medications lowered significantly, from 1.43 to 0.17 medications in the high CCT group and from 1.55 to 0.33 medications in the low CCT group.

Table 3. Mean number of medications after SLT

	High CCT group	Low CCT group	χ2-test *p*-value
At baseline	1.43 ± 0.70 (n=58)	1.55 ± 0.94 (n=77)	0.44
1 week	1.43 ± 0.70 (n=58)	1.57 ± 0.94 (n=77)	0.34
1 month	0.91 ± 0.71 (n=58)	1.12 ± 1.04 (n= 77)	0.20
3 months	0.47 ± 0.63 (n=58)	0.60 ± 0.85 (n=77)	0.32
6 months	0.33 ± 0.54 (n=58)	0.51 ± 0.75 (n=77)	0.29
12 months	0.32 ± 0.79 (n=41)	0.33 ± 0.63 (n=60)	0.91
18 months	0.17 ± 0.38 (n=24)	0.33 ± 0.60 (n=33)	0.23

Abbreviations: n= number of patients
No statistically significant differences ($p < 0.05$)

Figure 2. Mean number of medications after SLT.



Discussion

It is well known that measuring IOP with the Goldmann applanation tonometer (GAT) is influenced by the thickness of the cornea, since the design of the GAT was based on a CCT of 500 µm. Consequently, thicker corneas generally yield higher IOP

values and thinner corneas lower IOP readings than the 'true' IOP[15,19,22,23,31]. However, there is eviden-ce to suggest that the association between CCT and POAG

severity is more than just a tonometry artefact. Several studies have proposed CCT as an independent risk factor for POAG and an important predictor of the evolution of OHT to POAG[18,19,25]. CCT could also be an indicator for an independent mechanism of glaucoma based on the biological properties of ocular tissues like the posterior sclera and the lamina cribrosa[16,29,31,32].
Since SLT relies on biochemical properties of the tissue of the eye[33,34,35] and CCT may be an index for tissue qualities, it is not unthinkable that CCT should influence the outcome of SLT.

In our study, we recorded a significantly larger cup disc ratio in patients with thinner cornea compared to those with thicker cornea. This concurs with the study of Pakravan et al. who suggested that thinner corneas may be a marker for more deformable discs, prone to the effects of increased IOP[29]. Jonas et al. also described the high association between thin corneas and more pronounced glaucomatous optic nerve, but noticed that thin corneas were not associated with a higher risk for glaucomatous visual field progression[22]. We can agree with this, although the patients with low CCT and those with high CCT showed a difference in cup to disc ratio, we did not record a significant difference in visual field parameters or OCT of the optic nerve head between the two groups.

Shazly et al. and Kooner et al. recorded a greater reduction of IOP in patients with low CCT following SLT[12,36].
In our trial, we recorded a comparable percentage of IOP reduction between the high and the low CCT groups at all time point, except at 18 months. At that point, the number of patients was reduced (24-33 patn) to about half the number at baseline (58-77 patn), this makes the results less reliable.

At baseline, our groups showed a significantly different IOP. This may have been a tonometry artefact, mean CCT was 584 µm in the high CCT group compared to 517 µm in the low CCT group. This significant difference can be due to overestimation of the IOP in the high CCT group and an underestimation in the low CCT group, while the 'true' IOP is less different between the two groups[29].

As can be expected after SLT[37-39], SLT lowered the number of glaucoma medications, from 1.43 to 0.17 in the high CCT group and from 1.55 to 0.33 in the low CCT group.

CCT was obtained using a hand held pachymeter, which is only one of many methods of measuring CCT. Studies have shown that, depending on the method used, different CCTs may be obtained[23]. Also, a larger number of patients would add significance to the results.

Conclusions

At no point, a significant difference could be found between the IOP of the group with high CCT compared to the group with low CCT. SLT can be considered an efficient therapy in glaucoma in patients with both thinner and thicker corneas.

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CHAPTER 7. Impact of lens extraction

Lens extraction is known to lower the IOP. If the mechanism, by which this happens, overlaps with SLT, it can be expected that SLT would have less effect in pseudophakic patients (with implantlens) than in phakic patients , who still have their own lens.

We compared the efficacy of SLT in pseudophakic and phakic patients.

Selective laser trabeculoplasty in pseudophakic and phakic eyes: a prospective study.

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Abstract

Aim

To compare the efficacy of selective laser trabeculoplasty (SLT) in replacing medical therapy in pseudophakic and in phakic eyes.

Materials and Methods

Subgroup of a prospective randomized clinical trial including patients with primary open angle glaucoma or ocular hypertension controlled with medication. 38 pseudophakic eyes were matched with 38 phakic eyes. SLT was offered as a way to decrease medication while maintaining the same low eye pressure. SLT was performed over 360°, at 3 nanosec, spot size 400µm, 100 spots. Data (intraocular pressure (IOP), number of medications needed) were measured at 1 hour, 1 week, 1, 3, 6 and 12 months. An independent-samples t-test was performed to compare baseline characteristics of the phakic and the pseudophakic group and differences in evolution of mean IOP and number of used medications. Chi-squared analysis was performed to investigate proportions of fast, slow and non-responders.

Results

The mean IOP measurement was 13.00 ± 2.88 mmHg in the phakic group (38 eyes) and 13.51 ± 3.06 mmHg in the pseudophakic group (38 eyes) ($p > 0.05$). This changed little after SLT and IOP lowering effect was comparable between the two groups. Main aim however was to lower the amount of medication needed. In the phakic group medication lowered from 1.29 ± 0.62 at baseline, to 0.15 ± 0.46 after 12 months, a reduction of 88.37%. In the pseudophakic group, used medication changed from 1.71 ± 1.04, to 0.41 ± 0.61, a 76.02% reduction. The differences were not statistically significant at any time point ($p > 0.05$).

There was a trend towards IOP lowering occurring faster in the pseudophakic group (50% of patients after one week) than in the phakic group (68% of patients after more than 4 weeks). The difference was not significant ($p > 0.05$).

Conclusions

IOP lowering effect of SLT is comparable between phakic and pseudophakic eyes.

Introduction

Cataract and glaucoma are the main leading causes of blindness in the world[1]. In the aging population, they frequently occur together. Clear corneal phacoemulsification (CCP) is associated with significant and sustained reduction in intraocular pressure (IOP) in both normal subjects and patients with primary open angle glaucoma (POAG)[2-6]. Several hypotheses have been proposed explaining the mechanism of IOP decrease. One of the more supported theories describes the increased outflow of aqueous humour by endogenous secretion of prostaglandins and interleukins[7].

Selective laser trabeculoplasty (SLT) is a relatively new technique to lower IOP. Most studies on the effectiveness of SLT compare rather small populations and lack power. However, recently two large meta-analyses were performed[8-9]. They provided robust evidence that there is no significant difference in IOP lowering effect between SLT and medication or between SLT and the more established argon laser trabeculoplasty (ALT).

The mechanism by which SLT works shows some similarities to the mechanism by which IOP is decreased after lens extraction. Release of several inflammatory mediators is responsible for lowering of the outflow resistance at the trabecular meshwork (TM). In SLT this is supposed to work by: 1. Attraction of macrophages that clean up debris, 2. Stimulating the formation of healthy TM tissue and 3. Remodelling of the extracellular matrix of the TM[10-12].

In a retrospective study comparing SLT in pseudophakic and phakic patients, Shazly et al. recorded a delayed SLT response among pseudophakic patients at two weeks while the long-term effectiveness of SLT appeared the same in both groups[13]. They argued that SLT and CCP might share a common pathway involving inflammation, prostaglandin release and interleukin release, which may be depleted after CCP, thus slowing down the response to SLT.

Rosenfeld et al. compared the efficacy of SLT versus ALT in pseudophakic patients and found no significant differences in the IOP lowering effects between the two methods[14]. Several retrospective studies compared the efficacy of SLT in pseudophakic and phakic eyes and found no significant differences[15-18]. We are not aware of any prior prospective clinical trial in the literature that compares the efficacy of SLT in pseudophakic and phakic eyes.
The purpose of this study was to examine the response to SLT in pseudophakic and phakic eyes in patients with POAG or ocular hypertension (OHT) in terms of IOP lowering effect, speed of response and possibility to decrease medication.

Subjects and Methods

Study design and subjects

Subgroup study of a larger prospective randomized clinical trial including 143 consecutive patients at the glaucoma consultation at Jan Palfijn Hospital, Merksem, Belgium. Enrolment occurred from January 2014 to July 2015. The main goal of the study focused on the use of SLT in order to lower the amount of prescribed anti-glaucoma medication and examine effects of SLT on the quality of life. Approval of the ethics committee was obtained (EC 4313), we followed the guidelines of the Helsinki Declaration. Trial registration information: Selective laser trabeculoplasty (SLT) as replacement therapy in glaucoma patients, NTR 5417.
Data were recorded at baseline, at one hour, one week, one, three, six and twelve months post-SLT.

Inclusion criteria concerned primary open angle glaucoma (POAG) or ocular hypertension (OHT) controlled with medical therapy. Only patients with recording of all data at all time points were included. Patients had to agree to sign an informed consent form.
Exclusion criteria were other types of glaucoma than open angle glaucoma, previous filtering surgery or laser trabeculoplasty treatment. Patients with corneal disease that inhibited good visualization of the TM and patients on systemic steroids were also excluded from the study.

Of the original study, we extracted all pseudophakic eyes, 38 eyes of 20 patients. All pseudophakic patients had their cataract removed through uneventful phacoemulsification with implantation of an intraocular lens in the capsular bag by the same surgeon under topical anaesthesia at least one year before inclusion in the study.

From the remaining 123 patients, we selected 38 eyes of 20 patients that were matched to the pseudophakic group in terms of demographic parameters (age, sex) and glaucoma parameters (baseline IOP with medication, type of glaucoma, central corneal thickness, cup disc ratio, visual field mean deficit, optical coherence tomography focal loss of volume, IOP max before medication).

This study was not designed to create additional IOP lowering effect, because IOP was already controlled with medication. Main goal of the original study was to maintain the same low IOP after SLT but with less medication and possibly improvement on the quality of life.

Baseline examinations

At baseline, a full ophthalmological examination was conducted, including a medical history review, best-corrected visual acuity measurement, IOP measurement using Goldmann applanation tonometry (mean of two measurements was taken), slit lamp examination of the anterior segment (conjunctival injection, tear breakup time, cornea, iris, lens appearance, gonioscopy), central corneal thickness (CCT) measurement, dilated fundus examination, visual field examination by computerized perimetry (program 24-2, Humphrey Field Analyser 745i, Zeiss, Jena, Germany), Optical Coherence Tomography (OCT) of the optic disc and recording of glaucoma medications and artificial tears used prior to SLT.
All OCT scans were performed with the spectral-domain OCT RTVue (Optovue, Fremont, USA). We used focal loss of volume (flv) as determinant for the OCT (Zhang, American Glaucoma Society, Washington, March 1, 2014).

Maximal IOP was calculated as the mean of three measurements taken at different time points before starting anti-glaucoma medication. IOP at baseline was calculated as the mean of the Goldmann measurements made on the three last examinations before laser treatment. The same examiner performed all examinations.

Laser technique

A frequency doubled, Q-switched Nd:YAG laser was used, emitting a wavelength of 532 nm, coupled to a slit lamp delivery system (Lumenis Selecta Duet 5 ™). We used single pulses with a pulse duration of 3 nanosec and spot size of 400µm. Laser energy was initially set at 0.9 mJ and increased in steps of 0,1 mJ until minimal bubble formation was observed. We aimed to achieve minimal bubble formation during the whole treatment.

All patients received 360° treatment of the trabecular meshwork. All treatments were applied by the same experienced surgeon (MDK).
Immediately before the laser procedure a drop of pilocarpine 1% and apraclonidine 0.5% were instilled in the treated eye. Immediately after the laser treatment, one drop of apraclonidine 0.5% was given in the treated eye. For the postoperative treatment patients were randomized for one of the three treatment regimen: dexamethasone drops 3 times daily, indomethacin collyre 3 times daily, or no drops. The second eye was treated one week later. All patients continued with the same anti-glaucomatous medical treatment after SLT.

Postoperative management

Patients were examined at 1 hour, 1 week, 1, 3, 6 and 12 months. At each visit, variables recorded included IOP, slit lamp examination of anterior and posterior segment, subjective complaints, number of glaucoma drugs and artificial tears.

Anti-glaucoma drops were continued until IOP was more than 2 mmHg below target pressure, at which point they were stopped one by one. For example a Latanoprost-timolol combination was considered as a combination of two separate medications, the

first step entailed a switch to Latanoprost if possible, the second step involved the discontinuation of the use of Latanoprost at the next visit if possible. If IOP went above target IOP at any time point, medication was started again.

Statistical methods

An independent-samples *t*-test was performed to compare baseline differences between the phakic and pseudophakic group for continuous variables (e.g. age, IOP at medical baseline, vision, cup-disc ratio, central corneal thickness, visual field mean deficit, OCT focal loss of volume, IOP before treatment, number of medications at baseline).

A generalized linear model approach was applied to investigate the difference in evolution of mean IOP for both groups at all time points. To deal appropriately with ordinal and nominal data, an ordinal logistic regression was executed to investigate the time-evolution in number of used medications, with the overall effect of time on number of taken medications (5 time points) and between-subjects factor of patient group (phakic or pseudophakic). For both types of analysis values of the Wald Chi-Square test are reported.

In order to investigate differing proportions of fast-, slow- and non-responders between phakic and pseudophakic patients, a Chi-squared analysis for nominal data was performed. Results of statistical analysis with p-values < 0.05 were considered to be significant.

Results

Patient demographics

Patients were matched for IOP at baseline, cup disc ratio, central corneal thickness (CCT), visual field mean deficit and OCT focal loss of volume. Mean age in the pseudophakic group was higher (77.61 ± 5.05 years) than in the phakic group (72.82 ± 12.22 years). Visual acuity was better in the pseudophakic group (0.81 ± 0.25) than in the phakic group (0.65 ± 0.3) on Snellen chart.

IOP at baseline was comparable between both groups (13.51 ± 3.06 mmHg in the pseudophakic, 13.00 ± 2.88 mmHg in the phakic group), and low, as this was a population with controlled IOP under medication. At baseline 34 eyes of the phakic group (86.84%) and 36 of the pseudophakic group (94.74%) were taking prostaglandin analogues. Beta-blockers were used as second medication in 11 eyes of the phakic group (28.95%) and 15 of the pseudophakic group (39.47%).

Only the use of alpha-adrenergic agonists was different between the two groups. There is some debate about the influence on SLT outcome by carbo-anhydrase inhibitors and prostaglandin analogues[19-20], but alpha-adrenergic agonists have not been found to affect SLT efficacy in clinical studies.

Table 1. Baseline characteristics of population			
Parameters	**Phakic group N=38**	**Pseudophakic group N=38**	**t-test *p****
Demographic parameters			
Age (years)	72.82 ± 12.22	77.61 ± 5.05	0.03*
Sex (male/female) (%)	57.89 / 42.11	57.89 / 42.11	0.99
Glaucoma parameters			
IOP baseline with medication (mmHg)	13.00 ± 2.88	13.51 ± 3.06	0.46
POAG/OHT (%)	94.74 / 5.26	97.37 / 2.63	0.16
Vision	0.65 ± 0.3	0.81 ± 0.25	0.01*
CCT (µm)	534.37 ± 34.99	539.21 ± 35.33	0.55
Cup disc ratio	0.75 ± 0.26	0.77 ± 0.18	0.72
Visual field MD	6.13 ± 6.39	6.27 ± 5.43	0.92
OCT FLV (%)	4.98 ± 4.75	6.11 ± 4.39	0.29
IOPmax before medication (mmHg)	21.75 ± 5.19	24.84 ± 5.53	0.46
Medication at start			
Total number (mean)	1.29	1.71	0.16
Prostaglandin analogues (%)	86.84	94.74	0.40
Beta-blockers (%)	28.95	39.47	0.34
Carbonic anhydrase inhibitors (%)	10.53	21.05	0.21
Alpha-adrenergic agonists (%)	0	15.79	0.01*
SLT parameters			
Energy (mJ)	1.04 ± 0.30	1.08 ± 0.24	0.62
Number of spots	102.66 ± 11.15	103.63 ± 9.48	0.68

Abbreviations: SD standard deviation; IOP, intraocular pressure; POAG, primary open angle glaucoma; OHT, ocular hypertension; CCT, central corneal thickness; MD, mean deviation in dB; OCT, optical coherence tomography; FLV, focal loss of volume; IOP before medication, IOP before anti-glaucoma medication.
*Statistically significant difference at $p < 0.05$

All patients had a minimum follow up of 6 months, 24 eyes had a 12 months follow up in the phakic group, 29 in the pseudophakic group.
All patients received 360° treatment of the trabecular meshwork, a mean of resp. 102.66±10.22 non-overlapping spots were placed in the phakic group and 103.63±9.48 in the pseudophakic group with a mean energy of resp. 1.04±0.30 and 1.08±0.24mJ (Table1).

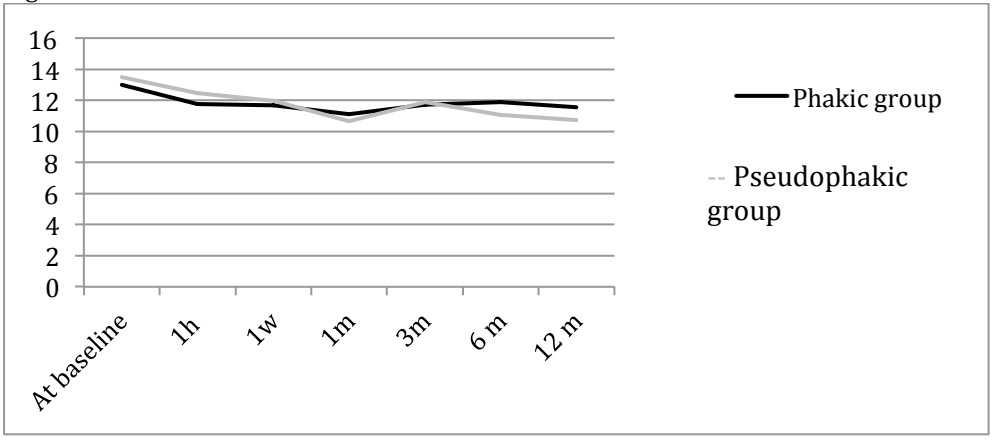
IOP-evolution

The mean IOP changed little in both groups. Baseline IOP was low in both groups as they were well controlled with medication. The aim of SLT was to decrease the number of medications needed, rather than have extra IOP lowering.

