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Efficacy of Selective Laser Trabeculoplasty in Patients with Open-angle Glaucoma or Ocular Hypertension: A Systematic Review and Meta-Analysis

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Abstract

Purpose: To determine the efficacy of selective laser trabeculoplasty (SLT) in lowering intra-ocular pressure (IOP) levels and reducing the number of medications in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

Methods: A systematic review was conducted by searching various databases including MEDLINE (Ovid), EMBASE (Ovid), CINAHL, Cochrane Library, Web of Science- Core Collections, BIOSIS Previews, and Scopus. Duplicates were removed and articles were screened using EPPI Reviewer 4. A meta-analysis was conducted using STATA 13.0. Weighted mean difference (WMD) was computed and the heterogeneity statistic was assessed using the I^2. Fixed and random effects models were computed based on heterogeneity.

Results: We identified 31 articles that met our inclusion criteria. We found that Sequential SLT versus pharmacotherapy had an IOP-lowering effect favoring pharmacotherapy: WMD= 5.92% (95% CI [3.06, 8.79]) and WMD= 2.73% (95% CI [0.24, 5.23]) at 6 and 12 months, respectively. Adjunctive SLT had a greater IOP-lowering effect compared to pharmacotherapy, WMD= -8.98% (95% CI [-17.19, -0.77]). A significant reduction in the post-operative medications was observed up to 17 months. No serious complications were reported.

Conclusion: Adjunctive SLT may lead to significant reduction in IOP compared to topical medications. Additional studies need to be conducted on SLT alone, without previous treatment in order to determine its IOP-lowering effect.

Keywords

Open-angle glaucoma, Ocular hypertension, Intra-ocular pressure, Selective laser trabeculoplasty, Prostaglandin analogs, Beta-blockers, Carbonic anhydrase inhibitors, Alpha agonists, Pharmacotherapy

Abbreviations

ACG: Angle Closure Glaucoma

ALT: Argon Laser Trabeculoplasty

CAI: Carbonic Anhydrase Inhibitor

CI: Confidence Interval

ELT: Excimer Laser Trabeculoplasty

Emtree: Embase Subject Heading

IOP: Intra-ocular Pressure

IOPR: Intra-ocular Pressure Reduction

LPI: Laser Peripheral Iriodotomy

MeSH: Medical Subject Heading

mL: milliliter

Mm Hg: Millimeters of Mercury

N: Number of Eyes

ND:YAG: Neodymium: Yttrium-aluminium garnet-laser

NTG: Normal Tension Glaucoma

OAG: Open-angle Glaucoma

OHIP: Ontario Health Insurance Plan

OHT: Ocular Hypertension

p:p-value

PACG: Primary Angle Closure Glaucoma

PGA: Prostaglandin Analogs

POAG: Primary Open-angle Glaucoma

RCR: Retrospective Chart Review

RCT: Randomized Clinical Trial

SD: Standard Deviation

SLT: Selective Laser Trabeculoplasty

TM: Trabecular Meshwork

WMD: Weighted Mean Difference

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Chapter 1

1.1 Introduction

This thesis aims to evaluate selective laser trabeculoplasty (SLT) as an intervention to treat patients who are diagnosed with open-angle glaucoma (OAG) or ocular hypertension (OHT). Ophthalmologists use glaucoma medications as their primary form of treatment for glaucoma patients[1], due to robust data supporting their efficacy[2–10]. SLT is a laser treatment option that was introduced by Dr. Latina and colleagues in 1995[11].The first clinical study published that reported on the efficacy of SLT was in 1998[12]. Over the past two decades, there has been a vast amount of literature that has been published on the efficacy of SLT. We conducted this systematic review and meta-analysis with the intention of assessing the influence of SLT on intra-ocular pressure (IOP) levels and its impact on reducing the amount of required topical glaucoma medications.

1.2 Epidemiology of Glaucoma

Glaucoma is the second most common cause of legal blindness in industrialized nations[13]. In 2013, the worldwide prevalence of glaucoma for a population aged 40 to 80 years was estimated to be approximately 3.54% (95% CI [2.09%, 5.82%]) of the global population[14]. Specifically, in North America, the prevalence of glaucoma was estimated to be 3.55% (95% CI [1.98%, 5.81%])[14]. The incidence is estimated to be approximately 0.5 to 2.5% per year[15]. By 2020 there will be approximately 79.6 million people estimated to be affected by glaucoma worldwide and 11,114,117 people (95% CI [7 947 390, 16 230 278]) will become bilaterally blind from glaucoma[16]. By the year 2040, the global prevalence of glaucoma is expected to rise to 111.8 million[14].

The prevalence numbers are assumed to be underestimated given that approximately one-third of individuals with glaucoma are undiagnosed[17]. If glaucoma goes untreated, it can lead to blindness. Glaucoma is one of the top three causes of visual impairment and blindness worldwide[18]. The percentage of people who go blind per year because of

glaucoma is approximately 0.55%[15].Blindness is defined as a visual acuity score of less than 3/60[19], which means that what a person sees at three meters, a person with normal vision sees at 60 meters. Since more than 80% of visual impairment is avoidable[18], not diagnosing and not treating glaucoma puts an unnecessary strain on the health care system.

1.3 Organization of Thesis

This thesis is organized into four main sections. Chapter 2 provides a detailed literature review including the history of glaucoma, the types and treatment of glaucoma, the costs associated with glaucoma treatment, and the purpose and objectives of this thesis. Chapter 3 provides details on the methodological approach used to investigate the research questions. It discusses the search strategies, inclusion and exclusion criteria, the article screening process, and the quantitative measures used to analyze the results. Chapter 4 provides figures, tables and a summary of the results produced. Chapter 5 provides a comprehensive discussion on the results including the overall interpretation of the findings, the strengths and limitations, and future policy and research implications.

Chapter 2

2 Literature Review

2.1 Definition and History of Glaucoma

"Glaucoma" comes from the Greek word glaucosis, which is defined as the 'blue-green hue of the affected eye'[20]. In the 10th century, Arabian physicians noted the connection between glaucoma and increased pressure inside the eye. In 1622, Richard Bannister noted that chronic glaucoma could be associated with elevated intraocular pressure, and was the first to document these findings in English[21]. From the 10th century to the 19th century, ophthalmologists from around the world have noted similar characteristics of increased pressure inside the eye. Elevated intra-ocular pressure (IOP) levels were accepted as a distinguishing symptom of glaucoma in the mid-19th century[21].

Several clinical studies conducted in the 1990s have shown that many glaucoma cases had other causes besides elevated intraocular pressure levels[20]. The definition of glaucoma shifted from being solely defined by elevated IOP levels to being defined by its optic nerve damage and associated vision loss[20].

2.2 Pathophysiology of Glaucoma

A clear fluid referred to as the aqueous humor is produced by the ciliary body and fills the anterior and posterior chambers of the eye[22]. The rate of fluid production is approximately 2.5 microliters/minute[22]. Fluid inside the eye must be under some pressure at all times to keep it from collapsing. The fluid exits the anterior chamber through the trabecular meshwork (TM) or the uveoscleral outflow. The TM is a sponge-like structure which consists of three layers[23]. The resistance to fluid outflow increases as fluid passes each layer of the TM and enters the Schlemm's canal. Fluid that does not flow to the TM, flows into the supraciliary space and ciliary muscle and then goes to the scleral substance or the emissarial canals or is absorbed into the uveal blood vessel; this outflow is called the uveoscleral outflow[24]. The uveoscleral outflow only accounts for approximately 4 to 45% of aqueous humor outflow[24]. Treatment is aimed at the TM

because the TM outflow is IOP dependent, while the uveoscleral outflow is independent of IOP[24].

Too much pressure caused from not having enough fluid exiting the eye may result in elevated eye pressures. Pressure on the optic nerve may result in optic nerve damage[22]. The optic nerve is located at the back of the eye and has approximately 1.2 million nerve fibers[25]. The optic nerve travels from the back of each eye and joins together at the optic chiasm[22]. Electrical impulses travel along the optic nerve, optic tract, lateral geniculate body and finally the occipital lobe where the images are interpreted by the brain[22]. Due to the damage of the optic nerve, the retinal nerve cells eventually die, disrupting the connection between the eye and the brain[26], resulting in vision loss.

The main distinguishing feature from other neuropathic diseases is that the presence of glaucoma results in a progressively large optic nerve cup[25]. As the optic nerve loses nerve fibers, the cup becomes larger. The cup-to-disc ratio ranges from 0 to 1[25]. The larger the cup-to-disc ratio, the larger the optic nerve damage. Another factor that makes glaucoma different from other neuropathic diseases is that the treatment is aimed at lowering the intra-ocular pressure, whereas other neuropathic diseases usually have normal intra-ocular pressure levels.

2.3 Types of Glaucoma

The majority of glaucoma diseases fall under one of three categories: open-angle glaucoma (OAG), ocular hypertension (OHT) and angle closure glaucoma. This thesis will focus on OAG and OHT.

2.3.1 Open-angle Glaucoma

The drainage angle, which is located between the cornea and the iris, is what determines whether a patient has open-angle glaucoma or closed-angle glaucoma[27]. If the drainage angle is open, this is referred to as OAG. OAG is generally a bilateral disease, but may often also be asymmetric[28]. OAG is characterized as either primary or secondary. Primary OAG accounts for almost 90% of all glaucoma cases[5]. Secondary OAG is any form of

OAG that has an identifiable cause[22]. Patients with OAG who have IOP levels greater than 21 mm Hg are referred to as high tension glaucoma patients[27]. Patients with glaucomatous nerve damage, who have IOP levels lower than 22 mm Hg, account for approximately 15% of all OAG cases[28]. These patients are referred to as normal tension glaucoma (NTG) patients. OAG is usually asymptomatic and patients may notice a loss of peripheral vision after approximately 40% of nerve fibers have been damaged[28].

2.3.2 Ocular Hypertension

Ocular hypertensive (OHT) patients have an open drainage angle and have IOP levels over 21 mm Hg. They do not show signs of optic nerve damage or visual field defects[29]; this group of patients are referred to as glaucoma suspects[22].

2.3.3 Angle Closure Glaucoma

Angle closure glaucoma (ACG) is a less common form of glaucoma, and has a drainage angle that is closed when it is examined by the gonioscopy lens[25]. ACG is also characterized as primary or secondary. Primary ACG occurs when there is a pupillary block that cause the angle to close[22]. Secondary ACG is when there are underlying reasons other than a pupillary block that causes the angle to close. This type of glaucoma may be associated with symptoms of pain, nausea and decreased vision[25].

2.4 Glaucoma Risk Factors

There are several different risk factors associated with the development of glaucoma. The risk factors are divided into three different groups: elevated IOP, demographic factors, and medical factors.

2.4.1 Intraocular Pressure (IOP)

Intraocular pressure (IOP) refers to the fluid pressure in the eye[30]. High IOP levels, IOP levels above 21 mm Hg, is not a necessary cause for developing glaucoma, but it does increase the likelihood of developing the disease[25]. The Baltimore Eye Survey and the Barbados Eye Study found that IOP was an important factor correlated with higher prevalence and incidence rates[31]. It has been well-documented that the relative risk of developing glaucoma increases as an individual's IOP levels increase[25]. Approximately26.1% of patients who have IOP levels greater than or equal to 35mm Hg have glaucoma versus only 0.7% of patients who have IOP levels less than 15mm Hg have glaucoma[25]. Also, those who have an IOP asymmetry between their eyes have a higher likelihood of developing glaucoma[20].

2.4.2 Demographic Factors

Age is one of the strongest determining factors for developing glaucoma, as the frequency of glaucoma cases increases with age[20]. The majority of glaucoma cases develop after the age of 40 or 50 years[32]. The American Academy of Ophthalmology has recommended that those between 40 and 64 get assessed for glaucoma every 2-4 years and those over the age of 65 get assessed every 1-2 years[25]. The reason for the increase in risk with increasing age is that nerve fibers are lost throughout one's lifetime[26]. The more nerve fibers are lost, the wider the cup-to-disc ratio becomes resulting in an increased risk of developing glaucoma[22]. Race also plays a role in the prevalence of glaucoma cases. It has been reported that African Americans are more likely than Caucasians to develop primary open-angle glaucoma and to become blind from it[25]. Asians are more likely to develop primary angle closure glaucoma (PACG)[16]. Approximately 0.3 to 2.6% of Asians will develop PACG compared to 0.1% to 0.6% of all other races[25].

2.4.3 Medical Factors

Diseases such as thyroid disease, obesity, diabetes, emphysema and cardiovascular disease are risk factors that may lead to glaucoma[20]. There is a strong positive correlation between taking steroids and developing glaucoma[20]. The IOP levels are elevated in approximately 16% of those on steroids[20]. Also, if there is a history of glaucoma in one's family, the likelihood of developing glaucoma will increase[32]. To an extent, an individual's genetic code can determine whether they can tolerate a high IOP level[26].

2.5 Assessment of Glaucoma

Early detection of the disease is essential to prevent as much vision loss as possible. There are several measurement tools that ophthalmologists use to accurately diagnose glaucoma. Testing for glaucoma usually involves measuring the IOP levels, observing the optic nerve, and testing visual fields[32]. Results from these tests are required in order for an ophthalmologist to make a correct glaucoma diagnosis.

2.5.1 Tonometry

Tonometry is a procedure that ophthalmologists use to measure the IOP levels[25]. The Goldmann applanation tonometer is the most commonly used tool to measure IOP[22] and is considered the gold standard[30,31]. An anesthetic eye drop is placed into the patients' eye, then the IOP is measured by placing a biprism plastic tip against the cornea and flattening the cornea[25]. The IOP is based on the principle that the force required to flatten a certain defined area of the cornea is proportional to the IOP[25]. IOP measurement is also dependent on the thickness of the cornea[22]. When the cornea is thick, the IOP levels are over estimated, and when the cornea is thin, the IOP levels are usually underestimated[22]. Other less common tools to measure tonometry include the Tonopen and the Perkens; these two tools are portable applanation tonometers[25]. The pascal dynamic contour tonometer, pneumatotonometer and Schiotz tonometer are also used to measure IOP levels[25].

2.5.2 Gonioscopy

Visualization of the anterior angle of the eye is referred to as gonioscopy[8]. Whether this angle is wide or narrow affects the aqueous outflow. Gonioscopy involves examining the angle of the anterior chamber using binocular magnification and a special goniolens[22].Several types of goniolenses are used. Goldmann and Posner-Zeiss are two types that have mirrors to view the angle between the cornea and the iris[22]. The Koeppe lens is a goniolens used with an illuminator and a handheld binocular microscope[22]. The results from the gonioscopy gives an idea of whether the patient has open or closed-angle glaucoma.

2.5.3 Ophthalmoscopy

The ophthalmoscope is a tool used to assess the optic disc. Correct evaluation of the optic nerve head is imperative. If the optic nerve head is incorrectly classified, this can result in a glaucoma patient remaining untreated or a non-glaucoma patient receiving treatment[33]. To assess the optic disc, the ophthalmologist dilates the pupils with eye drops and uses a slit lamp with a hand held lens to observe the optic nerve[32]. Evaluation of the optic nerve requires the ophthalmologist to first assess the size of the optic nerve head[26]. The cup-to-disc ratio is how the doctors assess the size of the optic disc[22]. Generally a cup size of 0.2 to 0.3 is considered normal[25]. The values 0.2 and 0.3 are converted into percentages; therefore a cup size that occupies 20% to 30% of the disc is considered normal. If the cup-to-disc ratio is greater than 0.5 with visual field loss and high IOP levels, then the patient may have glaucoma[22].

2.5.4 Perimetry

Perimetry is the measurement of visual fields[25]. The visual field assessment measures both central and peripheral vision in order to find any blind spots that exist. The most common form of perimetry is when a patient is instructed to keep one eye fixed on a target that is directly in front of them while the other eye is covered[25]. The patient must press a button every time he/she sees a light flash. The computer records the location of the flash and whether the patient pressed the button[22]. This procedure examines the

sensitivity of peripheral vision to flashes of light that are briefly presented at various peripheral points.

2.6 Treatment of Glaucoma

Even though increased eye pressure is no longer included in the definition of glaucoma, reduction of eye pressure remains the main form of delaying the progression of optic nerve damage[25]. The primary form of treatment to prevent vision loss is pharmacotherapy.

2.6.1 Medications

Topical medications are the first line therapy for OAG. Most glaucoma medications are applied through eye drops or oral digestion[34]. There are four main classes of medications used to lower the eye pressure. Prostaglandin analogs are currently the most popular first line medication drugs because they have the fewest side effects[25]. Prostaglandin analogs work by increasing the aqueous outflow[25]. Latanoprost (Xalatan) was the first prostaglandin analog developed for glaucoma[25]. Travoprost (Travatan) and brimatoprost (Lumigan) are other prostaglandin analogs. These drugs are efficient and require once a day dose. Beta blockers, which are the second most commonly prescribed drugs, work by decreasing the aqueous production in the eye[25]. They are not used as frequently as prostaglandin analogs because they may be less effective at lowering IOP levels[34]. This class of drugs works by inhibiting the sympathetic nervous system, which is involved in the production of the aqueous humour[34]. Beta-blockers include Timolol, Levobunolol (Betagan), and Betaxolol (Betoptic). Timolol is the most commonly used beta-blocker[25]. Carbonic anhydrase inhibitors (CAI) are a class of drugs that work by reducing the aqueous production by about 40-60%[22]. They inhibit the enzyme carbonic anhydrase which reduces the fluid production[25]. The CAIs are not used frequently because they have systemic side effects that limit their long term use[22]. Once the patient is taken off of this drug, the side effects are usually reversible. These drugs are rarely used alone and are usually prescribed in combination with other classes of drugs. Alpha agonists are another class of drugs that decrease IOP levels by decreasing the production of fluid at the ciliary

body and they additionally help with the aqueous outflow[25]. The most commonly used drugs under this class are Brimonidine (Alphagan) and Apraclonidine (Iopidine)[25].

2.6.2 Laser Therapy

Laser therapy has been gaining popularity. The first reported use of laser therapy, which is also called laser trabeculoplasty, for patients with OAG was in the 1970s, approximately 40 years ago[35]. The pressure reduction from laser therapy decreases the medical therapy and postpones surgery, if it is required. Argon laser trabeculoplasty (ALT) is a laser that was first introduced by Wise and Witter[36] in 1979 through their pilot study. ALT uses a spot size of 50 micrometers, between 500 and 1000 megawatts of energy output and a pulse duration of 0.1 seconds, which is applied to the junction of the anterior and posterior TM[35]. In 1983, Anderson and Parish[37] found that brief pulses of selectively absorbed optical radiation could cause damage to selected pigmented tissues. They proposed selective photothermolysis, which made precise aiming of the laser unnecessary because properties in the tissue provided target selectivity so that only the pigmented tissues would be affected by the laser[38]. Selective laser trabeculoplasty (SLT) was introduced in 1995 by Latina and Park[11]. The intention was to create a laser similar to the argon laser, but without creating collateral damage to the non-pigmented tissue in the TM. In 1998 Latina and colleagues[12] published a pilot study and found that SLT treatment was effective at lowering IOP in patients with or without previous ALT treatment[12]. SLT is a frequency doubled, Q-switched neodymium: Yttrium-aluminium garnet-laser (ND: YAG) with a wavelength of 532nano-meters, a pulse duration of 3 nano-seconds and a spot size of 400 micrometers [12]. Because of the 3 nano-second pulse duration in SLT compared to the 1 second pulse duration in ALT, the electromagnetic energy in SLT does not have enough time to be converted into thermal energy, resulting in no heat being generated[39]. This means that SLT does not burn the TM, and that multiple SLT procedures are possible with minimal side effects relating to damage to the TM.

Laser treatment works by directing the laser beam at the TM, causing the tissue to shrink, which improves the drainage of fluid through the TM and ultimately lowers the IOP[22].

Laser treatment also stimulates the creation of new cells and helps get rid of waste in the TM[22]. A theory regarding the mechanism through which the laser procedure works to decrease the IOP is the result of cellular activity stimulated by the laser's energy[40]. After SLT is performed, there is an increase in the number of macrophages in the TM[40]. Macrophages are cells that are involved in the removal of cellular debris that is generated during tissue remodeling, and efficiently clear cells that have died[41]. This allows an increased outflow of the fluid from the eye[40].