The findings resulting from the generalized linear model approach demonstrated a non-significant interaction between time and IOP-evolution (Wald Chi-Square = 3.23, $p = 0.78$), demonstrating that the evolution in IOP over time did not differ between both patient groups. As a consequence, we were not allowed to perform any post-hoc tests for each separate time point in order to compare both patient groups. (Table 2, figure 1).

Table 2. Mean IOP		
Time	Phakic group Mean IOP (mm Hg)	Pseudophakic group Mean IOP (mm Hg)
At baseline	13.00 ± 2.88	13.51 ± 3.06
At 1 hour	11.76 ± 3.72	12.45 ± 4.65
At 1 week	11.66 ± 2.98	11.97 ± 4.08
At 1 month	11.11 ± 3.28	10.66 ± 3.82
At 3 months	11.74 ± 3.06	11.89 ± 4.98
At 6 months	11.89 ± 3.71	11.08 ± 2.96
At 12 months	11.54 ± 3.12	10.75 ± 3.37

Figure 1. Mean IOP after SLT



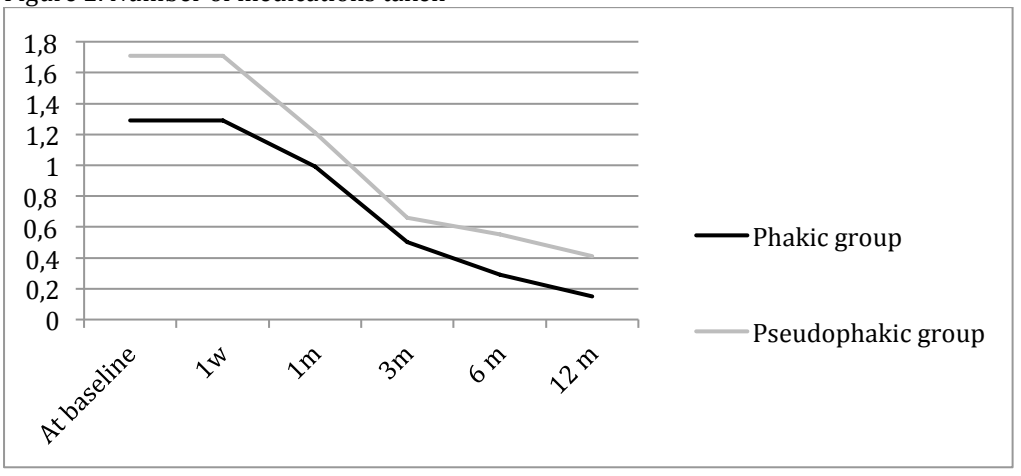
Number of medications

The number of glaucoma medications lowered in both groups (Wald Chi-Square = 163.47, $p < 0.001$) (Table 3, figure 2).

Table 3. Number of medications taken		
Time	**Phakic group Mean # med**	**Pseudophakic group Mean # med**
At baseline	1.29 ± 0.62	1.71 ± 1.04
At 1 week	1.29 ± 0.62	1.71 ± 1.04
At 1 month	0.99 ± 0.69	1.21 ± 1.26
At 3 months	0.50 ± 0.51	0.66 ± 1.05
At 6 months	0.29 ± 0.46	0.55 ± 0.83
At 12 months	0.15 ± 0.46	0.41 ± 0.61

Abbreviations: # med, number of medications

Figure 2. Number of medications taken



In the phakic group the number of medications changed from a mean of 1.29 at baseline to 0.15 after one year or 88.37% reduction of medications. In the pseudophakic group the amount of medications lowered from a mean of 1.71 to 0.41, which entails a mean reduction of 76.02%. No interaction was observed between the patient groups and evolution in time (Wald-Chi Square = 4.00, $p = 0.68$); the reduction in number of medications in both groups was comparable.

Total success was defined as controlled IOP after SLT without further need of medication; this was achieved in 21 eyes (87.50%) of the phakic and 21 eyes of the pseudophakic group (72.41%). Qualified success was considered as IOP below target IOP with less medication than before SLT. This was reached in 100% of both the phakic and the pseudophakic eyes.

Speed of response

Patients who had an IOP more than 2 mmHg below target IOP were told to lower their medication one by one. A second medication was stopped after a minimum wash out period of three months. The eyes in which medication could be diminished after check up at 1 week were considered fast responders. Those who could lower medication after 4 or 12 weeks were registered as slow responders. Those who could not lower their medication after 12 weeks were considered non-responders.

In the phakic group we found 11 fast responders (29%), 26 slow responders (68.5%) and one non-responder (2.5%). The pseudophakic group contained 19 fast (50%), 17 slow (45%) and 2 non-responders (5%). Although these percentages suggest a larger number of fast responders in the pseudophakic group than in the phakic group, the differences between the two groups were not statistically significant (Wald-Chi Square=4.35, p=0.11).

Discussion

Cataract surgery can lead to a lowering of the IOP, both in normal[2-5] and glaucomatous eyes[4,6,21-23] but the physiopathology is still unclear. After lens extraction, increase of the anterior chamber depth and opening of the anterior chamber angle have been demonstrated[3,24]. Diminished production of aqueous by the ciliary body and enhanced outflow at the TM by flushing during surgery and following release of inflammatory mediators have also been proposed to contribute to the IOP lowering effect of cataract surgery[3].

Selective laser trabeculoplasty (SLT) is a safe and efficient IOP lowering treatment[25-27]. It can be used as primary, adjunctive and replacement therapy in open angle glaucoma and ocular hypertension[8,9,28]. The mechanism of SLT is still unclear. SLT produces too little tissue changes to work mechanically, like argon laser trabeculoplasty[29]. It is more likely that selective targeting of TM pigmented endothelial cells stimulates the production of interleukins that will attract macrophages who clean up debris at the TM [30]. On the other hand a cellular mechanism enhancing rejuvenation of the trabeculum has been found[11,12].
If SLT would work through the same mechanism as phaco emulsification to lower IOP, it could be expected that the IOP lowering effect of SLT would be lower in pseudophakic eyes because the mechanisms have been depleted partially or the pathways have already been activated.

Lindegger et al. measured more IOP reduction in a phakic group compared to pseudophakic eyes at one month. However, they did not demonstrate a significant difference at any other time point (1 day, 3 months and every 3 months up to 43 months)[31]. Shazly et al.[13] reported that IOP reduction following SLT was higher in phakic than in pseudophakic eyes 2 weeks after SLT, but reached the same level at 3 months and remained comparable for the entire follow up of 30 months.

Several retrospective studies (ranging from 18[16] to 40[31] pseudophakic and 21[32] to 113[31] phakic eyes) have also compared the IOP lowering effect of SLT in pseudophakic and phakic eyes: the groups op Werner et al.[16], Kalbag et al.[17] and Seymenoglu et al.[15] found no significant difference in SLT efficacy or success rates between phakic and pseudophakic eyes. The same findings were reported in several studies by Lee et al.[33-35]
Our study is in keeping with these studies; we found no significant differences between the pseudophakic and the phakic patients at any time point up to a follow up of one year. IOP lowering effect was comparable, as was the decrease in number of medications needed.

Speed of selective laser trabeculoplasty effect

Nagar et al. noted that the IOP lowering effect after SLT is predominantly immediate; with a lower IOP after one week. Her group recorded 10-15 % of slow responders, whose IOP lowering only occurred 4 to 12 weeks after SLT[36]. We can confirm the presence of fast and slow responders. We found more fast responders in the pseudophakic group (50%) than in the phakic group (29%), the difference was however not significant ($p > 0.05$). In the phakic group, reaction to SLT was slower in 71% of the patients. Therefore, one should always wait 3 months to evaluate the full effect of SLT.

The major limitation of our study is the limited follow up period of 12 months. However, previous investigators have shown that the IOP lowering effect of SLT after cataract extraction persists for at least 24 months[22].
The second limitation is the limited number of eyes (76) examined. More extensive prospective investigation is needed. There was no significant difference between pseudophakic and phakic eyes in terms of IOP lowering effect and decrease of medication needed. Within one week after SLT, 40% of the eyes responded with IOP lowering 57% responded after 1 to 3 months. At least 3 months time has to be given before drawing conclusions on the IOP lowering effect of SLT.

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Lage druk

Altijd dat gedruppel
na een tijdje
doet dat zeer.
Het werkt niet meer
je hebt er last van,
nee, dan beter zonder.

Dus zo'n laser
helpt de mensen.
Vraag is nu alleen
is dat bij een hoge druk
of helpt hij iedereen?

Mdk

CHAPTER 8. Comparison of SLT in normal and high tension glaucoma

SLT efficiency is influenced by very little parameters. But lower pre-laser IOP is known to lower the effect of SLT. Therefore, it is postulated that SLT may not be very efficient in normal tension glaucoma (NTG).

In this study we compared the efficacy of SLT in patients with NTG to that in patients with primary open angle glaucoma.

Prospective study on the effect of selective laser trabeculoplasty in normal tension glaucoma.

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Abstract

Purpose

Compare the effect of selective laser trabeculoplasty (SLT) in normal tension glaucoma (NTG) patients with its effect in primary open angle and ocular hypertension patients (POAG/OHT), considering both evolution of intraocular pressure (IOP) and mean number of medication.

Method

A prospective trial of 145 patients on glaucoma medication. Patients were offered SLT as a means to diminish medication use. Both eyes of the patient underwent SLT. Laser was performed over 360°, 100 spots, 3nsec, 400 µm. IOP and medication were recorded at 1 hour, 1 week, 1, 3, 6, 12 and 18 months. Results were compared with a control group of patients that remained on medication.

Results

IOP changed little after SLT, as the groups were controlled under medication. Nevertheless, SLT was able to achieve additional IOP reduction: 9% and 6% respectively after 12 and 18 months in the NTG group and 19% and 2% respectively in the POAG/OHT group.

The use of medication lowered significantly: from a mean of 1.20 in the NTG group to 0.19 and from 1.71 to 0.31 in the POAG/OHT group. This was a significant change compared to the control groups. Mean reduction of medication after SLT was comparable between the NTG and the POAG/OHT group at 1 week, 1 month, 3, 6 and 12 months.

Conclusions

The efficacy of SLT is not inferior in NTG patients compared to POAG or OHT patients.

Introduction

Normal tension glaucoma (NTG) is a type of progressive optic neuropathy, where intra ocular pressure (IOP) is within the statistically normal range (≤ 21 mmHg). However, these patients show optic nerve damage and visual field loss like in patients with primary open angle glaucoma (POAG) related to an elevated IOP[1-3].
Pathogenesis of NTG seems to involve both IOP dependent and IOP independent mechanisms, that work individually or in combination. Increased IOP can distort the lamina cribrosa and interfere with axoplasmatic flow or create hypo-perfusion of the optic nerve head. On the other hand a high incidence of vascular insufficiency has been demonstrated in NTG patients, leading to perfusion deficits of the optic nerve head, the retina, the choroid and the retro-bulbar vessels[2,4-6].

For many years it was unclear whether lowering IOP in NTG patients from somewhere within the normal range to a lower value, was useful. However, the Collaborative Normal Tension Glaucoma Study showed that there was a slower progression of visual field loss, in NTG patients with 30% or more lowering of their IOP[1].

Laser trabeculoplasty has demonstrated its efficacy in lowering IOP in POAG[7,8]. Studies on its use for NTG patients are scarcer. The incidence of NTG in different populations is variable. In the western world, 30 to 40 per cent of people with glaucomatous visual field defect have normal IOPs[9,10]. A much higher incidence of NTG has been reported in Asian populations, with NTG accounting for as many as 77 to 92% of the primary open angle glaucoma (POAG) patients, in Korea and Japan respectively[2,3]. Several Asian studies report on the use of SLT in NTG patients[3,11-13] and one study in the USA[14]; information on SLT and NTG in a European setting is rare.

We aimed to examine the efficiency of SLT in NTG patients in a prospective study, assessing evolution of IOP and medication use after SLT.

Materials and Methods

Study design and subjects

A prospective, randomized clinical trial including 145 patients of the glaucoma consultation at ZNA Jan Palfijn Hospital, Merksem. The trial was registered as NTR5417. Approval of the ethics committee of the clinic was obtained (4313 MEC).

Inclusion criteria concerned patients with primary open angle glaucoma (POAG), normal tension glaucoma (NTG) and ocular hypertension (OHT), controlled with medical therapy. Only patients with recording of all data at minimal time points were included. Patients had to agree to sign an informed consent form.

Exclusion criteria were other types of glaucoma than open angle glaucoma and previous trabeculectomy or SLT. Patients with a corneal disease that inhibited good visualization of the trabecular meshwork (TM) and those taking systemic steroids were also excluded from the study.

POAG was defined as IOP above 21 mmHg on several separate occasions and different hours, open angle on gonioscopy and either glaucomatous visual field defects on Humphrey visual field analyser, optic disc changes on funduscopy and/or loss of retinal nerve fibre layer on Optical Coherence Tomography (OCT).
OHT was set as a mean IOP higher than 21 mmHg in the absence of field or disc changes or defects in retinal nerve fibre layer.
NTG was defined as analogue changes in visual field, optic disc and/or retinal nerve fibre layer but with a Goldmann applanation measured IOP always ≤ 21 mmHg[13,4].

Randomization was performed with a computer-generated allocation schedule; only after introduction of patient data, the allocated group became clear. Both eyes received SLT. Primary outcome measures were IOP and/or medication lowering effect of SLT.

Baseline examinations

At baseline a full ophthalmologic examination of both eyes was conducted, including best-corrected visual acuity, IOP measurement by Goldmann applanation tonometry (two measurements were taken and the mean calculated), slit lamp examination of the anterior segment (conjunctival injection, cornea, iris, lens appearance), corneal thickness measurement, gonioscopy, dilated fundus examination, visual field examination by computerized perimetry (program 24-2, Humphrey Field Analyser 745i, Zeiss, Jena, Germany) and Optical Coherence Tomography (OCT) of the optic nerve head. All OCT scans were performed with the spectral-domain OCT RTVue (Optovue, Fremont, USA). IOP at start was calculated as the mean of the last three measurements made prior to SLT on different days and hours.

Laser technique

A frequency doubled, Q-switched Nd:YAG laser was used, emitting at 532 nm, with a pulse duration of 3 nanosec, a spot size of 400 μm and pulse energies ranging from 0,2 to 1,7 mJ, coupled to a slit lamp delivery system.
Using the 400 μm spot size, the entire width of the trabecular meshwork was irradiated with each pulse. The laser energy was initially set at 0,9 mJ and a single laser pulse was delivered at the 12 o'clock position. If a cavitation bubble appeared, the laser energy was reduced by 0,1 mJ increments until minimal bubble formation was observed. Treatment was then continued at this energy level[15]. If no cavitation bubble was observed, the pulse energy was increased by steps of 0,1 mJ until bubble formation.

Immediately before the laser procedure a drop of pilocarpine 1% and apraclonidine 0.5% were instilled into the treated eye. After the laser treatment, patients received Indomethacin 0.1% or Dexamethasone 0.1% three times a day for one week or no anti-inflammatory drops, following study protocol. The observation that post-laser treatment did not make a difference in IOP or medication lowering effect of SLT was published previously[16].

Postoperative management

Patients were examined at 1 hour, 1 week, 1, 3, 6, 12 and 18 months after SLT. At 6 months the same parameters as at baseline were assessed. Glaucoma drops were continued until IOP was more than 2 mmHg below target pressure, at which point they were stopped. Fixed combinations were considered to be two medications and were stopped one by one. At least three months of wash out period passed before a second medication was stopped.

Statistical methods

A paired-samples t-test was performed to compare baseline differences between the groups for continuous variables (i.e. age, IOP at baseline, best-corrected visual acuity, central corneal thickness, cup disc ratio, visual field mean deficit and pattern standard deviation, OCT focal loss of volume, IOP before treatment, number of medications at baseline). A Chi-squared analysis was performed to compare sex and type of glaucoma.

A second paired-samples t-test was executed to investigate the difference in evolution of mean IOP for both groups at all time points. The same analysis was run to investigate the time-evolution in number of used medications.
Results of statistical analysis with p-values < 0.05 were considered to be significant.

Results

Population

72 patients were appointed to the SLT group, 69 of them completed a minimum six months of follow up, giving a total of 135 eyes. Among these were 56 NTG eyes and 79 eyes with POAG or OHT. 73 patients were assigned to the control group, 61 appeared at the scheduled appointments, 116 eyes were retained. 36 had NTG, 80 had POAG or OHT.
The mean follow up was 12.76 ± 5.97 months. Demographic and baseline characteristics are shown in table 1.

No significant differences were present between the SLT and the control group in terms of mean age, sex, type of glaucoma, best-corrected visual acuity, central corneal thickness (CCT), visual field, OCT, IOP before start of medication and mean medication taken at baseline.