2.6.2.1 Application of SLT

The ND: YAG Q-switched laser can be administered to the TM over multiple degrees of application. The most common degrees of treatment over the TM as reported in published studies are 90, 180, 270, or 360 degrees. Furthermore, each ophthalmologist has their own preference on the number of laser spots to be applied, and whether to apply the laser spots contiguously or non-contiguously. As with any other medical procedure, the guiding principle for SLT treatment is to apply the least amount of treatment to the TM as possible in order to achieve the desired benefit[42]. Several studies with mixed results have assessed whether this difference in the application of the laser beam throughout the TM affects the IOP-lowering effect of SLT treatment. Several studies have reported that the SLT degree may make a difference[43,44], or may not make any difference[45,46] on the IOP-lowering effect.

2.6.3 Surgical Treatment

If medical therapy or laser therapies do not work, surgical treatment is recommended. Trabeculectomy is the most common form of surgical treatment (often referred to as filtration procedure)[22]. This procedure reduces the IOP levels by creating another passageway for the fluid to flow out by removing part of the TM[47]. Finally, when laser or surgical treatment does not work, the ophthalmologist may decide to destroy the ciliary body, which is responsible for aqueous humor production[22].

2.6.4 Aim of Treatment

All treatment for glaucoma patients is aimed at lowering the IOP inside the eye. The Early Manifestation Glaucoma Trial[48] found that lowering the IOP levels was linked to a decrease in glaucoma progression, and The Ocular Hypertension Treatment Study[49]concluded that IOP reduction (IOPR) lowered the chance of ocular hypertensives to develop glaucoma. Ophthalmologists aim to select an IOP target in which no glaucoma progression will occur; this IOP target is different for each patient since each patient reacts to treatment differently[50].Other methods, such as vascular neuroprotective or metabolic management were conducted in animal experiments but their influence on glaucoma progression in humans has not yet been established in randomized clinical trials[31].

Additionally, ophthalmologists need to make sure that the treatment they provide is also reducing the IOP fluctuations. Although some studies have shown that there is no link between IOP fluctuations and glaucoma progression[48], other studies[51] have shown that there is a link. A patient who has an average IOP of 12 mm Hg and a fluctuation between 11 mm Hg and 13 mm Hg has a reduced likelihood of developing glaucomatous damage compared to a patient who also has an average IOP of 12 mm Hg but a fluctuation between 10 mm Hg and 16 mm Hg[50].

2.6.5 Treatment Strategies

Various treatment options could be available to a patient. The first treatment option is to put the patient on medications, and if this is unsuccessful, after at least a 4-5 week wash-out of medications, the patient is provided laser treatment. In this study, this is referred to as Sequential SLT, where SLT is provided after a wash-out period of medical treatment. The second option is to provide medications as primary treatment, and to provide SLT while concurrently remaining on medical treatment. In this study, his is referred to as Adjunctive SLT treatment. The majority of published studies assess the clinical outcomes of these two groups of patients- Sequential SLT and Adjunctive SLT. The differing effects of these two treatment strategies remains unknown. SLT could be provided as

primary treatment and if unsuccessful, SLT is repeated or medications are given. Finally, a patient could be prescribed a medications-only option in which prostaglandin analogs are given as a first line of treatment, beta-blockers as a second line of treatment, CAIs as third and alpha agonists as a fourth line of treatment. This thesis will focus on the efficacy of SLT when it is provided as primary, sequential or adjunctive treatment and the efficacy of medications-only treatment.

2.7 Cost of Treatment

2.7.1 Cost of Medical Therapy

Some patients prefer pharmacotherapy because it is a less invasive treatment alternative[52]. Also, any side effects associated with pharmacotherapy usually cease when the medications are discontinued. Since glaucoma is a chronic condition, treatment becomes costly over a patient's lifetime. If an individual is over the age of 65 and has a valid Ontario Health Card, he/she qualifies for the Ontario Drug Benefit Plan[53]. The Ontario Drug Benefit Plan covers the majority of the anti-glaucoma medications prescribed. If an individual is not 65 yet, the Trillium Drug Program is available for persons who have an Ontario health card[54]. All of the drugs that are covered by the Ontario Drug Benefit Plan are also covered in the Trillium Drug Plan. The difference is that someone who is under the Trillium Drug Plan is required to pay a deductible of approximately 4% of their net income per year into this plan[54]. Additionally, if the individual is employed, some employers will offer medical drug coverage.

2.7.2 Cost of Laser Treatment and Surgery

The average cost of bilateral SLT treatment at 180 degrees was $370 in 2003[55]. The costs of laser therapy have not changed much over the past decade. Seider et al[56] found that the average cost of bilateral SLT is approximately $675.76. Fortunately in Ontario, patients with glaucoma at any age who are Ontario Health Insurance Plan (OHIP) covered can receive free yearly eye examinations. Any follow-up assessments are also covered. Furthermore, if the patient requires SLT treatment, it is completely covered through OHIP.

2.7.3 Cost of Medical Treatment compared to Laser Treatment

A cost comparison study was conducted by Seider et al[56]comparing patients who were provided SLT treatment concurrently with medication treatment (Adjunctive SLT) and patients who were only prescribed medications. The Adjunctive SLT group had bilateral treatment and was required to take a 2.5 milliliters (mL) medication once a day. The medications-only group was required to take a 5mL medication 2 to 3 times daily. They found that when SLT was compared to brand name glaucoma medications, SLT became less costly within one year, but when SLT was compared to generic medications, SLT became less costly between 13 and 40 months. Stein et al[1] conducted an analysis looking at the cost effectiveness of treating OAG patients with prostaglandin analogs, laser trabeculoplasty, or no treatment and they found that prostaglandin analogs were cost effective and provided a better health-related quality of life. However, these results assumed that there was perfect compliance with glaucoma medications, which is often not the case. Further, authors concluded that if a patient did not adhere to the medications, laser treatment would be a cost effective alternative. Finally, Lee and Hutnik[55] conducted a 6-year cost comparison of Primary SLT with medical therapy. They found that when SLT was repeated every two years compared to mono-drug therapy, SLT became cost effective in the second year. When a patient who received SLT treatment every two years was compared with a patient who was on combination drug therapy, SLT was consistently cost effective. Combination drug therapy includes patients who are on two or more glaucoma medications. Lee and Hutnik[55] reported a cost savings for SLT patients of $206.54, $1668.84, $2992.62 over 6 years compared to patients on mono-, bi- and tri- drug therapy.

Based on these studies, the number of medications, as well as generic or brand name drugs a patient is required to take determines cost effectiveness of SLT compared to medical therapy.

2.8 Purpose

2.8.1 Efficacy of SLT

Previously published studies have reported an average 18-40% reduction post SLT treatment[57]. Latina et al[12] conducted a study including 30 patients with uncontrolled OAG and showed a 23.5% reduction from baseline at 26 weeks. Melamed et al[58]studied effects of Primary SLT treatment in 45 patients diagnosed with OAG or OHT and found a 30% reduction in IOP from baseline up until 18 months post SLT treatment. Overall, the effectiveness of SLT has been shown to be successful through previously conducted clinical trials[11,12].

2.8.2 Previous Systematic Reviews and Meta-Analyses

To our knowledge, to date one systematic review[59] and three meta-analyses[60–62]have been conducted comparing SLT with topical glaucoma medications. Each study assessed the IOP reduction, which was measured in millimeters of mercury (mm Hg).

Li et al (2015)[60] conducted a meta-analysis on studies comparing SLT to topical glaucoma medications. In total, they found five studies. The outcomes considered were intra-ocular pressure reduction (IOPR), SLT success rate defined as achieving a 20% or greater reduction in IOP, and complications associated with SLT. They concluded that both SLT and topical medications provided similar reduction in IOP in patients with OAG.

Wong et al(2014)[61] performed a meta-analysis comparing SLT with ALT, and SLT with topical glaucoma medications, and reported side effects (complications) post SLT. Overall, they found that SLT had comparable IOP-lowering effects as medications.

Peng et al (2014)[62] conducted a systematic review and meta-analysis of RCTs comparing prostaglandin analogs to SLT. They found three studies that were included in the analysis. Overall, their analysis showed that IOP reduction favored prostaglandin analogs, with a WMD= [-0.85 mm Hg (95% CI-1.43, -0.27)], and no significant heterogeneity (I^2=0%, P=0.8) between studies.

McAlinder et al (2013)[63] conducted a systematic review of studies comparing SLT with other treatment methods for glaucoma patients. A subsection of this article directly compared SLT versus topical glaucoma medications. Authors summarized results found in four studies and found that there was no significant difference between the two treatment alternatives.

Li et al (2015)[60], Wong et al (2014)[61], and Peng et al (2014)[62] conducted their meta-analyses including the same studies. Overall, two[60,61]of the meta-analyses showed no difference in IOP-lowering effect between SLT and medications-only and one[62] study favored medications-only (prostaglandin analogs).

Furthermore, to the best of our knowledge, there has been no systematic review and meta-analysis evaluating the effect of SLT as primary, sequential or adjunctive treatment.

2.8.3 Gap in Knowledge

The differences in IOP-lowering effect of patients on pharmacotherapy compared to patients who received SLT as either sequential, adjunctive, or primary treatment remains unknown. This systematic review and meta-analysis is aimed to explore difference in treatment strategies. Further, this was the first study evaluating the effect of SLT on the reduction in post-operative medications over a period of six to 60 months.

Moreover, there have been a vast number of studies that have shown SLT to be safe and effective. If providing SLT sequentially, adjunctively or as primary treatment is more effective at lowering IOP levels than pharmacotherapy, then this could be an impetus for ophthalmologists to change current treatment practice for glaucoma patients. Based on the literature, cost-analyses have concluded that the majority of patients do not adhere to the medication instructions, which can worsen the visual field damage. By providing SLT-a cost-effective approach from the patient's perspective- the visual field damage that occurs from noncompliance of the drug regimen can be prevented.

2.8.4 Aims and Objectives

The aim of this thesis was to conduct a systematic review and meta-analysis on the efficacy of SLT. The primary objective was to investigate the effect of SLT as primary, sequential or adjunctive treatment on the IOP levels and on the number of medications. The secondary objective was to assess the reported complications associated with SLT treatment. Below are the research questions and the associated hypotheses.

Primary Research Questions:

1) Does providing SLT, as primary, sequential, or adjunctive treatment significantly reduce the IOP levels compared to topical glaucoma medications?

   Hypothesis: Providing SLT does significantly reduce the IOP levels compared to topical glaucoma medications-only treatment.

2) Does providing SLT as an adjunctive treatment significantly reduce post-operative topical glaucoma medications?

   Hypothesis: SLT does significantly reduce the post-operative glaucoma medications.

Secondary Research Question (Exploratory):

3) What are the complications associated with SLT?

Chapter 3

3 Methods

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) [64] were adhered to (APPENDIX 1). This systematic review was retrospectively registered with the Review Registry of Systematic Reviews and Meta-Analyses under the unique identifying number reviewregistry185. The methods section contains information on the database and grey literature searches, the inclusion and exclusion criteria, screening process, data extraction, quality assessment, quantitative measures used for the meta-analysis, publication bias and how missing data were dealt with.

3.1 Databases Searched

MEDLINE (Ovid), EMBASE (Ovid), CINAHL and Cochrane Library were searched from January 1997 to July 2016. Six concepts: open-angle glaucoma, prostaglandin analogs, beta-blockers, alpha agonists, carbonic anhydrase inhibitors, and selective laser trabeculoplasty were used in the search. Articles included from MEDLINE were searched by matching the medical subject heading (MeSH) terms with the keyword terms of the two concepts ‘glaucoma’ and ‘selective laser trabeculoplasty’ using the Boolean operator AND which was then combined with four classes of drugs using the Boolean operator OR. The same search strategy was used for EMBASE and CINAHL. In EMBASE, Emtree terms- which had the same function as the MeSH terms- were used. For Cochrane library, keywords were used since the option to input subject heading terms was not available. APPENDIX 2 provides a detailed search strategy for each of the databases.

3.2 Grey Literature Sources

Grey literature were searched from the following databases: Web of Science-Core Collections, BIOSIS Previews, and Scopus. The same six concepts described above were searched. These three databases did not have subject heading options; therefore, keyword searches were conducted.

3.3 Inclusion and Exclusion Criteria

Articles studying human subjects over the age of 18 were included. If the age of the subjects was not specified, then the use of the word 'adult' in the article was assumed to be referring to subjects over 18 years of age. The age limit was included in some database searches; however, not all of the databases (Cochrane Library, BIOSIS Previews, Web of Science-Core Collections and Scopus) had the option of including these limits. English written studies published after 1997 were included. 1997 was chosen as the cut off year because SLT was invented by Latina and colleagues in 1995 and underwent clinical trials beginning in 1997[12]. Randomized clinical trials (RCTs), prospective non-RCTs, cohort, retrospective, and observational studies were included. The articles included discussed SLT as an intervention; the study either compared SLT directly with medications or assessed if SLT reduced the required medications. Studies with sample size of at least 20 eyes at baseline and follow-up time points were included. Based on ophthalmic literature, a sample size of 20 or more eyes is considered to be a good quality study. Studies with follow-up data of at least 6 months or greater were included as the literature states that SLT could be repeated every six months[65]; and we wanted to assess the IOP-lowering effect after a point where SLT could be repeated, if necessary. Some studies provided a follow-up time as a range, for example, 4-6 months. These studies were included in the analysis because there was no way of separating the patients who were followed-up for four months from those who were followed-up for six months. The study was included in the analysis if the medications being compared to SLT were from the following four classes: prostaglandin analogs, beta-blockers, carbonic anhydrase inhibitors, or alpha agonists. There was no restriction placed on the country in which the study was conducted. The exclusion criteria were any studies that assessed the effect of repeat SLT treatment and any patients that had previously undergone glaucoma surgery.

3.4 Article Screening Process

Two independent reviewers, Muna Hassan (MH) and Emaad Mohammad (EM), screened the articles using EPPI Reviewer 4[66] (EPPI) (by EPPI-Centre, Social Science Research Unit, the Institute of Education, the University of London, UK). The articles were uploaded

onto EPPI by converting the document into a RIS file. Once the files were uploaded from the different databases and grey literature sources, they were screened for duplicates. We selected the option to have EPPI automatically remove the duplicates. Each article was assessed again to determine if there were any more duplicates. Once this was done, the screening phase was initiated. Throughout the screening process the two screeners, MH and EM, held frequent meetings either face-to-face, through Skype or by telephone to merge agreements and disagreements and to resolve disagreements at each level of screening.

In total, there were three levels of screening. Level one involved screening only the title of the article. Articles evaluating SLT were carried on to level two screening. The articles that were included after level two analyzed 20 or more eyes, had six months or greater follow-up time, and were research articles. If the abstract did not provide enough information to answer these three questions then the 'Unsure' option was selected. All articles that were recorded as 'Unsure' were included into the next level of screening. After level one and two were screened, the reviewers MH and EM met to discuss any differences in results. Level three screening involved reading the entire article. Each reviewer independently reviewed the articles remaining in level three. All of the articles included in the analysis either directly compared SLT with medical therapy or looked at SLT as an intervention with the aim of examining if SLT reduced the amount of medications. Articles were included for meta-analysis after reconciling disagreements. Level 1, 2, and 3 screening questions are provided in APPENDIX 3.

3.4.1 Cohen's Kappa Statistic

The Cohen's kappa statistic was measured to determine the reliability of the data collection method. Cohen's kappa statistic is a measure to determine the level of inter-rater agreement between categorical items. It is widely used compared to the percentage agreement statistic because it takes into account any agreement that may have occurred by chance[67]. As a result, when an assessor wants to determine the inter-rater agreement, the percentage agreement statistic is much higher than the kappa statistic.

In the article screening process, the kappa statistic represents the extent to which the reviewers assign the same inclusion, exclusion, or unsure decision to the same articles. This value is calculated using the formula below:

$$\kappa = \frac{\Pr(a) - \Pr(e)}{1 - \Pr(e)}$$

Pr (a) represents the observed agreement and Pr (e) represents chance agreement[67]. The kappa statistic produces a value that lies between -1 and +1. A kappa value is often accompanied by a p-value and a confidence interval. If the kappa statistic is less than zero then that represents less than chance agreement, 0.01- 0.02 represents slight agreement, 0.21- 0.40 represents fair agreement, 0.41- 0.60 represents moderate agreement, 0.61- 0.80 represents substantial agreement and 0.81- 0.99 represents almost perfect agreement[68].

3.5 Outcomes

3.5.1 IOP Reduction

One of the primary outcomes was the intra-ocular pressure reduction (IOPR) from baseline. The IOPR variable was calculated by subtracting the IOP at each follow-up time from the reported IOP at baseline. IOP was measured in millimeters of mercury in all included studies.

3.5.2 Medication Reduction

The other primary outcome was the reduction in medications. Each drug was defined as one medication. For example, if a patient was taking latanoprost and timolol, in two separate bottles, this was classified as two medications. If these two drugs were combined in one bottle, they counted as two medications. After SLT treatment, if the patient only required latanoprost, then this counted as one medication, and the medication reduction in this case was one. The medication reduction was assessed as the difference in required medications pre-and-post SLT treatment.

3.5.3 Complications

The secondary outcome was an exploratory outcome. We gathered data on any reported minor or major complications associated with SLT. The adverse events were reported in a list format, and the number of times the complication was reported in other studies were tallied and presented in a table.

3.6 Data Extraction

All data were extracted from a data extraction sheet, using Excel. The data extraction sheets are provided in APPENDIX 4-5.

3.6.1 Baseline and Follow-up

Data on author, year of publication, study design, SLT degree, type of glaucoma, baseline and follow-up IOP levels, type of medications used, number of patients enrolled and/or number of eyes enrolled, and mean age at enrollment were extracted. Additionally, for studies that assessed pre-and-post-operative medications, data were gathered on medications taken at baseline. Follow-up data were gathered on the number of remaining eyes, the IOP levels at each follow-up time, and medications at each follow-up time. The extracted data were used to perform descriptive statistics and meta-analysis.

3.7 Quality Assessment

The Downs and Black[69] checklist was used to assess the methodological quality in the RCTs and non-RCTs. This checklist was selected because it was one of the few checklists geared towards all types of study designs. The highest possible score was 32. A higher score was indicative of better overall quality. Furthermore, the Downs and Black[69] checklist is a 27-item questionnaire that is divided into five sections: Reporting, External Validity, Bias, Confounding and Power. The five sections help pinpoint why a study's overall quality may have been low. Each quality assessor, Muna Hassan (MH) and Emaad Mohammad (EM), assessed the articles individually. A meeting was held to discuss any differences in answers; once a consensus was reached, the assessors decided

on a final score for each article. The inter-rater reliability score was calculated using the Kappa statistic. APPENDIX 6 provides a copy of the Downs and Black checklist.

3.8 Quantitative Measures used in the Meta-Analysis

3.8.1 Meta-Analysis

Clinical practice is becoming more and more grounded on evidence-based medicine. Evidence-based medicine is a systematic, quantitative, preferentially experimental approach to using medical information[70]. Specifically, a meta-analysis is a quantitative synthesis of independent studies for the purpose of integrating the findings into one effect estimate to determine if an effect exists or if an effect is positive or negative[70]. The outcomes of a meta-analysis may contribute a more precise estimate of the treatment effect or risk factor than each of the individual studies. It can also settle controversies arising from conflicting studies.

In this study, a meta-analysis was conducted using STATA 13.0[71] to determine a pooled effect estimate for the IOP reduction between patients that were treated with medications-only and patients that were given SLT treatment. We also conducted a meta-analysis to determine the pooled effect estimate for the reduction in medications for patients with SLT treatment. It was assumed that because a meta-analysis is the highest form of evidence-based medicine, these pooled results would provide a precise and bias-free estimate compared to the individual effect estimates.

3.8.1.1 Effect Measures

The extracted mean and standard deviation (SD) of the IOP at baseline and end points were used to compute the mean IOP reduction ($IOPR$), percentage of IOP reduction ($IOPR\%$), within group standard error (SE_{IOPR}), and standard error of percentage of IOP reduction ($SE_{IOPR\%}$) using the equations below[2]:

$$IOPR = IOP_{baseline} - IOP_{endpoint}$$

$$IOPR\% = \frac{IOPR}{IOP_{baseline}} * 100$$

$$SE_{IOPR} = \sqrt{SE_{baseline}^2 + SE_{endpoint}^2}$$

$$SE_{IOPR\%} = \frac{SE_{IOPR}}{IOP_{baseline}} * 100$$

The SD of the percentage of IOP reduction ($SD_{IOPR\%}$) was calculated using the formula: $SD_{IOPR\%} = SE_{IOPR\%} \times \sqrt{n}$.