Table 1. Baseline characteristics of the population			
Parameters	**SLT group n=135**	**Control group n=116**	***p***
Demographics			
Age (years)	68.35 ± 12.59	72.09 ± 11.72	0.07
Sex (F/M)	67 (49.63%)/ 68 (50.37%)	58 (50%)/ 58 (50%)	0.95
Glaucoma parameters			
IOP baseline with medication (mmHg)	13.94 ± 3.52	12.51 ± 3.43	0.001*
NTG/POAG-OHT	56 (41.48%)/ 79 (58.52%)	36 (31.03%)/ 80 (68.97%)	0.09
BCVA	0.80 ± 0.26	0.81 ± 0.22	0.82
CCT (µm)	545.68 ± 43.13	549.01 ± 40.29	0.53
Cup disc ratio	0.74 ± 0.22	0.76 ± 0.69	0.69
Visual field MD	5.46 ± 6.72	5.40 ± 7.05	0.95
Visual field PSD	4.52 ± 3.73	4.37 ± 3.53	0.73
OCT FLV	4.53 ± 4.41	5.32 ± 5.09	0.19
IOP before medication (mmHg)	23.26 ± 5.67	22.88 ± 4.33	0.55
Medication at start			
Total number (mean)	1.50 ± 0.85	1.40 ± 0.67	0.31
Prostaglandin analogues	120 (88.89%)	90 (77.59%)	0.02*
Beta-blocker	50 (37.04%)	57 (49.14%)	0.09
Carbonic anhydrase inhibitor	20 (14.81%)	12 (10.34%)	0.29
Alphamimetics	10 (7.41%)	4 (3,45%)	0.17

Abbreviations: n, number of patients; F, female; M, male; IOP, intraocular pressure; NTG, normal tension glaucoma; POAG, primary open angle glaucoma; OHT, ocular hypertension; BCVA, best-corrected visual acuity, CCT, central corneal thickness; MD, mean deviation; PSD, pattern standard deviation; OCT, Optical Coherence Tomography; FLV, focal loss of volume in %

*Statistically significant difference ($p < 0.05$)

There was a significant difference in IOP at baseline, with a higher mean IOP in the SLT group; 13.94 mmHg compared to 12.51 mmHg in the control group. A larger percentage of patients in the SLT group took prostaglandins at baseline. However, pre-laser use of prostaglandins has proven to have no influence on the efficiency of SLT[17].

Laser technique

We used a Lumenis Selecta II laser (Lumenis, Dreieich, Germany). Mean energy used was 1.09 ± 0.31 mJ. Patients received a mean of 102.37 ± 9.34 spots over 360° of the TM. The same experienced surgeon (MDK) applied all treatments.

Evolution of IOP

IOP did not change significantly over time in both SLT and control groups, as was expected in this medically controlled population. There was no significant IOP difference between NTG patients that received SLT and those that remained on medication. At baseline, there was a higher IOP in the group of POAG/OHT patients that had SLT compared to their control group. This difference remained after SLT. See table 2.

Table 2. IOP evolution after SLT (mmHg)

	NTG	NTG		POAG OHT	POAG OHT	
Parameters	**SLT group**	**Control group**	***p***	**SLT group**	**Control group**	***p***
Before SLT with medication	12.07 ± 2.47 (n=56)	11.10 ± 2.83 (n=36)	0.09	15.31 ± 3.52 (n=79)	13.14 ± 3.49 (n=80)	<0.001*
6 months	10.30 ± 2.82 (n=56)	9.80 ± 2.95 (n=36)	0.57	12.92 ± 3.31 (n=79)	11.10 ± 4.03 (n=79)	0.006*
12 months	11.18 ± 2.58 (n=45)	9.04 ± 2.67 (n=23)	0.80	11.70 ± 3.25 (n=56)	11.50 ± 4.11 (n=40)	0.002*
18 months	10.86 ± 3.80 (n=21)	8.18 ± 3.43 (n=11)	0.06	13.58 ± 3,90 (n=36)	10.23 ± 3.46 (n=26)	0.001*

*Statistically significant difference ($p < 0.05$)

Although IOP was controlled under medication, SLT was able to produce an additional IOP reduction of 9% and 6% respectively after 12 and 18 months in the NTG group and 19% and 2% respectively in the POAG/OHT group.

The percentage of IOP reduction after SLT was comparable between the NTG and the POAG/OHT group at most time points. At 18 months after SLT, the reduction in IOP was significantly less in the POAG/OHT group. See table 3.

Table 3. IOP reduction after SLT (%)			
Parameters	**NTG group**	**POAG/OHT group**	**t-test *p***
1 hour	12.07 (n=56)	12.63 (n=79)	0.18
1 week	7.35 (n=56)	14.97 (n=79)	0.34
1 month	21.03(n=56)	20.11 (n= 79)	0.86
3 months	17.62 (n=56)	12.80 (n=79)	0.38
6 months	12.38 (n=56)	11.86 (n=79)	0.92
12 months	8.66 (n=45)	19.38 (n=56)	0.39
18 months	6.09 (n=21)	2.05 (n=36)	0.01*

* Statistically significant difference ($p < 0.05$)

Evolution of medication

Compared to their control groups, the use of medication lowered significantly both in the NTG and the POAG/OHT group. From 1.2 to 0.19 medications in the NTG group and from 1.71 to 0.31 in the POAG/OHT group. See table 4, figure 1.

Table 4. Evolution of medication after SLT						
	NTG	**NTG**		**POAG /OHT**	**POAG /OHT**	
Time	**SLT group**	**Control group**	***p***	**SLT control**	**Control group**	***p***
Before SLT	1.20 ± 0.62 (n=56)	1.19 ± 0.52 (n=36)	0.99	1.71 ± 0.92 (n=79)	1.49 ± 0.71 (n=80)	0.06
6 m	0.30 ± 0.54 (n=56)	1.19 ± 0.52 (n=36)	<0.001*	0.52 ± 0.75 (n=79)	1.41 ± 0.74 (n=80)	<0.001*
12 m	0.20 ± 0.66 (n=45)	1.17 ± 0.49 (n=23)	<0.001*	0.43 ± 0.71 (n=56)	1.50 ± 0.85 (n=40)	<0.001*
18 m	0.19 ± 0.40 (n=21)	1.18 ± 0.40 (n=11)	<0.001*	0.31 ± 0.58 (n=36)	1.58 ± 0.99 (n=26)	<0.001*

* Statistically significant difference ($p < 0.05$)

Figure 1. Evolution of medication use after SLT

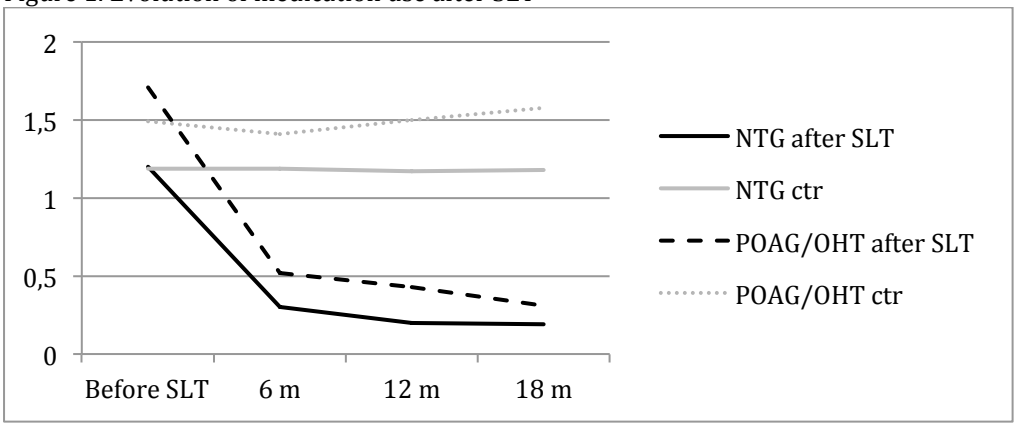
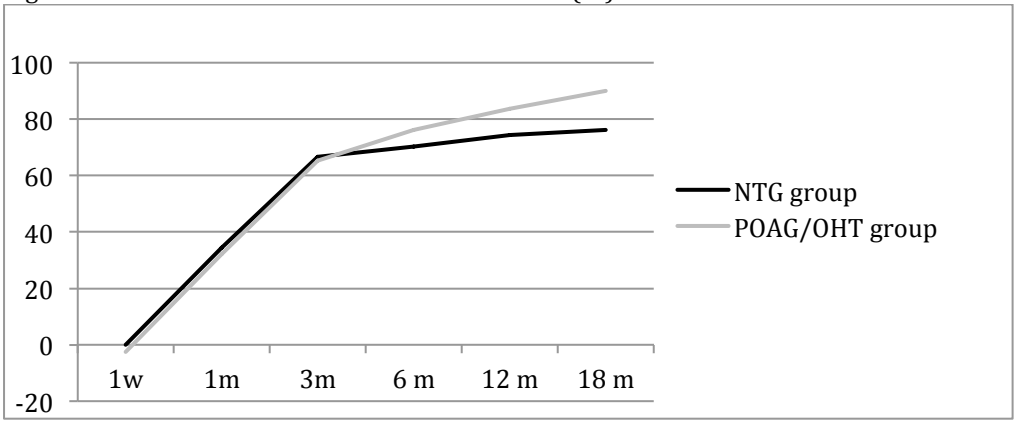


Table 5. Mean reduction of medication after SLT (%)			
Time	**NTG group**	**POAG/OHT group**	**t-test**
1 week	0 (n=56)	-2.53 (n=79)	0.23
1 month	34.52 (n=56)	32.07 (n=79)	0.76
3 months	66.67 (n=56)	65.40 (n=79)	0.87
6 months	70.24 (n=56)	76.16 (n=79)	0.42
12 months	74.44 (n=45)	83.63(n=56)	0.36
18 months	76.19 (n=21)	90.05 (n=36)	0.08

* Statistically significant difference ($p < 0.05$)

Figure 2. Mean reduction of medication after SLT (%)



The mean reduction of medication after SLT was comparable in the NTG and the POAG/OHT group, at all time points. See table 5, figure 2.

In the NTG group, 76% of the medication could be stopped after 18 months, in the POAG/OHT even 90%. In the control group, mean medication use remained the same.

Discussion

IOP reduction remains the most important modifiable risk factor to slow down the progression of NTG. This can be achieved with medication, laser or surgery. Since its launch in 1997 by Latina et al.[15], SLT has proven to be efficient[7,8] and to bypass the inconveniences[18,19], costs[20] and side effects[21,22] of medication. High pre-laser IOP has proven to be predictive of better IOP lowering results after SLT[23-26]. This may make it less applicable for NTG patients.

SLT works on a cellular[27] and a biochemical level[28], enhancing the outflow capacity of the trabecular meshwork with minimal tissue damage[29]. However, the pathogenesis of NTG seems to be different from the mechanisms active in POAG and OHT. Changes in the lamina cribrosa and axoplasmatic flow and a high incidence of vascular insufficiency have been demonstrated in NTG patients[2,4-6]. Therefore, it is not inconceivable that eyes with NTG may react differently to SLT than POAG or OHT eyes.

Lee et al. published prospective studies[3,30] on the use of SLT in NTG patients, proving the value of SLT. A single session of SLT achieved an additional 15% IOP reduction, while using 27% less medication at one year[3]. Their patients were Asian. In an Asian population, the prevalence of NTG varies from 77 to 92%[2,3]. In our European population, only 30 to 40 per cent of people with glaucomatous visual field defects have normal IOPs[9,10].

Our study confirms the usefulness of SLT in European NTG patients. We started out with a group of patients, controlled under medication. SLT was able to keep the IOP low in the NTG and the POAG/OHT group to a comparable degree. Although IOP was controlled under medication, SLT was able to produce an additional IOP reduction in the NTG group of 9% and 6%, and of 19% and 2% respectively in the POAG/OHT group, after 12 and 18 months.

Laser also lowered the amount of medication needed to the same amount in both groups, a 76% reduction of medication in the NTG group and a 90% reduction in the POAG/OHT group after SLT. The difference was not significant. We were able to compare these groups to control groups that stayed on their medication and the medication changes were significant at all time points.

Our study has its limitations; IOP measurement before SLT was performed between 8 am and 4 pm. Diurnal changes in IOP were not evaluated further. The three measurements before baseline were taken with an interval of 4 to 6 months between examinations. We recognize the consistency of the baseline IOP values may be limited.

Conclusions

The efficacy of SLT is not inferior in NTG patients compared to POAG or OHT patients.

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Zachte krachten

Ik ben een fan
van zachte krachten,
hou niet van forceren.
Je helpt er niemand mee vooruit
en maakt alleen maar brokken.
Rustig aan
en stap voor stap
is meestal heel wat beter.

Zo'n lijf
dat zelf herstellen kan
wat leeftijd heeft verprutst.
Dat zichzelf verjongen kan,
beweging kan hervinden.
Daar heb ik echt een zwak voor,
daar wil ik mee aan werken.

Het is wel extra leuk
als de patient
dat ook kan merken.

Mdk

CHAPTER 9. Impact on quality of life

Local side effects and the toxic effect of eye drops become worse in the long run. Therefore reducing the number of medications by SLT can be expected to improve quality of life, but could this be measured?

We examined objective and subjective parameters of quality of life in patients after SLT and in the control group that remained on topical medication.

Quality of life in glaucoma patients after selective laser trabeculoplasty.
De Keyser M[1], De Belder M[2], De Groot V[1,3].
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Assessment of QoL

QoL scales can be complicated, not user-friendly and contain a myriad of complex mathematics. In a review of 2008, Severn et al tried to highlight the strengths and weaknesses of several QoL-tests on the market [1].

- NEI-VFQ 25

The National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) is easy to use, has been translated into many languages and forms the basis of a number of ocular studies. The NEI-VFQ was designed to capture influence of vision on multiple dimensions of health-related quality of life, such as emotional well-being and social functioning [2]. Within a study of a few years, vision normally does not evolve significantly in glaucoma patients. So, for us, a vision-based quality of life-test would not do.

- COMTOL

The Comparison of Ophthalmic Medication for Tolerability (COMTOL) is a 37 items, 13-domain tool with 4 global questions. It is specific for ophthalmic medication tolerability and has good internal consistency, reproducibility and reliability [1]. As a general tool for glaucoma its use is limited but for our study, this could have been a useful test. COMTOL also places a heavy emphasis on vision-related functional outcomes and less on the side effects of more recent prostaglandin treatments, which are very dominant in modern treatment[3].

- TSS-IOP

Atkinson et al. examined patient's satisfaction with their glaucoma therapy using a new test, the Treatment Satisfaction Survey for Intraocular Pressure (TSS-IOP). The questionnaire is designed to assess patient satisfaction with various elements associated with topical medications to control intraocular pressure. The validation study portion was presented by Atkinson et al. in 2003, and a clinical application of the test in 2004[3].

In Day's study, patients who were prescribed a single medication showed statistically greater satisfaction than those patients on multiple medicines with several parameters. These included side effects and eye irritations as well as convenience of use and effectiveness.

A significant correlation was demonstrated between patient satisfaction and ocular irritation, conjunctival hyperaemia and ease of use of the drops. Patient's reluctance to use medications correlated significantly with factors regarding ease of use and convenience of use[4]. We were given kind permission by Pfizer to use this survey for the duration of our study.

Conclusion

NEI-VFQ25 and COMTOL capture mainly the influence of vision-related problems in glaucoma patients [43,44]. Within our study period, we did not expect deterioration of vision. The TSS-IOP was found most appropriate [45,46].

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Abstract

Aim

To compare quality of life and treatment satisfaction between patients who had selective laser trabeculoplasty (SLT) and those on medication.

Materials and Methods

A prospective clinical trial was conducted in 143 glaucoma patients that received SLT and a control group that continued using anti-glaucoma medication. Tear break-up time (BUT), punctuate keratitis, need for help, use of artificial tears and the treatment satisfaction survey of intraocular pressure (IOP) were measured at baseline, 6 and 12 months.

Results

SLT was able to reduce the mean number of medications needed from 1.56 ± 0.81 to 0.42 ± 0.66 at six months and to 0.33 ± 0.69 at one year.

Punctuate keratitis was observed significantly less often (12.24%) after SLT than before (35.94%) ($p = 0.03$). Use of artificial tears and BUT did not change significantly after SLT ($p > 0.05$). At baseline, patients in the SLT group were significantly less convinced of medication effectiveness ($p = 0.006$) and complained more about side effects ($p = 0.003$). After SLT, these patients had significantly more confidence in their therapy ($p < 0.001$), showed less side effects ($p = 0.006$), complained less about changes in appearance of the eyes ($p = 0.003$) and were less inconvenienced by the use of eye drops ($p < 0.001$).

Conclusion

SLT is able to improve treatment-related quality of life in glaucoma patients.

Introduction

Glaucoma is the second leading cause of blindness in the world[1]. Currently, the only modifiable risk factor for glaucoma is raised intraocular pressure (IOP). Only lowering of the IOP is known to delay glaucoma onset and slow down disease progression[2]. The first line therapy of glaucoma consists of ocular hypotensive drugs. As in all chronic diseases, medical adherence is problematic[3,4]. Decades of taking local medications can also reduce quality of life of glaucoma patients through local and systemic side effects[5,6].

Local side effects like irritation and a toxic effect on the anterior eye segment have been demonstrated for the preservative of anti-glaucoma medication, most often benzalkonium chloride (BAK)[7], as well as for the active components of glaucoma drops[8]. Long term use of these eye drops is associated with ocular surface disease [7] and induces a range of complaints and signs like burning, stinging, dry eye syndrome, conjunctival hyperaemia, foreign body sensation and tearing[8,9]. These symptoms usually become worse in the long term and can result in lower adherence[4,8,10].

Selective laser trabeculoplasty (SLT) has proven to be a valid alternative to medication[11,12.] Using laser instead of medical therapy can get around the problems of compliance[4,9], and can diminish the costs[13] and side effects of anti-glaucoma drugs[14].

We hypothesized that treatment with SLT compared to continuing topical medication for controlled open angle glaucoma patients and patients with ocular hypertension (OHT), would improve patients' treatment-related quality of life (QoL).

Materials and Methods

Study design and subjects

This was a prospective clinical trial including 143 consecutive patients at the glaucoma consultation of Jan Palfijn Hospital, Merksem, Belgium. Enrolment occurred from January 2014 to July 2015.
Approval of the Ethics Committee of ZNA was obtained (EC 4313), we followed the guidelines of the Helsinki Declaration. Trial registration: NTR 5417.
Data were recorded at baseline, 1h, 1w, 1, 3, 6 and 12 months post-SLT.

Inclusion criteria concerned primary open angle glaucoma (POAG) or OHT controlled with medical therapy. Patients had to agree to sign an informed consent form.
Exclusion criteria were other types of glaucoma than open angle glaucoma, previous trabeculectomy or laser trabeculoplasty. Patients with corneal disease that inhibited good visualization of the trabecular meshwork and those taking systemic steroids were also excluded from the study.