The percentage reduction in medications and the average reduction in medications were calculated for the studies that assessed the post-operative reduction in medications.

The weighted mean difference (WMD) of the percentage of IOP reduction ($IOPR\%$) was the effect measure used for the forest plots comparing Sequential SLT and Adjunctive SLT with pharmacotherapy. The WMD of the average reduction in medications was the effect measure used for the studies that assessed the post-operative reduction in medications.

WMD was chosen as the effect size because the outcomes being analyzed were continuous variables—IOP and medications. Each study was assigned a weight, and this weight was multiplied by the IOP percentage reduction or reduction in medications. The values computed after these calculations provided the overall WMD. Depending on whether the fixed-effect or random-effects model was used, the overall WMD changed.

3.8.1.2 Heterogeneity

It is inevitable that effect estimates of independent studies would differ to some degree. Heterogeneity tests the amount of variability between the studies being pooled together. The variability that occurs because of the differing participants, interventions, or outcomes studied is called clinical heterogeneity. The variability that occurs because of the study design and risk of bias is called methodological heterogeneity[72]. Statistical heterogeneity results from either clinical, methodological, or both types of heterogeneity.

The heterogeneity value tests whether the effect estimates were different from each other for reasons other than random chance alone.

In this study, the null hypothesis for heterogeneity was that the studies shared a common effect size[73]**.** The values that quantified the inconsistency between the studies were the I^2, *Z*-value, and χ^2 statistics. The I^2 value was made up of the chi-squared value (χ^2) minus the degree of freedom (k-1), all divided by the chi-squared value (χ^2). This value was then multiplied by 100 to get a percentage. Higher I^2 value was indicative of higher between study heterogeneity[72]. Visually, one could ascertain if there was heterogeneity if the confidence intervals of the effect estimates between the studies did not overlap. If the I^2 is less than 40% then heterogeneity is not important, I^2 between 30% and 60% may represent moderate heterogeneity, I^2 between 50% and 90% may represent substantial heterogeneity and I^2 between 75% and 100% represents substantial heterogeneity[72]

3.8.1.3 Random-Effects and Fixed-Effect Models

In the fixed-effect model, it is assumed that there is only one true effect size for all of the studies, and the combined effect is the estimate of this common effect size[72]. This model assumes homogeneity, meaning that there are no differences in the study population; subject selection criteria and applied treatments. In a fixed-effect model, if the sample size is large enough, the standard error will approach zero.

On the other hand, in the random-effects model, it assumes that the true effect varies from study to study. Each study is estimating a different effect size. The weights assigned under the random-effects model are more evenly distributed and unlike the fixed effect model, large studies do not dominate and smaller studies do not get overlooked [73]. In the random effects model, the studies are weighted according to the inverse of their variance and the heterogeneity parameter[70]. Often, the random-effects model is used to interpret the summary of effects when the heterogeneity is significant. In this study, effect estimates from the random-effects model were used when the statistical heterogeneity exceeded I^2=50%.

3.9 Subgroup Analysis

3.9.1 SLT versus Medications Studies

Subgroup analyses were conducted using the SLT versus medications studies to determine if there was a difference in results based on the timing that the SLT procedure was provided. The timing of the SLT procedure was separated into three groups: primary treatment, sequential treatment and adjunctive treatment. Primary SLT referred to when a patient was newly diagnosed with glaucoma and was receiving SLT on treatment naïve eyes. Sequential SLT was when a patient initially was on medical treatment, was washed-out of the medications for about 4-5 weeks, and then received SLT treatment. Adjunctive SLT referred to when a patient was on pharmacotherapy treatment, and was provided SLT while continuing with their medical treatment.

3.9.2 Adjunctive SLT Studies

Subgroup analyses were conducted using the Adjunctive SLT studies that examined the post-operative reduction in medications. A subgroup analysis was conducted based on the SLT degree. The purpose was to determine if a difference in the results occurred based on the SLT degree. SLT is a laser procedure that is performed on the 360 degree trabecular meshwork (TM) where the fluid drains from the eye. Ophthalmologists perform SLT at varying degrees. Some ophthalmologists perform SLT on the entire TM (360 degrees), while others perform on 270, 180, or 90 degrees of the TM. For this analysis, we stratified the data into two groups: one group received 180 degrees of laser treatment and the other group received 360 degrees of laser treatment.

A subgroup analysis was also conducted based on the study design. The purpose was to determine if the design of the study had an effect on the results. The studies were stratified into two groups: those that were randomized clinical trials (RCTs) and those that were not RCTs.

3.10 Sensitivity Analysis

A sensitivity analysis was conducted to examine the robustness of the results by assessing to what extent the results are affected by a change in methods or assumptions[74]. In the primary analysis for the studies comparing SLT with medications, all studies were included irrespective of the quality. The sensitivity analysis was conducted to determine if removing the abstracts and non-RCT studies, which had the lowest overall quality, made an impact on the results. In the Adjunctive SLT studies that assessed the pre-and-post-operative medications, we removed the abstracts that were included in the primary analysis to determine how much of an effect they played on the results. The reason we removed the abstracts was because they had a lower overall quality score compared to the full studies. After performing the sensitivity analysis, if the results did not change from the primary analysis, then it was concluded that factors had little or no influence on the conclusions, which means that the results are robust[74]

3.11 Publication Bias

The purpose of a meta-analysis is to find and synthesize all the studies that meet the specified inclusion and exclusion criteria so that the most accurate summary effect estimates are presented. Often times publication bias occurs because the authors do not want to publish non-significant results[70,72]. Larger studies with significant results are more likely to be published than smaller studies with non-significant results[70]. Publication bias can also occur because publishers may not want to publish non-randomized or uninteresting results[70]. Another reason for missing studies may be the inclusion criteria that were created for the systematic review. Some studies could be missed through the database searching or the article screening process.

In order to assess publication bias, a funnel plot was created with Review Manager (RevMan)[75]. WMD was used as the unit of measure because the variable being analyzed was continuous. The standard error of the WMD was calculated and plotted on the y-axis of the graph and the WMD was plotted on the x-axis of the graph. If publication bias does not exist, the plot is expected to have a symmetric inverted funnel shape[70]. The top of the

funnel plot is occupied by larger studies with an effect size that is closer to the mean effect size. The smaller studies occupy the bottom of the funnel plot because they usually have larger standard errors and tend to spread across a wider range of effect estimate values. Even though funnel plot asymmetry could be due to publication bias, there may also be other reasons causing the asymmetry including high heterogeneity, differences in methodological quality, language bias, and time-lag bias[70].

3.12 Missing Data

The Cochrane Handbook for Systematic Reviews of Interventions (2008)[72] was used to calculate values that were not directly reported in the articles. Based on the data extraction sheets that we created, not all of the values were directly provided by the articles. Standard deviations that were not reported on the reduction of IOP were calculated either from the reported p-values or range[72]. Studies that had important values left blank were included in the charts, but excluded in the forest plots.

Chapter 4

4 Results

4.1 Study Characteristics

4.1.1 SLT versus Medications Studies

Of the 31 studies, 7[76–82] articles compared SLT with medications. Baseline characteristics of these 7 studies are reported in Table 1. In total, 5[77,78,80–82] out of the 7 studies conducted SLT at 360 degrees, one[76] study performed 180 degrees, and one[79] study reported results for 90, 180 and 360 degrees. All studies had the SLT laser initially set at 0.8mJ with an increase or decrease of 0.1mJ. Six[77–82] of the included studies were randomized controlled trials (RCT).

Three[77,78,81] studies provided SLT as adjunctive treatment with medical therapy. Three[79,80,82] studies provided SLT sequentially after about a 4 week wash-out period, and one[76] study provided SLT as primary and as sequential therapy. Four[76,79,80,82] studies compared SLT directly with a prostaglandin analog, and three[76,79,80] studies compared SLT with latanoprost. Three[77,78,81] studies compared SLT with a combination of medical drugs from all four classes of drugs. All additional information are provided in Table 2

Table 1: Baseline Characteristics of Included Studies Comparing SLT with Medications

Author, Year of Publication	SLT Timing	Degree/(Type of Glaucoma)	Study Design	N (Eyes)	SLT Group Mean Age(SD)	Medications Group Mean Age(SD)	SLT Group Mean IOP(SD)	Medications Group Mean IOP(SD)
Katz et al, 2012[82]	Sequential	360°(POAG/OHT)	RCT	127	53.5 (14.2)	53.5 (14.2)	25 (2.2)	24.5(2.2)
Lai et al, 2004[78]	Adjunctive	360°(POAG/OHT)	RCT	58	51.9 (14.7)	51.9 (14.7)	26.8 (5.6)	26.2 (4.2)
Lee et al, 2014[77]	Adjunctive	360° (POAG)	RCT	41	66.5(13.6)	65.5(12.7)	15.8(2.7)	14.5(2.5)
McIlraith et al, 2006[76]	Primary	180° (OAG)	Pro non-RCT	100	62(11)	63(11)	26 (4.3)	24.6(3.7)
	Sequential	180° (OAG)	Pro non-RCT	87	NR		26.5(4.5)	
Nagar, 2005[79]	Sequential	90° , 180° and 360°(OAG/OHT)	RCT	167	63(17)	63(17)	90 ° 24.5(NR) 180 ° 29.7(NR) 360 ° 30.2(NR)	29.2(NR)
Nagar, 2009[80]	Sequential	360° (POAG/OHT)	RCT	40	66.4(NR)	66.4(NR)	26.1(4)	22.8(4.5)
Tan et al, 2015[81]	Adjunctive	360° (POAG/OHT)	RCT	156	55.5(2.7)	55.5(2.7)	20.76(3.3)	20.54(3)

RCT: Randomized Control Trial; Pro non-RCT:Prospective Non-RCT; NR:Not Reported; N:Number of Eyes; SD: Standard Deviation;
POAG: Primary Open-angle Glaucoma; OHT:Ocular Hypertension; OAG: Open-angle Glaucoma; SLT: Selective laser trabeculoplasy; IOP: Intra-ocular pressure

Table 2: SLT Characteristics of Included Studies Comparing SLT with Medications

Author, Year of Publication	Medications Directly Before SLT	Medications Directly After SLT	Laser Spots, Contiguous versus Spaced, Degree	Medications Used
Katz et al, 2012[82]	-	-	100 laser spots over 360°	Prostaglandin analogs
Lai et al, 2004[78]	One drop of 1% apraclonidine 1 hour prior to treatment	One drop of 1% apraclonidine and 1% prednisolone acetate	100 non-overlapping laser spots over 360°	Beta-blockers, pilocarpine, dorzolamide, and latanoprost
Lee et al, 2014[77]	-	One drop of Alphagan and dexamethasone 0.1% and neomycin 0.5% twice a day for 1 day	Single burst mode through 360° of trabecular meshwork	Prostaglandin analogs or beta-blockers, followed by carbonic anhydrase inhibitors or alpha adrenergic agonist, then pilocarpine
McIlraith et al, 2006[76]	Brimonidine 0.2% and pilocarpine 1% 1 hour before treatment	One drop of brimonidine 0.2% and either prednisolone acetate 1% or ketorolac 0.5% immediately after therapy and Prednisolone acetate 1% or ketorolac 1% four times a day for 5 days	50(SD: 5) contiguous laser spots over 180°	Latanoprost
Nagar et al, 2005[79]	One drop of amethocaine 1%	Either dexamethasone 0.1% eye drops of ketorolac eye drops for four times a day for 5 days	90°: 25-30 laser spots, 180°: 48-53 laser spots, 360°: 93-102 laser spots	Latanoprost
Nagar et al, 2009[80]	One drop of amethocaine 1%	Non-steroidal anti-inflammatory drops (ketorolac tromethamine) four times a day for 5 days	100(SD: 5) non-overlapping spots over 360°	Latanoprost
Tan et al, 2015[81]	-	-	360°	Prostaglandin analogs, beta-blockers, carbonic anhydrase inhibitors and alpha-agonists

SLT: Selective laser trabeculoplasty; SD: Standard Deviation

4.1.2 Adjunctive SLT Studies

The baseline characteristics of the Adjunctive SLT studies are provided in Table 3. Data gathered included author, year of publication, type of glaucoma, study design, number of eyes, -mean age, mean number of medications, and the IOP levels at baseline. Of the 31 studies that were finalized after level three screening, 27[77,78,81,83–105] of the studies reported data on number of medications pre-and-post SLT. Out of the 27 studies, 16[77,81,83,87,89–91,95–97,99–102,105,106]studies reported data for 360 degrees of SLT treatment, 12[84–86,88,92–94,98,100,103,104,106] studies reported data on 180 degrees of SLT treatment, two[105,106] studies reported data on 270 degrees. Nine[77,78,81,84,86,94,102,104,105] studies were RCTS, one[85] was a partial RCT, as only patients receiving their first laser therapy were randomly assigned. Eight[89,90,95,96,98,100,103,106] studies were retrospective chart reviews, three[83,91,99] studies were observational studies, and two[87,97] studies were non-randomized clinical trials. There were a total of 1,742 eyes included in the analysis. Where the number of eyes were not reported, the number of patients were included, and it was assumed that there was an eye from each patient included in the analysis. The number of medications at baseline ranged from an average of 1.3[98] to 3.23[81] medications. The IOP levels at baseline ranged from 14.3mm Hg[99] to 26.8mm Hg[78]. Five[81,89,98,104,105] of the studies included were abstract only. Four[85–87,94] studies were conducted in Canada, nine[88,90,92,95,96,98,100,101,106] studies were conducted in USA and the remaining 14[77,78,81,83,84,89,91,93,97,99,102–105] studies were conducted outside of North America. Additional information regarding the SLT characteristics can be found in Table 4, and additional information regarding types of medications used can be found in Table 5.

Table 3: Baseline Characteristics of Studies Evaluating Adjunctive SLT

Author, Year of Publication	Type of Glaucoma	Study Design	N (Eyes)	Mean Age (SD)	Mean Medication (SD)	Mean IOP (SD)
Abdelrahman et al. 2012[83]	POAG	Prospective (SLT)	65	53.2(15)	2.25(0.97)	18.29(NR)
Babighian et al. 2010[84]	POAG	RCT (ELT vs SLT)	15	67(3.2)	2.2(0.7)	23.9(0.9)
Birt, 2007[85]	OAG	Partially RCT* (ALT vs SLT)	30	64(13.9)	2.9(1.2)	22.9(4.2)
Bovell et al. 2011[86]	OAG	RCT (ALT vs SLT)	89	69.7 (10.5)	2.6 (1.2)	23.8(4.8)
Bruen et al.2012[87]	OAG/OHT	Non-randomized cohort study (SLT)	74	71 (10)	2.0(1.0)	21.5(0.5)
Francis et al. 2005[88]	OAG	Non-RCT (SLT)	66	65.4(8.2)	2.8(1.1)	NR
Giocanti-Auregan et al. 2014[89] (abstract)	OAG	Retrospective (SLT)	46	NR	1.6(0.8)	22.8(3.8)
Greninger et al. 2014[106]	OAG	Retrospective Case Series (SLT)	110	74.1(10.5)	2.6(1.07)	18.7(NR)
Habib et al. 2013[90]	NTG	Retrospective Review (SLT)	104	70(10)	2.03(1.01)	19.6(3.7)
Hirneib et al. 2013 [91]	OAG	Observational (SLT)	68	68.5(13.3)	2.38(1.1)	18.1(5.2)
	POAG	Observational (SLT)	45	NR	NR	17.8(4.6)
Juzych et al. 2004[92]	Chronic OAG	RCR (SLT vs ALT)	41	71.9(8.8)	2.5(1.3)	23.9(2.6)
Kara et al.2013 [93]	POAG	Retrospective case series (SLT)	48	63(10)	1.9(1)	22.7(2.1)
Kent et al.2015[94]	PXG	RCT (SLT vs ALT)	45	72.9(9.8)	NR	23.1(4.2)
Khouri et al. 2014a [95]	OAG	Retrospective Review (1st SLT vs repeat SLT)	46	73(9)	1.7(0.9)	19.7(2.3)
Khouri et al. 2014b[96]	OAG	Retrospective Review (1st SLT vs repeat SLT)	51	NR	1.57(0.83)	19.9(3.2)
Koucheki & Hashemi 2012[97]	OAG	Prospective nonrandomized interventional study(SLT)	136	62.1(13.1)	2.3(0.7)	22(NR)
Lai et al. 2004[78]	OAG/ OHT	RCT (SLT vs Meds)	58	51.9(14.7)	-	26.8(5.6)
Leon et al. 2005[98] (abstract)	OAG	Retrospective (SLT)	49	NR	1.3(NR)	-

Table 3: Baseline Characteristics of Studies Evaluating Adjunctive SLT (Continued)

Author, Year of Publication	Type of Glaucoma	Study Design	N (Eyes)	Mean Age (SD)	Mean Medication (SD)	Mean IOP (SD)
Lee et al. 2014[77]	OAG	RCT (SLT vs Meds)	41	66.5(13.6)	2.3(1.1)	15.8(2.7)
Lee et al. 2015[99]	NTG	Prospective Cohort (SLT)	41	64.7(11.9)	1.5(0.8)	14.3(3.4)
Lowry et al. 2016[100]	OAG	Retrospective Interventional Comparative Case Series (ALT vs SLT)	100	75.54(10.6)	2.62(1.1)	18.5(4.2)
Rebenitsch et al. 2013[101]	OAG	RCR(SLT)	111	70.5(10.9)	1.5(1.26)	18.9(4.5)
Russo et al. 2009[102]	Chronic OAG	RCT (SLT vs ALT)	60	57.8(5.3)	2.3(1.3)	22.7(1.2)
Schlote & Kynigopoulos, 2016[103]	Advanced OAG	Retrospective Review (early vs advanced OAG)	36	73.8(9.7)	1.9(1.0)	22.1(4.1)
Tan et al.2015[81] (abstract)	OAG	RCT(SLT vs Meds)	78	55.5(2.6)	3.23(0.4)	20.7 (3.3)
Zaninetti & Ravinet, 2008[104] (abstract)	OAG	RCT(SLT)	67	69(8)	1.44(NR) *drops/patient	19.2(4.7)
Zhang et al. 2015[105] (abstract)	OAG	RCT(270 degrees)	67	NR	2.3(0.5)	NR
	OAG	RCT(360 degrees)	67	NR	2.1(0.4)	NR

*Partially RCT[85]: Patients that had undergone previous 360 degree ALT treatment, were assigned to receive SLT. Patients with no previous laser therapy were randomized by means of a coin toss.
*In this study[104], the medications were measured as the number of drops on average per patient
RCR: Retrospective Chart Review; RCT: Randomized Clinical Trial; OAG: Open-angle glaucoma; POAG: Primary Open-angle Glaucoma; PXG: Pseudoexfoliative Glaucoma; NTG: Normal tension glaucoma; SLT: Selective laser trabeculoplasty; ALT: argon laser trabeculoplasty; ELT: Excimer laser trabeculoplasty; Meds: Medications; NR: Not reported; N: Number of eyes; vs: versus; SD: Standard deviation

Table 4: SLT Characteristics of Studies Evaluating Adjunctive SLT

Author, Year of Publication	Degrees	Clock-hour	Laser spots	Contiguous versus Spaced Spots
Abdelrahman et al. 2012[83]	360	-	100	Contiguous (adjacent)
Babighian et al. 2010[84]	180	-	50	Adjacent
Birt, 2007[85]	180	Inferior	45-55	-
Bovell et al. 2011[86]	180	-	50	-
Bruen et al.2012[87]	360	-	60	Non-overlapping
Francis et al. 2005[88]	180	Inferior	55 (range: 49-70)	-
Giocanti-Auregan et al, 2014[89] (abstract)	360	Centered on trabecular meshwork	100 (SD:10)	Non-overlapping
Greninger et al. 2014[106]	180, 270, 360	-	94.3 (SD:49)	-
Habib et al. 2013[90]	360	-	102 (SD:15.2)	-
Hirneib et al. 2013 [91]	360	-	-	Non-overlapping
Juzych et al. 2004[92]	180	Nasal trabecular meshwork	50-55	Non-overlapping spots, adjacent
Kara et al.2013 [93]	180	Inferior or nasal	-	Contiguous
Kent et al. 2015[94]	180	Inferior or superior	50 applications	-
Khouri et al. 2014a [95]	360	-	-	-
Khouri et al. 2014b[96]	360	-	-	Non-contiguous
Koucheki & Hashemi 2012[97]	360	Mid-height of trabecular meshwork	100	Non-overlapping
Leon et al. 2005[98] (abstract)	360	-	-	-
Lee et al.2014[77]	360	-	121.8 (SD:30)	-
Lee et al.2015[99]	360	-	191 (SD:27.3)	-
Lowry et al. 2016[100]	180 to 360	-	95.8(SD:50.7)	-
Rebenitsch et al. 2013[101]	360	-	-	-
Russo et al. 2009[102]	360	-	60	Non-overlapping
Schlote & Kynigopoulos, 2016[103]	180	Inferior	50-70	Adjacent, non-overlapping
Tan et al. 2015[81] (abstract)	360	-	-	-
Zaninetti & Ravinet, 2008[104] (abstract)	180	Inferior	-	-
Zhang et al, 2015[105] (abstract)	270 or 360	-	-	-
SD: Standard deviation				