Randomization of patient allocation was performed with a computer-generated allocation schedule using a blocked allocation sequence of 6 possibilities per block. Patients were consecutively introduced into the study, only after introduction of the personal patient data, the allocated group became clear to patient and observer. Patients were assigned to a group to be treated with SLT or to the control group that continued on topical glaucoma medication. In the SLT group, both eyes received SLT, the right eye was treated first. Only one eye of each patient was used for this analysis, this was chosen by a blocked randomization schedule.

The study was not designed to create additional IOP lowering effect, because IOP was already controlled with medication before treatment with SLT. The main goal of this study involved changes of ocular surface, quality of life parameters and treatment satisfaction.

Baseline examinations

At baseline a full ophthalmological examination of each study participant was conducted, including a medical history review, best-corrected visual acuity measurement, IOP measurement using Goldmann applanation tonometry (mean of two measurements was taken), slit lamp examination of the anterior segment (conjunctival injection, tear break up time (BUT), cornea, iris, lens appearance, gonioscopy), central corneal thickness (CCT) measurement (iPac Pachymeter, Reichert, Depew, USA), dilated fundus examination, visual field examination by computerized perimetry (program 24-2, Humphrey Field Analyser 745i, Zeiss, Jena, Germany), Optical Coherence Tomography (OCT) of the optic nerve head and recording of glaucoma medications and use of artificial tears.

Need for help was defined as the complete dependency upon others to instil the glaucoma eye drops.

All OCT scans were performed with the spectral-domain OCT RTVue (Optovue, Fremont, USA). We used focal loss of volume (FLV) as determinant for the OCT[15].

IOP before treatment was calculated as the mean of three measurements taken on 3 different visits, each 4 to 6 months apart, before starting anti-glaucoma medication. IOP at baseline was calculated as the mean of the Goldmann measurements made on different time points on the three last visits before laser treatment.

For determination of BUT, a drop of 0,2% fluorescein solution was applied to the inferior fornix, and the participant was asked to close his/her eyes. Using the blue light of the slit lamp, the time in seconds between eyelid opening and the appearance of initial defects in the tear film was measured. The same examiner performed all examinations.

Laser technique

A frequency doubled, Q-switched Nd:YAG laser was used, emitting a wavelength of 532 nm, coupled to a slit lamp delivery system (Selecta Duet laser, Lumenis, Dreieich, Germany). We used single pulses with pulse duration of 3 ns and spot size of 400µm. The laser energy was initially set at 0,9 mJ and a single laser pulse was delivered at the 12 o'clock position. If a cavitation bubble appeared, the laser energy was reduced by 0,1 mJ increments until minimal bubble formation was observed. Treatment was then continued at this energy level[16]. If no cavitation bubble was observed, the pulse energy was increased by steps of 0,1 mJ until bubble formation.

Immediately before the laser procedure a drop of pilocarpine 1% and apraclonidine 0.5% were instilled into the treated eye. After the laser treatment, no anti-inflammatory drops were administered.

Postoperative management

Patients were examined 1 hour, 1 week, 1 month, 3, 6, 12 and 18 months after SLT. They received a clinical examination as part of their routine glaucoma care at 6 and at 12 months, comparable to the examinations at baseline. After SLT, anti-glaucoma drops were continued until IOP was more than 2 mm Hg below target pressure, at which point they were stopped one by one. A fixed combination of drugs was considered as a combination of two medications, the first step entailed a switch to a single medication. The second drug was stopped if possible, after respecting a minimal wash out period of three months. The number of applications daily was not changed during the study, a medication was continued at the normal frequency or stopped.

Quality of life

We used the Treatment Satisfaction Survey for Intraocular Pressure (TSS-IOP) to assess patients' satisfaction with their anti-glaucoma treatment. The TSS-IOP questionnaire is a patient reported outcome measure designed to assess patients' perception of the treatment used to lower their IOP [17]. The validation study was presented by Atkinson et al. in 2003[18], a clinical application of the test was published in 2006[11]. We translated the questions in Dutch, the patients' language. A non-exclusive right to use the TSS-IOP was granted to our study group by Pfizer in December 2013 for the duration of the trial protocol.

TSS-IOP contains four questions about perceived effectiveness of treatment (Questions 1, 2, 16, 17) in which patients are asked how satisfied they are about their treatment and how convinced they are that the treatment will maintain eye pressure within the normal range.

The questions concerning unintended treatment effects (Questions 3-5) inquire about burning or stinging of the eyes, feelings of grittiness or sandiness or the presence of crusts around the eyes.

Three questions examine whether the treatment induces redness of the eye or other changes in appearance (Questions 7-9, 18).
Convenience of use of the medication (Questions 10-12) inquires about the number of times per day a treatment has to be applied, at which time and if this can be easily remembered.
Ease of administration of the drops (Questions 13-15) concerns the difficulty of getting the drops into the eye and whether only one or more drops have been applied.

All of these questions are assessed by 5- to 7-level answers ranging from e.g. 'very sure' to 'very unsure'. Higher scores are indicative of greater satisfaction. The questionnaire was filled out at baseline, after 6 and 12 months. Patients were given time to do so in the waiting room, so as not to feel pressured by the physician to answer the questions in a certain direction. Patients did know if they were assigned to get SLT or not before answering the questionnaire.
Individual scores were computed by adding the scale values of the answers within an item, and transforming the resulting value into a score between 0 and 100[18].

Statistical analysis

An independent-samples t-test was performed to compare baseline differences between the SLT and the control group for continuous variables (i.e. age, IOP at baseline with medication, vision, cup-disc ratio, central corneal thickness, visual field mean deficit, OCT FLV, IOP before treatment, number of medications at baseline). A χ 2-test was used to compare baseline differences in sex and type of glaucoma (POAG or OHT).

A second independent-samples t-test was executed to investigate the difference in evolution of mean IOP for both groups at all time points. The same analysis was run to investigate the time-evolution in tear BUT. A χ 2-test was performed to examine the number of medications and need for help.
T-test was also performed to evaluate the BUT, whereas χ 2-test was used to investigate the occurrence of punctuate keratitis and the use of artificial tears.
Analysis of the TSS questionnaire was performed using a generalized linear regression-test. Results of statistical analysis with p-values < 0.05 were considered to be significant.

Results

Population

Demographic and baseline characteristics are shown in Table 1.
No significant differences were present between the SLT and the control group for most baseline characteristics. At baseline, more patients were taking prostaglandin analogues in the SLT compared to the control group. However, studies by Lai and Singh showed that pre-laser glaucoma medication, more specifically prostaglandins, does not influence the outcome of SLT[19,20].

Table 1. Baseline characteristics of the population			
	SLT group n=64	**Control group n=61**	***p***
Demographics			
Age (years)	68.59 ± 12.84	72.07 ± 11.79	0.17
Sex (M/F)	33 (51.56%)/ 31 (48.44%)	30 (49.18%)/ 31 (50.82%)	0.47
Risk factors*	1.52 ± 0.96	1.64 ± 1.32	0.13
Glaucoma parameters			
IOP before medication (mm Hg)	23.21 ± 5.28	22.92 ± 4.50	0.98
IOP at baseline with medication (mm Hg)	13.66 ± 3.35	12.47 ± 3.31	0.07
POAG/OHT	52 (81.25%)/ 12 (18.75%)	42 (68.85%)/ 19 (31.15%)	0.11
BCVA	0.85 ± 0.22	0.81 ± 0.22	0.28
CCT (µm)	545.66 ± 44.25	552.20 ± 40.46	0.24
Cup disc ratio	0.83 ± 0.82	0.76 ± 0.62	0.57
Visual field MD	5.07 ± 6.04	5.23 ± 6.59	0.99
Visual field PSD	4.43 ± 3.31	4.59 ± 3.72	0.84
OCT FLV	4.34 ± 4.52	4.88 ± 4.67	0.52
Medication at start			
Total number (mean)	1.56 ± 0.81	1.39 ± 0.67	0.57
Prostaglandin analogues	59 (92.19%)	48 (78.69%)	0.03**
Beta-blocker	26 (40.63%)	29 (47.54%)	0.44
Carbonic anhydrase inhibitor	10 (15.63%)	6 (9.84%)	0.34
Alphamimetics	5 (7.81%)	2 (3,28%)	0.27

Abbreviations: n, number of patients; M, male; F, female; IOP, intraocular pressure; BCVA, best-corrected visual acuity; POAG, primary open angle glaucoma; OHT, ocular hypertension; CCT, central corneal thickness; MD, mean deviation; PSD, pattern standard deviation; OCT, optical coherence tomography; FLV, focal loss of volume in %

*Risk factors: myopia, arterial hypertension, diabetes mellitus, migraine, vascular problems, and family history of glaucoma

** Statistically significant difference ($p < 0.05$)

Laser technique

All patients received a 360° treatment of the trabecular meshwork. We used a mean number of 102.03 ± 8.39 non-overlapping spots with a mean energy of 1.10 ± 0.30 mJ. The same experienced surgeon (MDK) applied all treatments.

Evolution of IOP and medication

Totally 72 patients were appointed to the SLT group, 64 of them completed a minimum six months of follow up, 49 were followed for one year. The control group contained 71 patients, 61 patients completed the minimal six months follow up schedule, 30 of them also completed the one-year follow up. No severe complications were recorded, data collection was stopped for practical reasons, resulting in limited follow up time.

IOP did not change significantly in both SLT and control groups, as was expected in this population of patients controlled under medication (Table 2)

In the SLT group, the mean number of medication needed lowered from 1.56 at baseline to 0.42 at six months and 0.33 after 12 months. The difference compared to the control group was significant at 6 ($p < 0.001$) and at 12 months ($p < 0.001$), as shown in Table 2.

In the control group at baseline, 42 patients (68.85%) were taking one anti-glaucoma medication, 15 patients (24.59%) were on two medications, 3 (4.92%) took three different medications and one (1.64%) took four medications.

Table 2 evolution of IOP/ medication use / need for help

Parameters	Time	SLT group	Control group	*p*-value
IOP (mm Hg)	Baseline	13.61 ± 3.37	12.53 ± 3.36	0.07
	6 months	11.58 ± 3.39	10.49 ± 4.39	0.14
	12 months	11.06 ± 2.90	10.93 ± 3.53	0.58
No. of medications	Baseline	1.56 ± 0.81	1.39 ± 0.67	0.57
	6 months	0.42 ± 0.66	1.38 ± 0.69	< 0.001*
	12 months	0.33 ± 0.69	1.33 ± 0.76	< 0.001*
Needed help (%)	Baseline	12 (19.67%)	18 (29.51%)	0.16
	6 months	6 (9.84%)	19 (31.15%)	0.002*
	12 months	6 (12.24%)	11 (36.67%)	0.01*

*Statistically significant difference ($p < 0.05$)

In the SLT group, the number of patients on one, two, three and four medications at baseline was 39 (60.94%), 16 (25.00%), 7 (10.94%) and 2 (3.13%) respectively. After one year, 38 (77.55%) of the patients in the SLT group no longer needed any medication to maintain their IOP. 7 patients (14.29%) were using one drop, 3 (6.12%) still needed two different drops and one patient (2.04%) needed three medications.

'Need for help' to instil the eye drops was comparable between the SLT and the control group at baseline, but patients in the SLT group needed significantly less help 6 ($p = 0.002$) and 12 months ($p = 0.01$) after SLT. See Table 2.

Anterior segment condition

Mean BUT was below normal (6.23-6.13) but comparable for SLT and control group at all time points, as shown in Table 3.

At baseline, 35.94 and 31.15% of patients showed punctuate keratitis, in respectively the SLT and the control group. Six months after SLT, there was a trend towards less punctuate keratitis (14.06%)(p = 0.14) in the SLT group, after 12 months, the difference in punctuate keratitis (12.24%) compared to the control group became significant (p = 0.03).
35.94% of the patients in the SLT group and 24.59% of the control group at baseline used artificial tears. The use of artificial tears did not change significantly in both groups during follow up. See Table 3.

Table 3. Anterior segment condition

	Time	SLT group	Control group	*p*-value
BUT (s)	Baseline	6.23 ± 2.89	6.13 ± 2.95	1
	6 months	6.61 ± 2.67	5.97 ± 2.44	0.21
	12 months	6.90 ± 2.87	6.27 ± 2.70	0.57
Punctuate keratitis (%)	Baseline	23 (35.94%)	19 (31.15%)	0.57
	6 months	9 (14.06%)	15 (24.59%)	0.14
	12 months	6 (12.24%)	9 (30.00%)	0.03*
Artificial tears (%)	Baseline	23 (35.94%)	15 (24.59%)	0.18
	6 months	20 (31.25%)	21 (34.43%)	0.85
	12 months	18 (36.73%)	13 (43.33%)	0.63

Abbreviations: BUT, tear break up time
* Statistically significant difference ($p < 0.05$)

QoL questionnaire

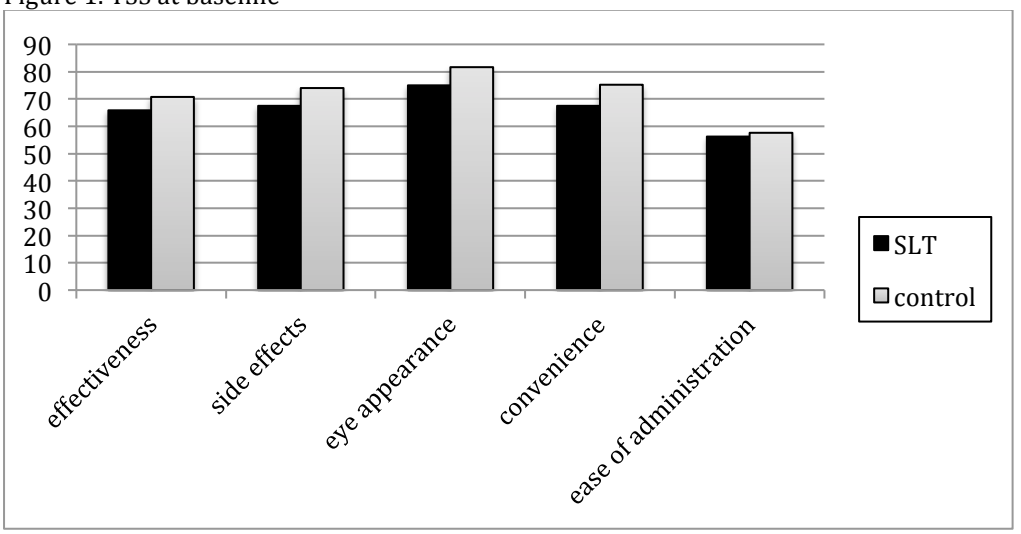
Table 4. TSS comparison between SLT and control group at baseline

Parameters	SLT group	Control group	*p*-value
Perceived effectiveness	65.79 ± 11.76	70.78 ± 11.96	0.006*
Side effects	67.51 ± 13.07	74.04 ± 12.06	0.003*
Appearance	74.93 ± 17.84	81.69 ± 13.05	0.01*
Convenience of use	67.56 ± 18.35	75.25 ± 13.71	0.01*
Administration	56.17 ± 21.20	57.64 ± 26.36	0.67

Abbreviations: TSS, treatment satisfaction survey
Statistically significant difference ($p < 0.05$)

At baseline, there was a significant difference between the SLT and the control group for all items except for ease of administration (Table 4, figure 1). Patients that knew an SLT would be performed, seemed more prone to complain about their earlier medication. Therefore, we further analysed the evolution of each item within the groups, see Table 5, figure 2.

Figure 1. TSS at baseline



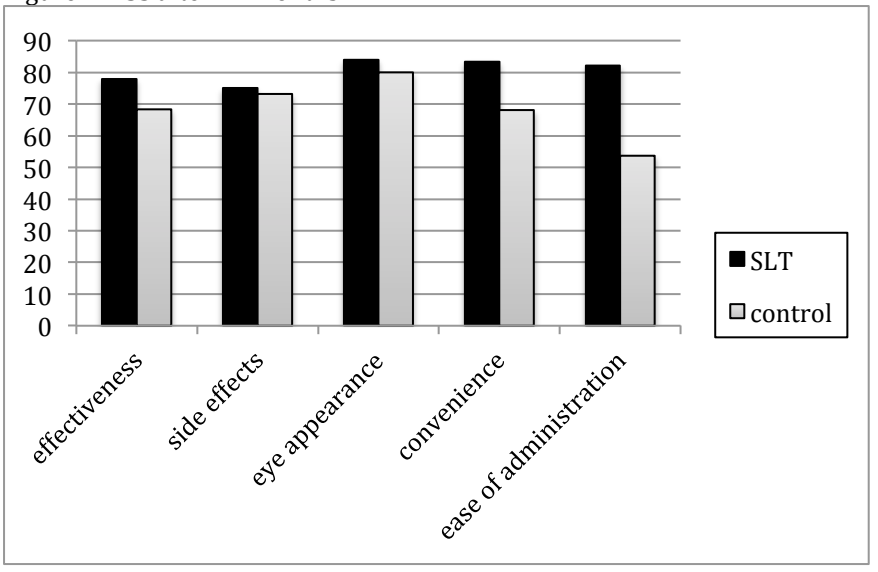
Higher values reflect greater satisfaction.

All items of the questionnaire (Perceived effectiveness of the treatment, side effects, eye appearance changes, convenience of use of therapy, ease of administration of eye drops) remained the same in the control group that continued using the same medication. However, all of the examined items improved significantly one year after use of SLT ($p < 0.001$), figure 2. Higher values reflect greater satisfaction.

Table 5. TSS evolution				
Parameters	**Groups**	**Baseline**	**12 months**	***p*-value**
Perceived effectiveness	**SLT**	65.79 ± 11.76	77.99 ± 14.07	< 0.001*
	Control	70.78 ± 11.96	68.33 ± 14.22	0.39
Side effects	**SLT**	67.51 ± 13.07	75.00 ± 16.18	0.006*
	Control	74.04 ± 12.06	73.19 ± 16.44	0.76
Eye appearance	**SLT**	74.93 ± 17.84	83.93 ± 14.38	0.003*
	Control	81.69 ± 13.05	80.00 ± 17.14	0.57
Convenience of use	**SLT**	67.56 ± 18.35	83.38 ±24.59	< 0.001*
	Control	75.25 ± 13.71	68.10 ± 23.73	0.07
Ease of admini-stration	**SLT**	56.17 ± 21.20	82.06 ± 26.94	< 0.001*
	Control	57.64 ± 26.36	53.68 ± 28.47	0.51

Abbreviations: TSS, treatment satisfaction survey
* Statistically significant difference ($p < 0.05$)

Figure 2. TSS after 12 months



Higher values reflect greater satisfaction.