Table 5: Medication Details of Studies Evaluating Adjunctive SLT

Author, Year of Publication	Medications directly Before SLT	Medications Directly After SLT	Medications provided for Glaucoma Treatment
Abdelrahman et al, 2012[83]	A drop of miotic (pilocarpine nitrate 2%) and brimonidine tartrate 0.2% (Alphagan)	Prednisolone acetate (1%) drops	-
Babighian et al, 2010[84]	Topical anesthesia with 0.4% benozinate in a single dose solution and 1% methylcellulose on the cornea	Topical steroid antibiotic association with tobramycin and dexamethasone eye drops four times a day for 14 days	53% Beta-blockers, 25% alpha-agonists, 33% CAI(topical), 13% CAI (oral), 93% PGA
Birt, 2007[85]	One drop of brimonidine 0.2%	Fluoromethalone 0.1% (Allergan) drops four times daily for 5 days	86% on Beta-blockers, 36% on CAI, 43% on Alpha-agonist, 83% on PGA, 6% on Pilocarpine
Bovell et al, 2011[86]	Apraclonidine or brimonidine tartrate 0.2%	Topical prednisolone acetate 1% for 5 days	53% PGA, 65% Beta-blockers, 31% Alpha-agonist, 62% CAI, 38% Pilocarpine, 78% Combination
Bruen et al,2012[87]	-	-	PGA, B-blockers
Francis et al, 2005[88]	-	One drop of brimonidine tartrate 0.2% and prednisolone acetate 1% three times daily for 4 days	Beta-blockers, CAI, Alpha-agonist, PGAs, pilocarpine(10 on 1 medication, 18 on 2, 14 on 3, 24 on 4 medications)
Greninger et al, 2014[106]	1 drop of topical proparacaine hydrochloride and apraclonidine hydrochloride 0.5%	1 drop of apraclonidine hydrochloride 0.5%	-
Hirneib et al, 2013 [91]	Tetracaine (0.5% used for anaesthesia	Flurbiprofene (0.03%) four times a day for 3 days	-
Juzych et al, 2004[92]	Topical tetracaine or proparacaine hydrochloride was used as anesthesia, eyes pretreated with apraclonidine 1.0%	Topical steroids 4 times daily for one week	-

Table 5: Medication Details of Studies Evaluating Adjunctive SLT (Continued)

Author, Year of Publication	Medications directly Before SLT	Medications Directly After SLT	Medications provided for glaucoma treatment
Kara et al,2013 [93]	1 drop of topical proparacaine hydrochloride 0.5%	1 drop of brimonidine (0.2%) and fluorometholong (Flarex) eye drops 4 times a day for one week	-
Kent et al, 2015[94]	1 drop of brimonidine 0.2% and pilocarpine 1%	-	-
Koucheki & Hashemi 2012[97]	1 drop of tetracaine (0.5%) in each eye	Flourometholone (0.1%) twice a day for 3 days	75% on PGA
Lai et al. 2004[78]	One drop of 1% apraclonidine 1 hour prior to treatment	One drop of 1% apraclonidine and 1% prednisolone acetate	Beta-blockers, Pilocarpine, Dorzolamide, and Latanoprost
Lee et al.2014[77]	-	One drop of Alphagan and dexamethasone 0.1% and neomycin 0.5% twice a day for 1 day	PGA or Beta-blockers, followed by CAIs or Alpha-agonist, then Pilocarpine
Lee et al. 2015[99]	-	A drop of brimonidine tartrate; dexamethasone 0.1% and neomycin 0.5% combination eye drop used twice a day for 1 day	Alpha-agonists or PGAs followed by topical, CAIs, then Beta-blockers
Lowry et al, 2016[100]	1 drop of topical proparacaine and iopidine 0.5%	1 drop of iopidine 0.5%	-
Russo et al, 2009[102]	-	1 drop of topical indomethacin 0.1% 4 times daily for 1 week	-
Schlote & Kynigopoulos, 2016[103]	Topical anesthesia with tetracaine eye drops, and eyes were pretreated with apraclonidine 1.0%	Topical non-steroidal anti-inflammatory eye drops 4 times a day for 1 week	-
PGA: Prostaglandin analogs; CAI: Carbonic Anhydrase Inhibitors; SLT: Selective laser trabeculoplasty			

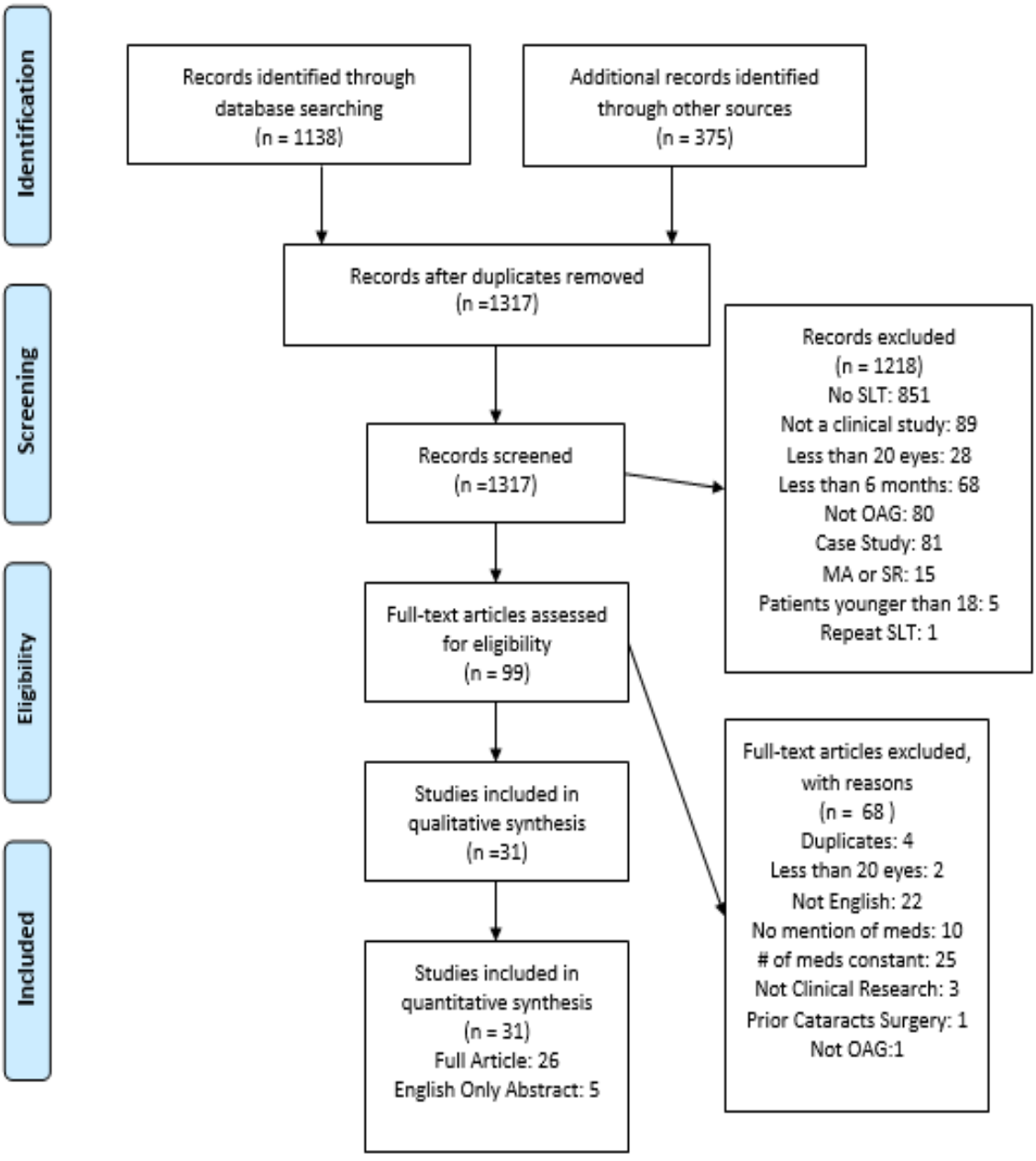
4.2 Study Selection

4.2.1 Screening

EPPI Reviewer 4.0(by EPPI-Centre, Social Science Research Unit, the Institute of Education, the University of London, UK), was used to screen the articles. Search strategies were used to gather articles from the journal databases MEDLINE (Ovid), EMBASE (Ovid), CINAHL, Cochrane Library and the grey literature databases including Web of Science-Core Collections, BIOSIS Previews, and Scopus. There were 1,138 articles identified from the journal databases and 375 articles included from the grey literature sources. One-hundred and forty eight duplicates were removed by EPPI Reviewer 4.0 and another 48 were manually removed by the reviewer (MH). A total of 1,317 articles were included for screening.

After screening, a total of 99 articles were included. After manually reviewing 99 articles, 31 articles met the inclusion and exclusion criteria and were included for quantitative and qualitative analysis. Figure 1 provides a PRISMA flow diagram outlining the screening process and the reasons for exclusion at each level.

Figure 1: PRISMA Flow Diagram



Abbreviations: SLT= Selective laser trabeculoplasty, OAG= Open angle glaucoma, MA= Meta-analysis, SR= Systematic review

4.2.2 Inter-rater Agreement

At each level of screening the inter-rater reliability was calculated using the kappa statistic. In the title and abstract screening, the percentage agreement was 89%, and the kappa score between the two reviewers (MH and EM) was 0.53. According to the kappa statistics guidelines, this was considered moderate agreement. Most of the differences in the agreement were due to articles that EM marked as ‘unsure’ and MH marked as ‘exclude’. For the full text screening, the percentage agreement was 91% and the kappa score was 0.82, which was considered almost perfect agreement.