Discussion

The medical treatment of glaucoma has a number of side effects, is expensive and often inconvenient to instil. Therefore it is not surprising that glaucoma frequently has a large impact on a patients' QoL[4,5,6]. The burden of its treatment, including cost[13,] inconvenience[7,8] tolerability[9] and QoL[4] can lead to poor or noncompliance, followed by progression of disease[10].

As in any chronic disease, noncompliance with drug therapy of glaucoma medication poses a therapeutic problem [3]. The addition of a second or third medication or therapeutic is correlated with a significant decrease in adherence [3]. Using eye drops more than once a day leads to a higher trend to disregard the treatment[17]. With effective laser trabeculoplasty, eliminating or reducing the need for glaucoma medications[13] may minimize the impact of compliance.

Lowering of medication

Compared to the control group on medication, SLT lowered the number of anti-glaucoma medications significantly ($p < 0.001$) and when still medication was needed after laser treatment, SLT simplified the treatment schedules. Similar findings have been reported by other studies[12,21-22].

In our study, use of SLT produced a mean drop of 1.23 medications. This is in agreement with the study from Lai et al.[19] who reported a mean of 0.99-1.08 less medications needed after SLT. Bovell et al. 25 reported a mean of 0.7 less medications, five years after using SLT.

Francis et al.[15,25] recorded a very large drop of medication, namely 2.0 drops per person after six months. However, they started with an average of 2.79 medications taken at baseline, while we started with a mean of 1.56 medications per patient.

Francis et al.[26] showed that 63% of their patients were able to discontinue all eye drops. In our study, 77.55% of the patients that were treated with SLT no longer needed medication after one year of follow up. The patients remaining on medication had a simplified treatment schedule.

The QoL study of Day et al.[17] demonstrated that glaucoma patients are more satisfied about their treatment when they only need to instil one medication instead of using several. This was in part due to the decreased ocular irritation associated with dosing less medication and partly related to greater convenience of use from instilling fewer dosages per day [8,17].

A very large cohort study by Nordstrom et al. demonstrated that physicians traditionally overestimate the adherence of their patients to their local glaucoma treatment. Nearly half of the patients discontinued the initially prescribed drop therapy completely within six months[4]. Using SLT can make us at least sure of actually treating the patient.

Need for help

Independence is part of patients' Qol. In a large cross sectional study on QoL in glaucoma patients, Odberg et al. found that 11% of glaucoma patients were dependent upon help from relatives or others to instil their medication[5]. In this context, Sleath et al.[27] showed that unmarried patients had significantly more problems than married patients in managing their glaucoma and confessed more often to be less than 100% adherent.

We recorded 12 patients in the SLT group (20%) and 18 in the control group (30%) at baseline that needed help from others to install their drops. This changed little in the control group, but the amount lowered significantly in the SLT group at 6 and at 12 months to 10 and 12% (p = 0.01), suggesting enhanced independence.

Anterior segment condition

As reported in several studies, ocular surface disease and reduced BUT are very common in glaucoma patients[7-9,14,28]. The severity of the reported symptoms is positively correlated to the number of IOP lowering medications used[9,14,28]. Leung et al. recorded a reduced BUT in 78% of glaucoma patients on local medication[28]. In our study, BUT was reduced in 72.80% of patients, we found no difference in BUT between the SLT and the control group at any time point.

At baseline, punctuate keratitis was recorded in 31.15 to 35.94 % of the patients. There was a trend towards less punctuate keratitis in the SLT group (14.06%) after six months, which became statistically significant after 12 months (12.24%)(p = 0.03). The incidence of punctuate keratitis at baseline was higher in our groups than in a report by Pisella et al.[9], which showed a prevalence of 19% among patients using glaucoma medication. Leung et al. recorded 22% of their patients showing corneal and conjunctival lissamine green staining[28]. Our progressive decrease may be explained by additional decrease of medication, or by the fact that epithelial recovery takes some time.

A large segment of our glaucoma patients were taking artificial tears at baseline: 35.94% in the SLT group and 24.59% in the control group. At the six months follow up this number was significantly lower in the SLT group (31.25%) while it was raised in the control group (34.43%). Being part of a study possibly drew attention to side effects (scratching, redness, sandy feeling), leading to more artificial tears use in the control group after 6 and 12 months.

In a study of Costa et al.[29] more glaucoma patients (53%) used artificial tears compared to their age-matched controls (18%) without glaucoma therapy. Pisella et al. registered use of artificial tears in 19% of their glaucoma patients[9]. Our findings seem to lie in between those of Costa and the ones from Pisella, confirming more need for artificial tears in patients on anti-glaucoma treatment.

Quality of life

Perceived effectiveness

Satisfaction or dissatisfaction with medication predicts patients' continuance of their treatment, the correct use of medication and compliance with the medication regimens[18]. In our study, patients that agreed to have an SLT done were less sure of the effectiveness of their medication (p = 0.006), complained more about its side effects (p = 0.003) and were bothered more by the inconvenience of using eye drops (p = 0.01). They had difficulties putting in the drops and using only one drop at a time, but this did not differ from the control group (p = 0.67).
After the laser treatment, all these parameters scored significantly better in the SLT group. Patients believed more in the effectiveness of treatment, had less burning and stinging of the eyes, the eye appearance improved and remaining medication was easier to remember and to apply.

Similar findings were reported by a treatment related study by Odberg et al., who took patients on glaucoma medication and examined their QoL. Half of their patients treated with laser or surgery evaluated their situation as improved after these operations[5]. Possible explanations were the relief by doctor and patient related to a lowering of the IOP or to a lesser need of medication. Odberg et al. stated that it is likely that a satisfactory regulation of the IOP without use of topical therapy will give patients a better QoL[5].

Nordmann et al., who did al large cross-sectional survey studying the link between patient-reported side effects of anti-glaucoma medication and vision-related QoL, reported that poor subjective treatment satisfaction was related to poor vision related QoL, which in turn could be connected to less compliance[6]. Since compliance is of major importance to get the full potential protective effect against visual field defect, tolerance of and satisfaction with treatment are a critical issue[17].

Side effects

Pisella et al. questioned a group of 4107 patients on anti-glaucoma medication, 61% of patients reported some kind of irritation. The prevalence of signs and symptoms was dose-dependent and increased with the number of preserved eye drops used by the patient[9]. Odberg et al.[5] noted complaints about side effects in 47% of their glaucoma patients. Most common cause of dissatisfaction were itching (24%) and pain (10%). Nordmann et al.[6] reported 62.4% of their glaucoma patients complained of at least one local side effect. Presence of local side effects correlated to poor treatment satisfaction and to additional visits to the ophthalmologist[6].

In a study of Schwartz et al. hyperaemia was noted by the physician in 19.5-31.5% of the patients on prostaglandin analogues for glaucoma, it was a common reason for medication change and responsible for additional therapeutic costs[30]. In our study the questionnaire

recorded a significant improvement in side effects and complaints about eye appearance after SLT.

Ease and convenience of use

Multiple medications and multiple daily administrations can be an inconvenience and, for a subset of patients with dexterity problems, present significant difficulties to its use. The costs and side effects (discoloration of eye lids) associated with wastage of product by missing the eye can be a substantial concern for patients[17]. Use of SLT minimized the inconveniences associated with the administration of medications ($p < 0.001$).

Limitations of this study

The TSS-IOP questions were translated taking into account translation, back-translation and cultural adaptation. TSS-IOP includes questions referring to the use of medication and ease of administration of eye drops. This is less applicable after SLT since this simplifies treatment schedules. However, problems with use and administration of medication can result in loss of compliance, so it should be taken into account when deciding to use SLT or not. Using a vision specific QoL questionnaire would have been another option, but vision does generally not change in glaucoma patients within the restrictions of a one to two year study period[31].

Clinicians tend to over-estimate compliance[3, 32] and underestimate the impact on QoL of glaucoma medication[5,6,7]. SLT can significantly lower the burden of treatment for glaucoma patients with respect to QoL, as well as convenience and tolerability of the treatment.

Conclusions

SLT significantly lowers the amount of anti-glaucoma medication needed and improves treatment-related QoL. Patients show less dependence upon help of others to instil drops, have less punctuate keratitis and less subjective side effects. They are convinced of the effectiveness of their treatment and have fewer problems applying any remaining drops.

Maybe SLT should become first-line treatment instead of medication in the therapy of glaucoma.

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Wetenschap

Het lijkt me echt de toekomst
een lichaam stimuleren
om rommel op te ruimen
dat zijn werking stoort

Met minimale energie
en wel gerichte punten
de prikkel geven die
de cellen doet bewegen
zodat ze afval netjes
in de bloedbaan voeren
en al dat weefsel zich
eens zo jong kan voelen

We hebben die machine
maar wat duurt het lang
voor dokters ze gebruiken
want druppels zijn in zwang

Een thesis dus, een reeks patiënten
en bewijzen met een klap
dat alles steeds verandert
ook in de wetenschap

Mdk

CHAPTER 10. Use of SLT as a replacement therapy

Medication can produce local and systemic side effects in glaucoma patients. SLT bypasses these problems.

We examined whether it was valid to replace medical therapy by SLT in terms of IOP control and number of medications needed.

Selective laser trabeculoplasty as replacement therapy in medically controlled glaucoma patients.

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World Glaucoma Congress, 28 June 2017, Helsinki, Finland

Abstract

Purpose
We examined selective laser trabeculoplasty (SLT) as a replacement therapy for medically controlled open angle glaucoma or ocular hypertensive patients.

Methods
A prospective randomized interventional clinical trial on 143 glaucoma patients. Patients were randomized to either receiving SLT or to the control group that continued on pressure lowering medication. Data were recorded 1 hour, 1 week, 1, 3, 6, 12 and 18 months after SLT. Primary outcome was number of medications at 12 and 18 months while maintaining a pre-determined target intraocular pressure (IOP).

Results
SLT reduced the number of medications from a mean of 1.5 at baseline to 0.35 after 12 months and 0.29 after 18 months. Meanwhile, SLT achieved more than 20% IOP lowering in 95% of eyes and more than 30% IOP lowering in 86% of eyes after 18 months. 77% of our eyes no longer needed any medication after SLT at 18 months.

Conclusion
SLT enabled a reduction in number of medications while maintaining good IOP control. SLT was able to completely replace medical therapy in 77% of eyes after 18 months. SLT as replacement therapy may reduce local and systemic side effects and prevent adherence issues.

Introduction

Glaucoma is the second main leading cause of blindness in the world and an extremely common disorder in the aging Western population[1]. Currently, only lowering of the intraocular pressure (IOP) has proven to delay disease onset and slow down its progression[2]. Ocular hypotensive drugs are typically the first line of therapy for glaucoma. However, decades of taking topical medications has a serious influence on quality of life (QoL)[3-5]. A toxic effect on the anterior eye segment has been demonstrated for the preservative, most often benzalkonium chloride[6,7], as well as for the active components of the anti-glaucoma drops[7].

Local medications induce a range of complaints and signs like burning, stinging, dry eye syndrome, conjunctival hyperaemia, foreign body sensation and tearing[7,8]. These symptoms usually become worse in the long term[7,9,10].
On the other hand, adherence to therapy poses a problem in the treatment of glaucoma[9,11,12], as in all chronic diseases. In the public hospital where this study was run, questionable adherence to topical medication formed the immediate impulse to look for an alternative treatment.

Selective laser trabeculoplasty (SLT) has proven to be a valid alternative to medication as first line therapy for both glaucoma and ocular hypertension[13,14]. The use of laser instead of medical therapy bypasses non-adherence[8,9], and can diminish costs[15] and side effects of anti-glaucoma drops by lowering or avoiding the need for topical medication[16].

We hypothesize that treatment with SLT can replace topical medication while maintaining IOP control. To the best of our knowledge, this is the first prospective randomized clinical trial examining the replacement of medication by SLT.

Materials and Methods

Study design and subjects

This is a prospective randomized interventional trial including 286 eyes of 143 consecutive patients at the glaucoma consultation of ZNA Jan Palfijn Hospital, Merksem, Belgium. Enrolment of subjects occurred from January 2014 to July 2015.
Approval of the Ethics Committee of ZNA was obtained (EC 4313); we followed the Tenets of the Declaration of Helsinki. Data were recorded at baseline, at one hour, one week, one, three, six, twelve and eighteen months post-SLT.
Investigators and patients were not masked to treatment allocation due to the nature of the treatments.

Inclusion criteria concerned primary open angle glaucoma (POAG) or ocular hypertension (OHT) controlled with medical therapy. Patients had to agree to sign an informed consent form.
Exclusion criteria were other types of glaucoma than open angle glaucoma, previous glaucoma surgery and previous laser trabeculoplasty. Patients with corneal disease that inhibited good visualization of the trabecular meshwork and those taking systemic steroids were also excluded from the study.

Randomization of patient allocation was performed with a computer-generated allocation schedule using a blocked allocation sequence of 6 possibilities per block (SLT or control, steroids in the right or the left eye after SLT, non-steroidal anti-inflammatory drops in the right or the left eye after SLT). Patients were consecutively introduced into the study; only after introduction of the personal patient data, the allocated group became clear to patient and observer. In the SLT group, if both eyes received SLT the right eye was treated first.

The study was not designed to create additional IOP lowering, because IOP was already controlled with medication before treatment with SLT. The main goal of this study involved changes in the number of medications.

Baseline examinations
At baseline a full ophthalmological examination of each study participant was conducted, including a medical history review. Patients were also asked if they had any of these risk factors: myopia, arterial hypertension, diabetes mellitus, migraine, vascular problems or a family history of glaucoma. Best-corrected visual acuity measurement was taken as well as IOP measurement using Goldmann applanation tonometry (mean of two measurements was taken), slit lamp examination of the anterior segment (gonioscopy), central corneal thickness (CCT) measurement (iPac Pachymeter, Reichert, Depew, USA), dilated fundus examination, visual field examination by computerized perimetry (program 24-2, Humphrey Field Analyser 745i, Zeiss, Jena, Germany), Optical Coherence Tomography (OCT) of the optic nerve head and recording of glaucoma medications.

OCT scans were performed with the spectral-domain OCT RTVue (Optovue, Fremont, USA). We used focal loss of volume (FLV) as determinant for the OCT[17].
IOP before treatment was calculated as the mean of three measurements taken on 3 different visits, each 4 to 6 months apart, before starting anti-glaucoma medication. IOP at baseline was calculated as the mean of the Goldman measurements made on different time points on the three last visits before laser treatment.

Laser technique

A frequency doubled, Q-switched Nd:YAG laser was used, emitting a wavelength of 532 nm, coupled to a slit lamp delivery system (Selecta Duet laser, Lumenis, Dreieich, Germany). We used single pulses with pulse duration of 3 nanosec and spot size of 400µm.

The laser energy was initially set at 0,9 mJ and a single laser pulse was delivered at the 12 o'clock position. If a cavitation bubble appeared, the laser energy was reduced by 0,1 mJ increments until minimal bubble formation was observed. Treatment was then continued at this energy level. If no cavitation bubble was observed, the pulse energy was increased by steps of 0,1 mJ until bubble formation[18].

Immediately before the laser procedure a drop of pilocarpine 1% and apraclonidine 0.5% were instilled into the treated eye[19]. After the laser treatment, anti-inflammatory drops (Indomethacin or Dexamethasone) or no drops were administered, following study protocol. The observation that this did not influence the efficiency of the laser, was published previously [20].

Postoperative management

Patients were examined 1 hour, 1 week, 1 month, 3, 6, 12 and 18 months after SLT. After SLT, anti-glaucoma drops were continued until IOP was more than 2 mmHg below target pressure, at which point they were stopped one by one. A fixed combination of drugs was considered as a combination of two medications, the first step entailed a switch to a single medication. The second drug was stopped if possible, after respecting a minimal wash out period of three months. The number of daily applications was not changed during the study, a medication was continued at the normal frequency or stopped.

Target pressure was calculated using the formula proposed by H. Jampel (Target IOP= maximum IOP – maximum IOP% - z, where z is an optic nerve damage severity factor) (Jampel, 1997).
When a patient no longer needed any anti-glaucoma medication after SLT treatment, the therapy was considered to be a full replacement therapy. Partial replacement was defined as lowering of the number of medications after SLT.
IOP rise >20% after an initially successful full replacement therapy was retreated with SLT.
The effectiveness of SLT after one year was evaluated using 3 criteria for success: (1) reduction of medications while maintaining IOP, (2) more than 20% IOP reduction, and (3) more than 30% IOP reduction compared to baseline IOP before SLT treatment.

Statistical methods

A paired samples t-test was performed to compare baseline differences between the SLT and the control group for continuous variables (i.e. age, IOP at baseline, vision, cup-disc ratio, central corneal thickness, visual field mean deficit, OCT FLV, IOP max (before

treatment), number of medications at baseline). A χ 2-test was used to compare baseline differences in sex and type of glaucoma (POAG or OHT).

A second paired samples t-test was executed to investigate the difference in evolution of mean IOP for both groups at all time points. A χ 2-test was performed to examine the number of medications. Results of statistical analysis with *p*-values < 0.05 were considered to be significant.

Results

Population

We included 286 eyes of 143 patients. 18 patients failed to show up for the minimal six months follow up, 244 eyes of 125 patients remained for analysis. 133 eyes of 67 patients were part of the SLT group, and 111 eyes of 58 patients belonged to the control group. Demographics, baseline characteristics, glaucoma severity and topical treatments are shown in Table 1.

No significant differences were present between the SLT and the control group in terms of sex, number of risk factors for glaucoma, IOPmax before start of medication, type of glaucoma, best-corrected visual acuity, CCT, visual field deficits, OCT, presence of pseudophakia and number of medications taken at baseline. This excluded all these factors as possible confounders.

The group that underwent SLT was significantly younger, with a mean age of 68.1 years, compared to a mean of 72.6 years in the group that remained on medication. IOP at baseline was higher in the SLT group, 13.97 mmHg compared to 12.57 mmHg in the control group. At baseline, more patients were taking prostaglandin analogues and alpha-mimetics in the SLT group. However, several studies showed that pre-laser glaucoma medication does not influence the outcome of SLT[21-23].

Laser technique

All patients received a 360° treatment of the trabecular meshwork. We used a mean number of 102.6 ± 9.2 non-overlapping spots with a mean energy of 1.1 ± 0.3 mJ. The same experienced surgeon (MDK) applied all treatments.
Apart from slight redness and irritation the first week after SLT, no significant adverse events were recorded. After one hour, a rise in IOP of ≥ 5mmHg was present in 5.3% of the patients, compared to baseline IOP.

Ten eyes (6.9%) needed a repeat SLT after a mean of 13.7 months. After this second SLT, four eyes no longer needed any medication, the six other eyes continued on anti-glaucoma medication.

Table 1. Baseline characteristics of the population			
Parameters	**SLT group n=133**	**Control group n=111**	***p*-value**
Demographics			
Age (years)	68.14 ± 12.57	72.58 ± 11.15	0.02**
Sex (M/F)	66 (49.62%)/ 67 (50.38%)	54 (48.65%)/ 57 (51.35%)	0.60
Risk factors*	1.47 ± 0.94	1.65 ± 1.30	0.54
Pseudophakia	40 (30,08%)	46 (41.44%)	0.28
Glaucoma parameters			
IOPmax before medication (mmHg)	23.33 ± 5.56	22.90 ± 4.27	0.12
IOP at baseline with medication (mmHg)	13.97 ± 3.53	12.57 ± 3.50	0.004**
POAG/OHT	114 (85.71%)/ 19 (14.29%)	94 (84.68%)/ 17 (15.32%)	0.84
BCVA	0.80 ± 0.26	0.80 ± 0.24	0.97
CCT (µm)	545.14 ± 43.22	548.41 ± 40.73	0.74
Cup disc ratio	0.84 ± 0.86	0.76 ± 0.71	0.46
Visual field MD	5.52 ± 6.75	5.51 ± 7.33	0.58
Visual field PSD	4.56 ± 3.75	4.36 ± 3.52	0.52
OCT FLV	4.56 ± 4.43	5.34 ± 5.10	0.22
Medication at baseline			
Total number (mean)	1.50 ± 0.85	1.41 ± 0.71	0.14
Prostaglandin analogues	118 (88.72%)	83 (74.77%)	0.02**
Beta-blocker	52 (39.10%)	58 (52.25%)	0.12
Carboanhydrase inhibitor	20 (15.04%)	12 (10.81%)	0.13
Alphamimetics	10 (7.52%)	3 (2.70%)	0.03**

Abbreviations: n, number of patients; M, male; F, female; IOP, intraocular pressure; BCVA, best-corrected visual acuity; POAG, primary open angle glaucoma; OHT, ocular hypertension; CCT, central corneal thickness; MD, mean deviation; PSD, pattern standard deviation; OCT, optical coherence tomography; FLV, focal loss of volume in %

*Risk factors: myopia, arterial hypertension, diabetes mellitus, migraine, vascular problems, and family history of glaucoma

** Statistically significant difference ($p < 0.05$)

Evolution of IOP

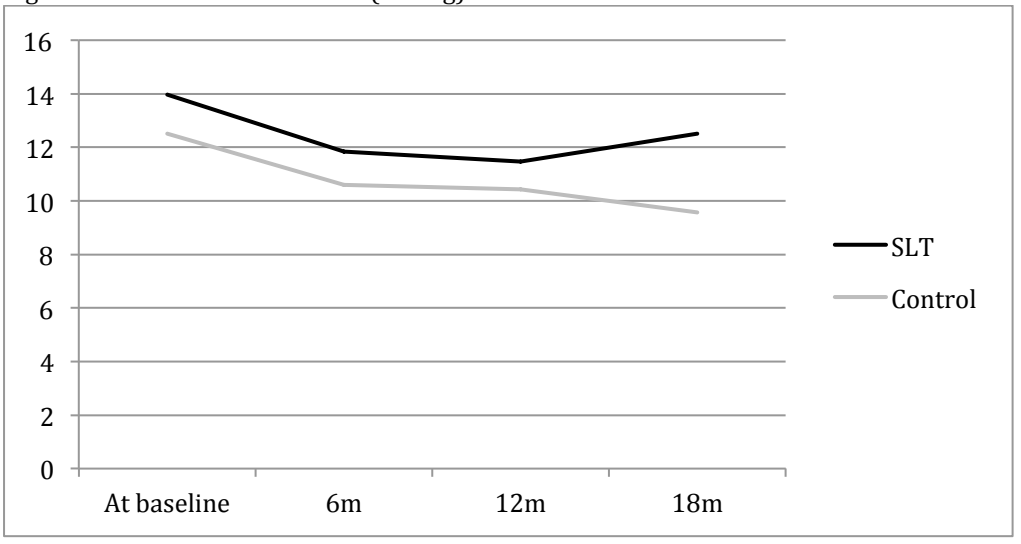
Baseline IOP was higher in the SLT group, 13.97 mmHg compared to 12.57 mmHg in the control group. This difference remained significant throughout the study. IOP remained low in both SLT and control groups, as was expected in this population of patients controlled under medication (Table 2, figure 1) Decrease in mean IOP over time in the control group was due to the different number of patients at 12 and 18 months.

Table 2. Evolution of mean IOP (mmHg)			
Time	**SLT group**	**Control group**	***p***
Baseline (n=133)	13.97 ± 3.53	12.57 ± 3.50	0.004*
6 months (n=133)	11.85 ± 3.39	10.59 ± 3.80	0.02*
12 months (n=100)	11.47 ± 2.97	10.44 ± 3.89	0.01*
18 months (n=58)	12.51 ± 4.00	9.57 ± 3.62	0.001*

Abbreviation: n, number of patients

*Statistically significant difference ($p < 0.05$)

Figure 1. Evolution of mean IOP (mmHg)



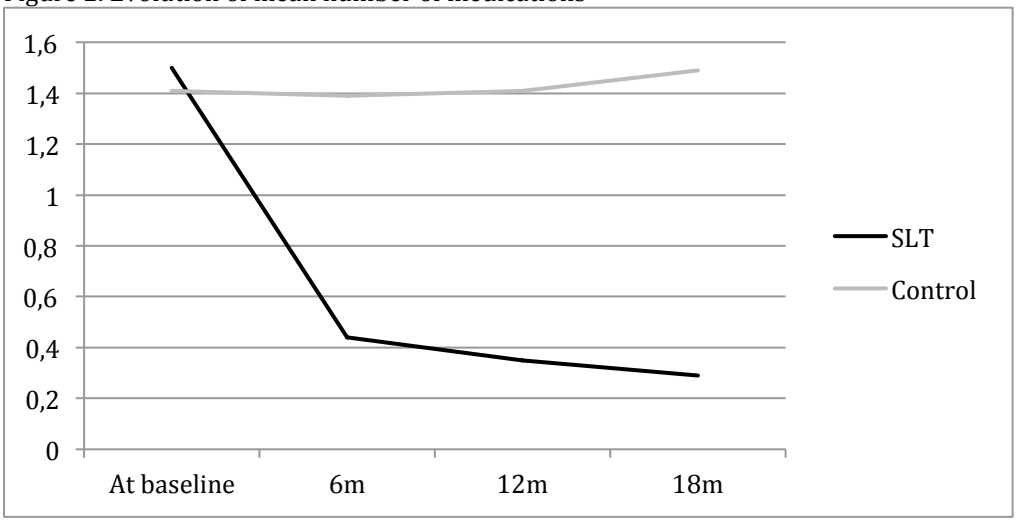
Evolution of medication

At baseline, there was no significant difference in number of medications between the two groups. In the SLT group, the mean number of medications lowered from 1.5 to 0.3 after 18 months. The difference compared to the control group was significant at all time points, as shown in Table 3, figure 2.

Table 3. Evolution of mean number of medications			
Time	**SLT group**	**Control group**	**χ 2 test *p*-value**
Baseline	1.50 ± 0.85	1.41 ± 0.71	0.33
6 months (n=133)	0.44 ± 0.68	1.39 ± 0.68	0.03*
12 months (n=100)	0.35 ± 0.70	1.41 ± 0.77	<0.001*
18 months (n=58)	0.29 ± 0.53	1.49 ± 0.89	<0.001*

Abbreviation: n, number of patients
*Statistically significant difference ($p < 0.05$)

Figure 2. Evolution of mean number of medications



Replacement therapy

Full replacement of the anti-glaucoma medication by SLT treatment was obtained in 77 eyes (77.0%) of the patients after 12 months and 43 eyes (74.1%) after 18 months. Partial

replacement (reduction of medications) was obtained in all other cases, no patient stayed on the same number of medications after SLT. 22.4% of the eyes needed one medication after 18 months, only two eyes (3,4%) still needed two medications.

After SLT mean IOP reduction compared to the IOPmax (before medical treatment) was 47.1% after 18 months. When success was defined as >20% reduction of IOP, SLT was successful in 94.8% of eyes, when >30% reduction was used as criterion, SLT was a success in 86.2%, see table 4.

Table 4. % of IOP reduction after SLT compared to IOPmax before medical treatment was initiated

Time	Mean IOP reduction (%)	Eyes with > 20% IOP reduction	Eyes with > 30% IOP reduction
6 months (n=133)	47.9 ± 13.93	129 (96.99%)	120 (90.23%)
12 months (n=100)	48.0 ± 18.07	93 (93.00%)	82 (82.00%)
18 months (n=58)	47.12 ± 17.90	55 (94.83%)	50 (86,21%)

Abbreviation: n, number of patients

Discussion

The medical treatment of glaucoma has associated local[6-8,24] and systemic side effects[25,26], is expensive[7,15,28] and often inconvenient. Therefore it is not surprising that glaucoma can have a large impact on a patients' QoL[3,4,9]. The burden of this treatment can lead to poor or noncompliance, followed by progression of disease[10,11]. Application of SLT can bypass these problems[13,14].

This study demonstrates that SLT can be used in patients that are well controlled with their topical medication. After SLT topical medications can be gradually diminished.

While maintaining good control, SLT substantially reduces the number of anti-glaucoma medications needed. In our study, SLT produced a mean reduction of medications of 1.15 after 12 months and 1.21 after 18 months. Bovell et al.[29] reported a mean reduction of 0.7 medications, five years after SLT. Francis et al.[30] recorded a mean reduction of 2.0 medications after six months. This group started with an average of 2.79 medications at baseline, while we started with a mean of 1.56 medications per patient. Only very few patient data are given by Francis et al., making it impossible to compare our patient groups.

In our study, 77% of the previously medically treated patients no longer needed any medication 12 months after SLT, and 74% after 18 months. All other patients were able to reduce their medication. In the replacement study of Francis et al.[30] 63% of patients were able to discontinue all eye drops after SLT.
Since compliance is known to improve[11,31] and side effects to decrease[6,8] when the number of medications lowers, this makes a huge difference for the patient[3,4] as well as for the efficacy of our therapy[10,32].

SLT can be used as replacement therapy in well-controlled patients. SLT lowers the IOP enough in a vast majority of patients. In this study more than 20% IOP lowering, compared to the initial IOPmax without any therapy, was achieved in 95% of patients after 18 months, and more than 30% reduction in 86% of the patients. In other trials, more than 20% reduction of IOP, one year after SLT was achieved in 55-82% of the patients[29,33-36].

Although several long term studies have shown excellent and sustained effect of SLT[22,34,37,38], the impression remains that the effect of SLT diminishes over time[29]. Several studies have already suggested that SLT is repeatable[22,29,39,40]. IOP lowering effect after repeat SLT has been shown to be similar to that of the initial SLT[41-43]. In our study, 10 eyes (6.9%) needed a retreatment after a mean of 13.7 months. Six eyes still needed one medication after the second SLT, four eyes remained medication-free.

Limitation of our study: our follow up was limited to 24 months. Longer follow up and a larger number of patients will add to understand the effect of SLT.

Conclusions

When using SLT in POAG or OHT patients that were well controlled with medical therapy, SLT maintained good IOP control with reduction of number of medications. SLT as replacement therapy can reduce problems of noncompliance and medication side effects.

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CHAPTER 11. Conclusions

General – chapter 1-2

Glaucoma is a chronical disease of the optic nerve. First line of therapy is typically eye drops. However, years of use of topical medication produces local and systemic side effects. Non-compliance is problematic, as in all chronical diseases.

Selective laser trabeculoplasty – chapter 3-4

Selective laser trabeculoplasty (SLT) is a relatively new method to lower intra ocular pressure (IOP)[1]. Its predecessor, argon laser trabeculoplasty (ALT)[2], lowered IOP by mixed mechanisms: 1. contraction of tissue at the laser site and opening up of the adjacent trabecular meshwork (TM)[3] and 2. release of inflammatory mediators that increase evacuation of humour at the TM. ALT created scarring of the TM and was therefore not repeatable, although its effect diminished over time[4].

SLT uses a much lower energy, a shorter laser time and spreads its energy over a larger spot surface. Only minimal tissue damage can be demonstrated after SLT[3]. Several inflammatory mediators have been detected after the use of SLT. Some of them attract macrophages and stimulate these to clear up local debris. Others seem to create a tissue reaction rejuvenating the TM and enhancing its permeability[5,6].

SLT has already proven to be as effective as ALT and as medication[7,8]. Still it has a hard time to break the dominance of topical medication as primary glaucoma therapy. We decided to study SLT in order to see if SLT could be useful as a replacement therapy in a glaucoma population.

Use of anti-inflammatory drops – chapter 5

ALT was known to cause redness of the eyes, irritation and IOP spikes[9]. Anti-inflammatory drops were used to counter these side effects of the laser. After SLT, the use of anti-inflammatory drops seems less necessary because the side effects are minor[10]. Still, no study was previously undertaken to determine whether anti-inflammatory drops were useful or needed after SLT. No studies examined whether its use influences the IOP lowering effect of the laser.

We compared the use of steroid drops (Dexamethasone), non-steroidal anti-inflammatory drops (Indomethacin) and no medication. We randomized patients to get one of these 2 drops in one eye (3 times daily for one week) after the SLT and no drop in the other eye. Inflammatory parameters were recorded at one hour, 1 week and 1 month after SLT.

Cells in the anterior chamber were very common 1 hour after SLT: in 57% of the patients in the Dexamethasone group and in 71% in the Indomethacin group. However, this sign became rare (resp. 3 and 6% of patients) after one week.

Pain and mild discomfort were reported respectively by 16 and 37% of patients, at one hour. This improved fast in most patients: 3-16% still complained after one week.

Redness of the eye appeared in 32 and 43% of patients after one hour and regressed more slowly. After one month still 10 and 37% of the patients complained of redness of the eyes. These pecentages were comparable to the situation before laser treatment and was probably due to the long-term use of anti-glaucoma medication.

None of the inflammatory signs (cells, pain, redness) showed a statistically significant difference between the Dexamethasone and the Indomethacin group. There was also no significant difference when the eyes with anti-inflammatory drops were compared to the eyes without drops.

Discussion

A transient IOP spike is often reported after SLT[1,9] and is definitely an unwanted side effect of the therapy. While using Apraclonidine[11] before SLT, we only measured an IOP spike in 8.5% of the Dexamethasone patients and 6% of the Indomethacin patients.

Again, there was no significant difference among the anti-inflammatory drop groups and the control group. This confirms the findings of Robin et al., who found the IOP spike after laser only to be influenced by the use of Apraclonidine but not by the use of anti-inflammatory drops[11].

Efficacy of the SLT was measured by the evolution of the IOP and the number of medications that were still needed to maintain good IOP control. The IOP in all groups was low to begin with, since the groups were all controlled under medication. So IOP lowered only slightly: from 13.46 mmHg with Dexamethasone and 14.82 mmHg with Indomethacin, to 11.91 and 11.87 mmHg respectively.

However, the difference in number of medications was much bigger: from 1.45 (Dexa) and 1.49 (Indo) medications before SLT to 0.45 and 0.23 medications six months after SLT. The difference in change of mean number of medications was not significant between the three groups.

Conclusion

SLT creates little inflammatory signs. Local therapy with steroids or non-steroidal anti-inflammatory medication makes no significant difference compared to not using medication after SLT.

A transient IOP spike occurs in 2.9% (Indo control group) to 8.6% (Dexa group and Dexa control group) of patients and is not influenced by the use of anti-inflammatory medication.

The IOP lowering effect of SLT is also not changed whether or not anti-inflammatory medication is used. The number of medications needed diminishes to the same degree with and without the use of anti-inflammatory medication.

Effect of corneal thickness – chapter 6

Central corneal thickness (CCT) has shown to be an important parameter in glaucoma[12-16]. On one hand, it influences the IOP measurement. The Goldmann applanation tonometer has been designed for a certain CCT[17]: it tends to overestimate IOP in eyes with thick cornea and underestimate IOP in eyes with thin cornea[15,16].

On the other hand, CCT may provide information about tissue properties of the eye, reflecting the quality of e.g. the lamina cribrosa[18,19]. Since SLT relies on specific biochemical properties of the eye tissue, weaker tissue as reflected by a lower CCT might produce a diminished reaction to SLT. However, Shazly et al.[20] suggested that thinner corneas gave better IOP reduction after SLT.

We took a cut off of 550 µm and compared patients with thick cornea (CCT ≥ 550 µm) to patients with thin cornea (CCT<550 µm).
In our study, we recorded a significantly larger cup disc ratio in patients with thinner cornea compared to those with thicker cornea. This concurs with the study of Pakravan et al., who suggested that thinner corneas may be a marker for more deformable discs, prone to the effects of increased IOP [21].

However, because of the 'false' low IOP measured in patients with thin cornea[16,22], glaucoma may be more advanced before it is detected in these patients. In agreement with Jonas et al.[15] we noticed that thin corneas were not associated with higher visual field progression.

The mean percentages of IOP reduction showed no significant difference between the groups with high and low CCT. The mean number of medications also showed no significant differences.

Conclusion

Thinner corneas do not seem to influence the outcome of SLT.

Impact of lens extraction – chapter 7

Cataract and glaucoma are the two main causes of blindness in the world[23]. In the aging population they frequently occur together. Clear corneal phacoemulsification (CCP) is associated with significant and sustained reduction of IOP[24-26]. Increase in anterior chamber depth and opening of the anterior chamber angle have been described after CCP[25,27]. Release of inflammatory mediators has also been proposed to contribute to the IOP lowering effect of CCP[28].
If CCP triggers the same mediators as SLT does, it is not unthinkable that performing an SLT in patients with implanted lens (pseudophakic) would be less effective.

We matched a group of pseudophakic patients with a group of patientswho still had their own lens (phakic) for demographic parameters (age, sex) and glaucoma parameters (baseline IOP with medication, type of glaucoma, central corneal thickness, cup disc ratio, visual field mean deficit, optical coherence tomography focal loss of volume, IOP max before medication). Then we compared their SLT results.

In agreement with Werner et al.[29], Kalbag et al.[30] and Seymenoglu et al.[31] we also found no significant difference in SLT efficacy between phakic and pseudophakic eyes.

Nagar et al. [32] noted that the IOP lowering effect after SLT occurs either after one week (fast responders) or only after 4 to 12 weeks (slow responders). The group of fast responders was the biggest one in her study (85-90%). We found a trend towards more fast responders in the pseudophakic group (50%), whereas the slower response was more common in the phakic patients (71%).
We can agree with the guideline to wait at least 12 weeks or 3 months to evaluate the full effect of an SLT[32].

Conclusion

SLT has a comparable efficiency in phakic and pseudophakic patients.
Full effect of the SLT can only be evaluated after 3 months.

Use in normal tension glaucoma – chapter 8

Normal tension glaucoma (NTG) is a subgroup of open angle glaucoma (OAG) in which the IOP never rises above 21 mmHg[33-35]. Vascular insufficiency seems to be a more common feature in NTG patients, with perfusion deficits of the optic nerve head, the retina, the choroid and retro-bulbar vessels[34,36-38].
For many years, it was unclear whether lowering the IOP was useful in NTG patients. The Collaborative Normal Tension Glaucoma Study however showed that visual field loss progressed slower when IOP was lowered ≥ 30% in NTG patients[33].

SLT in NTG patients has been studied in Asia, where NTG comprises 77 to 92% of OAG. High pre-laser IOP has proven to be predictive of better IOP lowering results after SLT[39-42]. This may make SLT less applicable for NTG patients.

We compared the NTG patients in our study with the other OAG and OHT patients. Although IOP was controlled in our population, SLT was able to reduce IOP a further 9% and 6% after respectively 12 and 18 months in the NTG group. This is in line with the findings of Lee et al.[35]. This group recorded a 15% additional IOP reduction in NTG patients.

SLT also lowered the number of medication needed to the same amount in the NTG and the OAG/OHT groups (76% and 90% reduction of medication respectively). The difference was not significant.

Conclusion
SLT efficacy is not inferior in NTG patients compared to other OAG or OHT patients.

Impact on quality of life – chapter 9

Long-term use of topical medication is associated with ocular surface disease[47,48]. It induces a range of complaints like burning and stinging, as well as signs like conjunctival hyperaemia, punctuate keratitis and low Tear Break Up time[49].

We compared a group of patients that got SLT with a group of control patients, matched for age and sex, that remained on their own topical medication.

.1. SLT lowers number of medications

Compared to the control group, SLT lowered the number of medications needed significantly: with a mean drop of 1.23 medications. In other studies[29,50-52] the mean drop of medications varied between 0.7 and 2.0, depending upon the number of medications before SLT.
In our study, 77.55% of patients treated with SLT no longer needed medication and all others obtained a more simplified treatment schedule.

.2. Less need for help from others

Odberg et al.[54] found 11% of glaucoma patients to be dependent upon help from relatives to instil their medication. At baseline we recorded 20% of patients to be dependent upon help from others in the SLT group and 30% in the control group. After SLT, the need for help lowered to 12%, suggesting enhanced independence of a significant group of patients.

.3. Anterior segment recovers

Ocular surface disease and reduced tear break up time (BUT) are very common in glaucoma patients[47-49,55]. Leung et al. recorded a reduced BUT in 78 % of glaucoma patients on topical medication[56]. In our study, BUT was reduced in 72.80% of the

patients. The severity of the reported anterior segment symptoms is positively correlated to the number of IOP lowering medications used[48,55].

Since SLT lowers the amount of medications significantly, we expected to find an improvement of the BUT. However, there was no significant difference in BUT between the SLT group and the control group at any time point. Possibly, the time frame of the study (12-18 months) was too short for the tear film to recover after years of using topical medication.

Pisella er al.[48] recorded the presence of punctuate keratitis in 19% of their glaucoma patients, while 22% in the study of Leung et al.[56]. In our study, 35.94% of the patients showed punctuate keratitis in the SLT group and 31.15% in the control group. This lowered to 12.24% in the SLT group. The difference compared to the control group became significant after 12 months.

Costa et al. noticed that 52% of glaucoma patients were taking artificial tears, compared to 18% of age-matched controls without glaucoma medication[57]. Pisella et al. registered use of artificial tears in 19% of their glaucoma patients[48]. Our results lie in between these values, with 35.94% of patients using artificial tears in the SLT group and 24.59% in the control group. This number didn't change significantly.

.4. Subjective quality of life improves

Measuring quality of life is not easy. A number of questionnaires exist to capture the influence of vision related problems in glaucoma patients (NEI-VFQ 25, COMTOL)[43,44]. Since we did not expect deterioration of vision within our study, we used a questionnaire based on treatment satisfaction: the Treatment Satisfaction Survey for IOP (TSS-IOP)[45,46]. For this, we received the kind permission of Pfizer.

The first four questions of the TSS-IOP concerned the effectiveness of the treatment as perceived by the patient. Patients were asked how satisfied they were about the treatment and how convinced they were that the treatment would maintain eye pressure within the wanted range.

The 'unintented treatment effects' questions inquired about burning or stinging of the eyes, feelings of grittiness or sandiness or the presence of crusts around the eyes. Patients were also asked whether the treatment induced redness of the eye or other changes in appearance.

'Convenience of use' concerned the number of times per day a treatment had to be applied, at which time and if this was easy to remember. The topic 'Ease of administration' involved the difficulty of getting the drops into the eye and whether only one or more drops were usually applied.

.4.a Perceived effectiveness rises

Satisfaction or dissatisfaction with medication predicts patients' adherence to their treatment[46]. Nordmann et al.[58] reported that poor subjective treatment satisfaction was related to poor quality of life and to less compliance. The score for 'perceived effectiveness' went up significantly after SLT.

This is in line with the study of Odberg et al.[54] that showed that patients who had laser or surgery for their glaucoma, were significantly more satisfied about their therapy.

.4.b. Unintended treatment effects decrease

Pisella et al. [48] reported 61% of patients to have some kind of irritation in a group of 4107 patients on glaucoma medications. The prevalence of these signs and symptoms was dose-dependent [48]. Most common complaints were itching (24%) and pain (10%)[54].

Hyperaemia was noted by the physician in 19.5% of the patients on Latanoprost and in 39.4% of the patients on Bimatoprost in a study by Schwartz et al.[59]. It was a common reason for medication change and responsible for additional therapeutic costs[59]. In our study we recorded a significant improvement in the scores for side effects and complaints about eye appearance after SLT.

.4.c. Convenience of the therapy augments

Multiple medications and multiple daily administrations can be an inconvenience[60] and present significant difficulties to its use for a subset of patients with dexterity problems. Use of SLT minimized the inconveniences associated with the administration of medications. The score for ease of administration went from 56.17 before SLT to 82.06 after SLT (higher scores signify more patient satisfaction).

Conclusion

SLT significantly lowered the amount of glaucoma medications needed and improved treatment-related quality of life. Patients were less dependent upon help from others to instil drops, had less punctuate keratitis and less subjective side effects. They were more convinced of the effectiveness of their treatment and had fewer problems applying any remaining drops.

Use of SLT as replacement therapy – chapter 10

Ocular hypotensive drugs are still the first line of therapy for glaucoma. However, decades of taking topical medications has its toll in terms of local side effects[47,61,62]. It lowers

quality of life[54,58] and lowers adherence[57]. We hypothesized that SLT could replace topical medication while maintaining IOP control. This was the first prospective randomized clinical trial examining the replacement of medication by SLT.

244 eyes of 125 patients were included, 133 eyes had SLT, 111 eyes were controls. At baseline, the IOP was low in both groups, but significantly higher in the SLT group, 13.97 mmHg compared to 12.57 mmHg in the control group. In both groups, the mean IOP

lowered only slightly. This could be expected, since the study was not aimed at further reducing IOP.

The difference in number of medications used was not significant between the two groups at baseline. In the SLT group the medication use dropped significantly, from a mean of 1.5 medications per patient to 0.29 medications after 18 months. In the control group a lowering of medications was also tried, but most patients returned to more medications: from 1.41 medications at baseline to 1.49 medications after 18 months.

Full replacement of the glaucoma medication by SLT treatment was obtained in 77% of the eyes after 12 months and 74% after 18 months. In a short study by Francis et al.[50] 63% of patients were able to discontinue all drops. Partial replacement (reduction of medications) was obtained in all other cases. 22% of the eyes needed one medication after 18 months, only 3% still needed two medications, none needed more.

Conclusions

When using SLT in POAG or OHT patients that were well controlled with medical therapy, SLT maintained good IOP control with significant reduction of number of medications.

General conclusions

SLT is a reliable therapy to use in patients with POAG, OHT and NTG. Its efficiency is independent of corneal thickness and presence of pseudophakia. Side effects of the therapy are minimal, use of anti-inflammatory therapy is not necessary.
Using SLT as a replacement therapy for topical medications maintained IOP at the desired low level, while diminishing the amount of medication needed. Patients confirmed improvement of quality of life.

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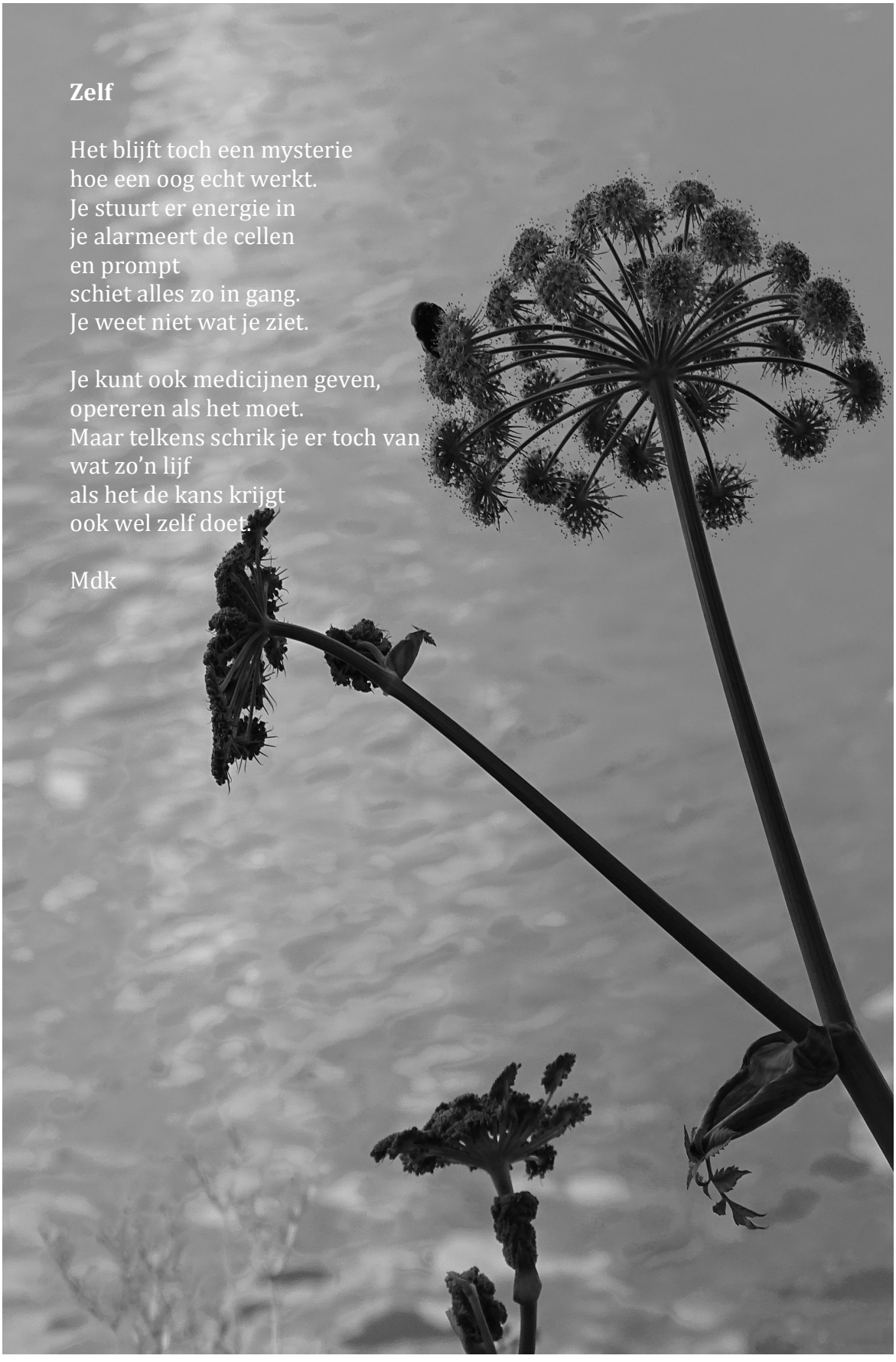
Zelf

Het blijft toch een mysterie
hoe een oog echt werkt.
Je stuurt er energie in
je alarmeert de cellen
en prompt
schiet alles zo in gang.
Je weet niet wat je ziet.

Je kunt ook medicijnen geven,
opereren als het moet.
Maar telkens schrik je er toch van
wat zo'n lijf
als het de kans krijgt
ook wel zelf doet.

Mdk



CHAPTER 12. Nederlandse samenvatting

Algemeen – hoofdstukken 1-2

Glaucoom is een chronische ziekte van de oogzenuw. De eerste lijn van therapie bestaat klassiek uit oogdruppels. Het jarenlang gebruiken van topische medicatie veroorzaakt echter locale en systemische nevenwerkingen. Therapietrouw vormt een problem bij glaucoompatiënten, zoals bij alle chronische zieken.

Selectieve laser trabeculoplastie – hoofdstukken 3-4

Selectieve laser trabeculoplastie (SLT) is een relatief nieuwe methode om de intraoculaire oogdruk (IOD) te verlagen[1]. Zijn voorganger, argon laser trabeculoplastie (ALT)[2], verlaagt de IOD via een gemengd mechanisme: 1. contractie van het weefsel op de plek van de laser met opentrekken van het aanpalende trabeculaire network (TN)[3] en 2. vrijstelling van inflammatoire mediatoren die de evacuatie van voorkamervocht ter hoogte van het TN verhogen. ALT veroorzaakt verlittekening van het TN en is bijgevolg niet herhaalbaar, hoewel zijn werking vermindert in de tijd[4].

SLT gebruikt veel minder energie, een kortere lasertijd en verspreidt zijn energie over een grotere oppervlakte. Na SLT werd dan ook slechts minimale weefselschade aangetoond[3]. De aanwezigheid van verschillende inflammatoire mediatoren werd aangetoond na het gebruik van SLT. Een aantal daarvan trekken macrofagen aan en stimuleren deze om lokaal debris op te ruimen. Andere mediatoren creëren een weefselreactie die leidt tot verjonging van het TN en verhoging van diens doorgankelijkheid[5,6].

SLT heeft al bewezen even efficient te zijn als ALT en als medicatie. Toch kan de techniek niet goed doorbreken als primaire therapie bij glaucoompatiënten. We onderzochten of SLT een goed alternatief kan bieden voor oogdruppels bij patiënten die al glaucoommedicatie namen.

Ontstekingswerende druppels - hoofdstuk 5

Van ALT was bekend dat het roodheid van de ogen veroorzaakte, evenals locale irritatie en pieken in de IOD [9]. Om deze neveneffecten van de laser op te vangen, gebruikte men ontstekingswerende druppels. Na SLT lijkt het gebruik hiervan minder zinvol vermits er weinig neveneffecten optreden. Tot nu toe werden echter geen studies uitgevoerd die onderzochten of ontstekingswerende druppels nuttig of nodig waren na SLT. Noch waren er studies die onderzochten of deze druppels het IOD dalende effect van de SLT verminderden.

Wij vergeleken het gebruik van steroidale druppels (Dexamethasone), niet-steroidale anti-inflammatoire druppels, namelijk Indomethacine, en geen druppels na de laser. Patiënten werden gerandomiseerd om één van de twee ontstekingswerende druppels in

het ene oog te krijgen, 3 maal per dag gedurende een week, en geen druppels in het andere oog. Ontstekingsparameters werden geregistreerd na een uur, een week en een maand.

De aanwezigheid van cellen in de voorkamer was zeer courant een uur na de SLT: bij 57% van de patiënten van de Dexamethasone group en bij 71% van de Indomethacine groep. Dit teken werd na een week erg zeldzaam: het kwam respectievelijk bij 3 en bij 6% van de patiënten voor.

Pijn en lichte hinder werden respectievelijk bij 16 en bij 37% van de patiënten gevonden een uur na de laser. Dit verbeterde bij de meeste patiënten snel: 3-16% kloegen nog steeds bij de controle na een week.

Roodheid van het oog kwam voor in 32 en 43% van de patiënten na een uur en trok geleidelijk weg. Na een maand vermeldden nog respectievelijk 10 en 37% van de patiënten rode ogen. Deze percentages waren vergelijkbaar met de toestand voor de laser en werd vermoedelijk veroorzaakt door het langdurige gebruik van anti-glaucoom medicatie.
Voor geen enkele van de ontstekingstekens werd een significant verschil opgemeten tussen de ogen die ontstekingswerende druppels kregen en de ogen die er geen gebruikten.

Discussie
Na SLT wordt soms een voorbijgaande IOD piek gerapporteerd. Dit is beslist een ongewenst neveneffect van de therapie[1,9]. Robin et al. toonden aan dat het voorkomen van deze piek niet beïnvloed wordt door het toedienen van ontstekingswerende druppels na de laser. De piek kom wel minder vaak voor bij het gebruik van Apraclonidine druppels voor de SLT[11].
Wij gebruikten systematisch Apraclonidine voor de SLT en maten een IOD piek op bij 8.5% van de Dexamethasone patiënten en bij 6% van de Indomethacine patiënten.

De efficiëntie van de SLT werd beoordeeld aan de hand van de evolutie van de IOD en van het aantal medicaties dat nog nodig was om een goede IOD controle te behouden. De IOD was in alle groepen laag vanaf het begin van de studie, vermits het ging om patiënten die onder controle waren met medicatie. De IOD verminderde dan ook weinig: van 13,46 mmHg met Dexamethasone en 14,82 mmHg met Indomethacine naar 11,91 en 11,87 mmHg respectievelijk.

Het verschil in aantal medicaties was beduidend groter en evolueerde van 1,45 (Dexamethasone) en 1,49 (Indomethasine) voor de SLT naar 0,45 en 0,23 medicaties zes maanden na SLT. Het verschil in het aantal medicaties was niet significant tussen de drie groepen.

Conclusie
SLT verwekt weinig neveneffecten. Locale therapie met steroiden of niet-steroidale anti-inflammatoire medicatie maakt geen significant verschil vergeleken met geen medicatie na de SLT.
Een voorbijgaande IOD piek kwam voor in 2,9% (Indo controle groep) tot 8,6% (Dexa groep en Dexa controle groep) van de patiënten. Dit werd niet beïnvloed door het gebruik van anti-inflammatoire medicatie.
Het IOD dalende effect van de SLT veranderde ook niet met het al dan niet gebruiken van anti-inflammatoire medicatie. Het aantal medicaties verminderde in dezelfde mate met en zonder het gebruiken van onstekingswerende druppels.

Effect van de corneale dikte - hoofdstuk 6
Centrale cornea dikte (CCT) is een belangrijke parameter binnen glaucoom[9]. Aan de ene kant beïnvloedt het de IOD meting. De Goldmann applanatie tonometer werd ontwikkeld voor een welbepaalde CCT (500 µm): in ogen met een dikke cornea neigt het toestel tot overschatting van de IOD en in ogen met een dunne cornea eerder tot onderschatting van de IOD[15,16].

Aan de andere kant weerspiegelt de CCT de kwaliteit van bijvoorbeeld de lamina cribrosa[18,19] en biedt dus informatie over bepaalde weefseleigenschappen van het oog. Vermits SLT op specifieke biochemische eigenschappen van het oog rekent, zou zwakker weefsel ook een minder sterke reactie op SLT kunnen vertonen.
Nochtans suggereerden Shazly et al.[20] dat dunnere cornea's een betere IOD reductie opleverden na SLT.

Wij vergeleken patiënten met een dikke cornea (CCT≥ 550 µm) met patiënten met een dunne cornea (CCT<550 µm).
In onze studie registreerden we een significant grotere cup disc ratio in patiënten met een dunne cornea vergeleken met die met een dikkere cornea. Dit sluit aan bij de studie van Pakravan et al., die suggereerde dat dikke cornea's een marker kunnen zijn voor een meer vervormbare papilkop. Deze zou ook gevoeliger zijn voor de effecten van een verhoogde IOD[21]. Nochtans, door de 'vals' lage IOD die wordt gemeten in patiënten met een dunne cornea[16,22] kan glaucoom al meer gevorderd zijn alvorens het gedetecteerd wordt in deze patiënten. Net zoals Jonas et al. merkten we op dat een dunne cornea niet geassocieerd was met een grotere gezichtsveld uitval[15].

De gemiddelde percentages van IOD reductive toonden geen significant verschil tussen de groepen met hoge en die met lage CCT. Het gemiddelde aantal medicaties evenmin.

Conclusie
Dikkere cornea's lijken geen invloed te hebben op het effect van de SLT.

Impact van lens extractie - hoofdstuk 7

Cataract en glaucoom zijn de twee belangrijkste redenen van blindheid wereldwijd [23]. In de ouder wordende westers populatie komen ze vaak samen voor. Clear corneal phacoemulsificatie (CCP) is geassocieerd met een significante en blijvende daling van de IOD[24-26]. Dit zou te wijten zijn aan een toegenoemen diepte van de voorkamer en het openen van de voorkamerhoek na CCP[25,27]. Ook het vrijkomen van onstekingsmediatoren zou bijdragen tot het IOD dalende effect van CCP[28].
Indien CCP dezelfde mediatoren doet vrijkomen als SLT, zou het kunnen dat het uitvoeren van een SLT in patiënten na een lensimplant (pseudophaken) minder efficiënt is dan in patiënten die hun eigen lens nog hebben (phaken).

We matchten een groep pseudophake patiënten met een groep phake patiënten voor demografische parameters (leeftijd, geslacht) en glaucoma parameters (vertrek IOD met medicatie, type van glaucoom, CCT, cup disc ratio, gezichtsveld mean deficit, optical coherence tomografie en IOD max voor medicatie). Dan vergeleken we hun SLT resultaten. Net zoals Werner et al.[29], Kalbag et al.[30] en Seymenoglu et al.[31] vonden we geen significante verschillen in de efficiëntie van SLT tussen de pseudophake en de phake ogen.

Nagar et al. [32] merkte op dat het IOD dalende effect van een SLT optreedt ofwel na een week (snelle respons) of na 4 tot 12 weken (trage respons). De groep van snelle responders was in haar studie het grootste (85-90%).
Wij vonden een trend tot meer snelle responders in de pseudophake groep (50%), terwijl de trage respons vaker voorkwam in de phake patiënten (71%). We kunnen akkoord gaan met de regel om minstens 12 weken of 3 maanden te wachten alvorens het volledige effect van de SLT te beoordelen.

Conclusie

SLT heeft een vergelijkbare efficiëntie in phake en pseudophake patiënten . Het volledige effect van een SLT kan pas na 3 maanden ingeschat worden.

Gebruik bij normale druk glaucoom - hoofdstuk 8

Normale druk glaucoom (NTG) is een subgroep van open hoek glaucoom (OAG) waarbij de IOD nooit boven 21 mmHg uit komt[33-35]. Bij NTG patiënten wordt vaak vasculaire insufficiëntie opgemerkt, met perfusiedefecten op de papilkop, de retina, de choroidea en retrobulbaire vaten[34,36-38]. Het was lang onduidelijk of het doen dalen van de IOD nuttig was bij NTG patiënten. De Collaborative Normal Tension Glaucoma Study toonde echter aan dat de aantasting van het gezichtsveld trager evolueerde wanneer de IOD 30% verlaagd werd in NTG patiënten[33].

Wij vergeleken de NTG patiënten in onze studie met de andere OAG en oculaire hypertensie patiënten. Hoewel de IOD gecontroleerd was in onze populatie, was SLT toch in staat de IOD extra 9% en 6% te doen dalen na respectievelijk 12 en 18 maanden in de NTG groep. Dit sluit aan bij de bevindingen van Lee et al.[35]. Deze groep registreerde een bijkomende IOD reductie van 15% in NTG patiënten.
SLT verlaagde ook het aantal medicaties die nodig waren evenveel in de NTG groep als in de OAG/oculaire hypertensie groep (76 en 90% reductie van medicatie respectievelijk). Het verschil was niet significant.

Conclusie
SLT efficiëntie is niet inferieur in NTG patiënten vergeleken met andere OAG of oculaire hypertensie patiënten.

Impact op kwaliteit van leven - hoofdstuk 9

Langdurig gebruik van topische medicatie gaat gepaard met aantasting van de oogoppervlakte[47,48]. Het lokt een waaier van klachten uit zoals branden en steken, en tekens zoals conjunctivale hyperemie, keratitis punctata en een lage traan-opbreek-tijd (BUT)[49]. We vergeleken een groep patiënten na SLT met een groep controle patiënten, gematcht voor leeftijd en geslacht, die op hun eigen medicatie bleven.

.1. SLT verlaagt het aantal medicaties

In vergelijking met de controle groep verlaagde SLT het aantal medicaties beduidend: met gemiddeld 1,23 medicaties per patient. In andere studies varieerde de gemiddelde daling van medicaties tussen 0,7 en 2,0 afhankelijk van het aantal medicaties genomen voor de SLT[29,50-52].

In onze studie had 77,55% van de patiënten die behandeld werden met SLT nadien geen medicatie nodig, alle anderen verkregen een vereenvoudigd behandelschema.

.2. Minder hulp nodig van anderen

Odberg et al. vonden dat 11% van de glaucoompatiënten afhankelijk was van de hulp van naasten om hun medicatie in te druppelen[54]. Bij het vertrekpunt registreerden wij dat 20% van de patiënten hulp van anderen nodig had in de SLT roep en 30% in de controle groep. Na SLT verminderde de nood aan hulp tot 12%, wat een grotere onafhankelijkheid suggereert van een significant aantal patiënten.

.3. Herstel van het voorsegment

Aantasting van het oogoppervlak en verminderde BUT komen vaak voor bij glaucoom patiënten[35]. Leung et al. stelden vast dat een verminderde BUT voorkwam bij 78% van de glaucoompatiënten op topische medicatie[56]. In onze studie was de BUT verlaagd bij

72,80% van de patiënten. De ernst van de voorsegmentsymptomen is positief gecorreleerd met het aantal oogdrukdalende druppels die de patiënt neemt [48,55].
Vermits de SLT het aantal medicaties beduidend vermindert, verwachtten we een verbetering van de BUT te vinden. Er werd echter geen significant verschil in BUT aangetoond tussen de SLT groep en de controle groep. Mogelijk was het tijdsbestek van de studie (12-18 maanden) te kort om de tranenfilm te zien recupereren na jarenlang gebruik van topische medicatie.

Pisella et al. observeerden keratitis punctate in 19% van hun glaucoompatiënten[48]. Leung et al. vonden 22%[56]. In onze studie vertoonde 35,94% van de patiënten keratitis punctate in de SLT groep en 31,15% in de controle grope. Dit percentage verminderde tot 12,24% in de SLT groep. Het verschil met de controle groep werd significant na 12 maanden.

Costa et al. merkten dat 52% van de glaucoompatiënten kunsttranen namen, in vergelijking met 18% bij leeftijdsgenoten die geen glaucoommedicatie gebruikten[57]. Pisella et al. signaleerde het gebruik van kunsttranen in 19% van hun glaucoompatiënten[48]. Onze resultaten liggen tussen deze twee waardes in, met 35,94% kunsttraangebruikers in de SLT groep en 24,59% in de controle groep. Er was geen significant verschil tussen beide.

.4. Subjectieve kwaliteit van leven verbetert
Opmeten van de levenskwaliteit is niet eenvoudig. Een aantal vragenlijsten kijken naar de invloed van problemen met het zien bij glaucoompatiënten (NEI-VFQ 25, COMTOL)[43,44]. Vermits we geen verslechtering van het zicht verwachtten binnen het tijdsverloop van onze studie, hebben wij een vragenlijst gebruikt die zich basseert op de tevredenheid over de behandeling: de Treatment Satisfaction Survey voor IOD (TSS-IOP)[45,46]. Hiervoor kregen we de vriendelijke toelating van de firma Pfizer.

De eerste vier vragen van de TSS-IOP onderzochten de mate waarin de patient de therapie als effectief ervaart. Patiënten werden gevraagd hoe tevreden ze over hun therapie waren en hoe zeker ze waren dat hun therapie de druk binnen het gewenste bereik kon houden.

De vragen rond 'onverwachte therapie effecten' polsten naar brandende en pikkende ogen, gevoelens van krassen of zand in de ogen en de aanwezigheid van korstjes rond de ogen. Patiënten werden ook gevraagd of de behandeling leidde tot rode ogen of andere veranderingen in het uitzicht van hun ogen. 'Gebruiksgemak' onderzocht het aantal keren per dag dat de therapie moest gebruikt worden, op welk moment en of dit gemakkelijk te onthouden was. Het topic 'gemak van toediening' behelstte de moeilijkheid om de druppels in het oog te krijgen en of er meestal een of meerdere druppels werden toegediend.

.4.a. Gevoel van efficiëntie verbetert

Tevredenheid of ontevredenheid rond zijn medicatie voorspelt of een patient therapie trouw zal zijn of niet[46]. Nordmann et al. merkten op dat ontevredenheid met therapie gerelateerd is aan slechte levenskwaliteit en minder compliance[58]. De score voor 'gevoel van efficiëntie' steeg beduidend na SLT.

Ook Odberg et al. toonden aan dat patiënten die een laser of heelkunde ondergingen voor hun glaucoom, beduidend tevredener waren over hun therapie[54].

.4.b. Neveneffecten van de therapie nemen af

Pisella et al. toonden dat 61% van hun glaucoompatiënten (4107 patn) op medicatie een of andere vorm van irritatie ondervond[48]. De prevalentie hiervan was dosisafhankelijk[48]. De meest voorkomende klachten waren jeuk (24%) en pijn (10%)[54].

Rode ogen werden door de arts opgetekend bij 19,5% van de patiënten op Latanoprost en bij 39,4% van de patiënten op Bimatoprost[59]. Dat vormde een veel voorkomende reden om van medicatie te veranderen en was verantwoordelijk voor bijkomende therapeutische kosten[59]. In onze studie zagen we een significante verbetering van de scores rond neveneffecten en roodheid van de ogen na SLT.

.4.c. Gebruiksgemak van de therapie verbetert

Verschillende medicaties gebruiken, meerdere keren per dag, kan onpraktisch zijn[60] en bijkomende problemen opleveren voor mensen met handigheidsproblemen. Het gebruik van de SLT minimaliseerde de ongemakken die geassocieerd zijn met het toedienen van oogdruppels: de score for 'gebruiksgemak' ging van 56,17 voor SLT naar 82,06 na de SLT (hogere scores betekenen grotere tevredenheid).

Conclusie

SLT doet het aantal medicaties significant dalen en verbetert de kwaliteit van leven. Patiënten waren minder afhankelijk van hulp van naasten om hun druppels in te druppelen, hadden minder vaak afwijkingen van de cornea (keratitis) en minder neveneffecten. Ze waren meer overtuigd van de werking van hun behandeling en hadden minder last met het toedienen van eventueel overblijvende druppels.

Gebruik van SLT als vervangtherapie - hoofdstuk 10

Oogdrukdalende druppels vormen nog steeds de eerste lijn van glaucoomtherapie. Decaden van locale medicaties nemen eisen nochtans een tol op het gebied van locale neveneffecten[47,61,62]. Het vermindert de kwaliteit van leven[54,58] en doet de therapietrouw afnemen[57]. Wij vertrekken van de hypothese dat SLT topische medicatie kan verminderen terwijl een goede IOD controle behouden blijft. Dit was de eerste prospectieve gerandomiseerde klinische studie die het vervangen van medicatie door SLT onderzocht.

244 ogen van 125 patiënten werden opgenomen in de studie: 133 ogen kregen een SLT, 111 ogen vormden de controle groep. Op het vertrekpunt was de IOD laag in beide groepen, maar significant hoger in de SLT groep: 13,97 mmHg vergeleken met 12,57 mmHg in de controle groep. In beide groepen verminderde de gemiddelde IOD slechts weinig. Vermits de studie niet bedoeld was om de IOD verder te doen dalen, lag dit in de lijn van de verwachtingen.

Het verschil in het aantal medicaties was bij het vertrekpunt niet significant. In de SLT groep daalde het medicatiegebruik beduidend: van gemiddeld 1,5 medicatie per patient

naar 0,29 medicaties na 18 maanden. In de controle groep werd ook geprobeerd het aantal medicaties te verminderen, maar de meeste patiënten keerden daarna toch terug naar verhoogde medicatie: van 1,41 medicaties op het vertrekpunt naar 1,49 na 18 maanden.

Volledige vervanging van de glaucoommedicatie na SLT werd bij 77% van de ogen verkregen na 12 maanden en bij 74% na 18 maanden. In een korte studie van Francis et al. konden 63% van de patiënten hun medicatie laten na een SLT[50]. Gedeeltelijke vervanging of reductie van het aantal medicaties werd bekomen in alle andere ogen. 22% van de ogen had na 18 maanden nog één medicatie nodig, 3% nog twee medicaties, niemand meer.

Conclusie
Wanneer we SLT gebruiken in OAG of oculaire hypertensie patiënten die goed gecontroleerd zijn met medicatie, kan SLT controle van de IOD bereiken met een significante reductie van het aantal benodigde medicaties.

Eindconclusie:

Deze studie heeft aangetoond dat een SLT behandeling even uitgesproken drukdaling geeft als het gebruik van oogdruppels. SLT kan voor patiënten met open hoek glaucoom en oculaire hypertensie gebruikt worden, evenals bij normale druk glaucoom. Het is toepasbaar na een lensextractie en is onafhankelijk van dikke of dunne corneae.
Het toepassen van SLT maakt een reëel verschil in de kwaliteit van leven van de patiënten, omdat ze niet langer of toch minder de lokale en systemische nevenwerkingen van anti-glaucoom druppels moeten ondergaan en ze ook niet meer kunnen vergeten in te nemen.

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CHAPTER 13. Curriculum vitae

Education

High School, Sciences-Latin
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Medical Doctor, 1987
University of Antwerp, Antwerp, Belgium

Specialisation Ophtalmology, 1991
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Work

Oogcentrum Van Hoorenbeeck-Zen, Antwerp, 1991-2011
Subspeciality: retina and glaucoma

ZNA Jan Palfijn, Merksem, Antwerp, 2011-2015
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Subspeciality: retina, glaucoma, pediatric ophthalmology

Publications related to this thesis

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