4.3 Quality Assessment

4.3.1 Downs and Black Risk of Bias Assessment

The score for reporting information sufficiently was 7.3 out of 10, on average. The overall score for external validity, which addressed issues of generalizability, was 2.3 out of 3, on average. The potential bias in the measurement of the intervention and the outcome was 4.4 out of 7, on average. The average confounding score was 2.2 out of 6. The score for the power of the study was 0.83 out of 5 on average. The reason this value was low was because the majority of the studies did not report on the probability of rejecting a false null hypothesis, also referred to as the power of the study, resulting in a score of 0. The quality scores were higher in the RCT studies with an overall score of 21.6 compared to 17.03 in all the studies. Table 6 provides a tabular form of the quality assessment results for the clinical trials and the observational studies included in the analysis.

The kappa statistic was used to assess the level of agreement between the individual ratings of each assessor (MH and EM). Tables 7 provides a detailed summary of the percentage agreement and the kappa statistic agreement for each study.

Table 6: Downs and Black Quality Assessment Average Score for each Category

Quality Index	**Overall Quality Score** (31 studies including RCTs and non-RCTs)		**RCTs**(12 studies)	
	Average Score	**Range**	**Average Score**	**Range**
Reporting	7.3	5-10	7.25	5-10
External Validity	2.3	0-3	2.08	0-3
Bias	4.4	1-6	8.1	1-6
Confounding	2.2	0-5	2.5	0-5
Power	0.83	0-5	1.67	0-5
Total	17.03 (53%)		21.6 (68%)	
Higher values are indicative of better performance in that category				

Table 7: Kappa Statistics Computed for Individual Studies

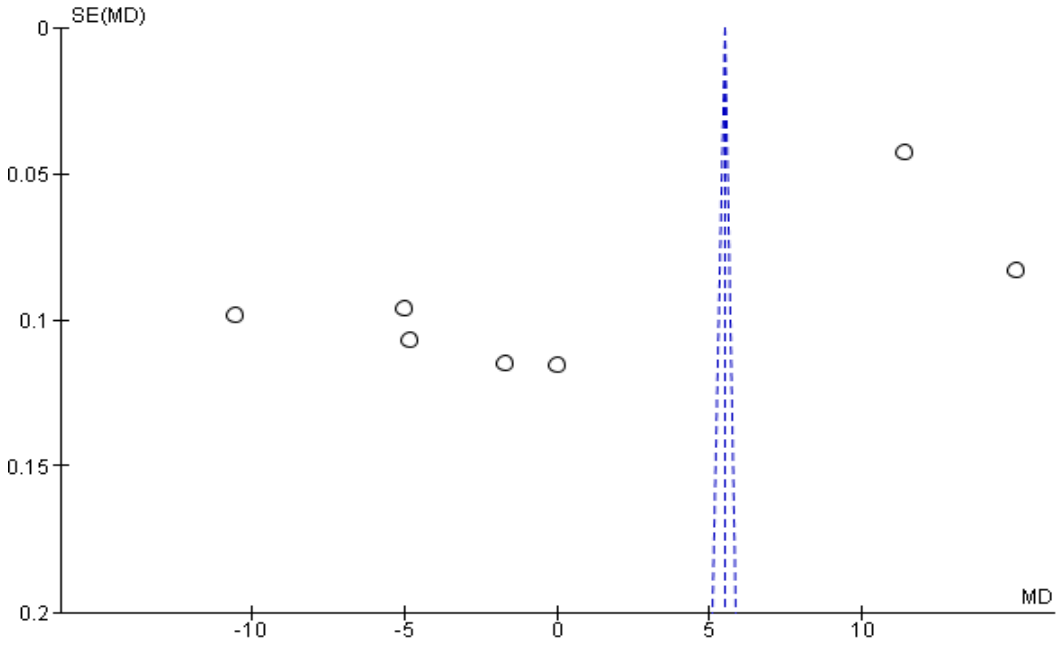
Author, Year of Publication	% Agreement	Kappa Statistic (SE)
Abdelrahman et al, 2012[83]	74.0%	0.49(0.17)
Babighian et al, 2010[84]	66.67%	0.31(0.15)
Birt, 2007[85]	55.6%	0.08(0.19)
Bovell et al, 2011[86]	70.3%	0.30(0.14)
Bruen et al,2012[87]	77.78%	0.52(0.19)
Francis et al, 2005[88]	75%	0.44(0.19)
Giocanti-Auregan et al, 2014[89]	70.3%	0.42(0.17)
Greninger et al, 2014[106]	66.67%	0.31(0.19)
Habib et al, 2013[90]	77.78%	0.55(0.19)
Hirneib et al, 2013 [91]	77.78%	0.56(0.17)
Juzych et al, 2004[92]	85.19%	0.69(0.19)
Kara et al,2013 [93]	66.6%	0.32(0.17)
Katz et al, 2012[82]	88.89%	0.72(0.19)
Kent et al, 2015[94]	70.37%	0.41(0.31)
Khouri et al, 2014a[95]	88.89%	0.75(0.19)
Khouri et al, 2014b[96]	92.59%	0.83(0.19)
Koucheki & Hashemi, 2012[97]	77.78%	0.47(0.19)
Lai et al, 2004[78]	88.89%	0.75(0.19)
Leon et al, 2005[98]	88.89%	0.74(0.19)
Lee et al, 2014[77]	70.37%	0.32(0.17)
Lee et al, 2015[99]	92.59%	0.84(0.19)
Lowry et al, 2016[100]	81.48%	0.62(0.18)
McIlraith et al, 2006[76]	77.78%	0.47(0.19)
Nagar et al, 2005[79]	85.19%	0.72(0.17)
Nagar et al, 2009[80]	81.48%	0.64(0.17)
Rebenitsch et al, 2013[101]	92.59%	0.83(0.19)
Russo et al, 2009[102]	81.48%	0.58(0.19)
Schlote & Kynigopoulos, 2016[103]	74.07%	0.40(0.19)
Tan et al, 2015[81]	92.59%	0.82(0.19)
Zaninetti & Ravinet, 2008[104]	92.59%	0.82(0.19)
Zhang et al, 2015[105]	92.59%	0.84(0.19)
Higher numbers are indicative of better agreement SE: Standard Error		

4.4 Publication bias

Figure 2 depicts the funnel plot for the studies comparing SLT with medications. If the fixed-effect estimate is true and no bias is present, then the dotted line triangle is centered on a fixed effect summary estimate and extends 1.96 standard errors either side and includes about 95% of the studies[72]. The WMD of the percentage reduction in IOP was plotted on the x-axis and the standard error of the WMD of the percentage reduction in IOP was plotted on the y-axis. The standard error on the y-axis decreased as we went up the funnel plot. None of the studies were plotted inside the pseudo 95% fixed estimate, suggesting that heterogeneity may be present. All of the studies were plotted near the middle and top of the funnel plot.

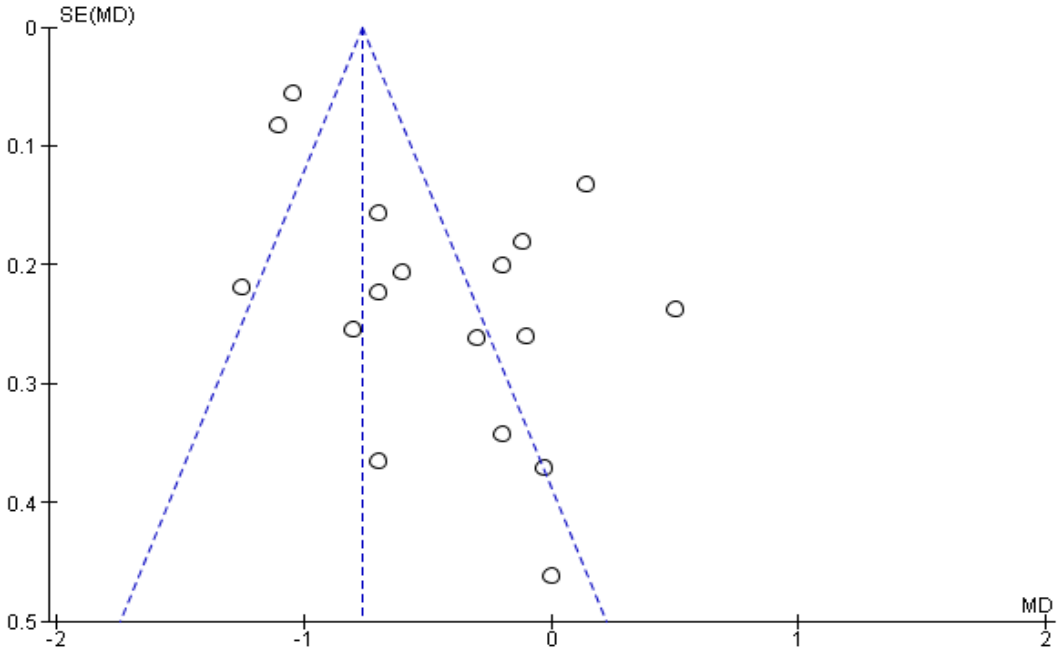
Figure 3 shows the funnel plot for the Adjunctive SLT studies examining pre-and-post-operative medications. The WMD of the reduction in medications was plotted on the x-axis and the standard error of the WMD of the reduction in medications was plotted on the y-axis. The majority of the studies were located to the right of the average effect estimate (the central line) and 8 of the 15 studies were located outside of the expected pseudo 95% interval, suggesting heterogeneity may be present. The bottom left corner of the funnel plot was empty, suggesting that smaller studies may not have been published. Although publication bias may be one reason for the asymmetry, there are several other reasons for funnel plot asymmetry which include: high heterogeneity, language bias, and availability bias.

Figure 2: Funnel Plot for Studies Evaluating SLT versus Medications



The standard error (SE) of the mean difference (MD) in the intra-ocular pressure percentage reduction is plotted on the y-axis. The MD of the intra-ocular pressure percentage reduction is plotted on the x-axis. N=7.

Figure 3: Funnel Plot for Studies Evaluating SLT as an Adjunctive Treatment



The standard error (SE) of the mean difference (MD) in the reduction in medications is plotted on the y-axis. The MD of the reduction in medications is plotted on the x-axis. N=17.

4.5 Impact on Intra-ocular Pressure Reduction (IOPR)

4.5.1 IOPR after SLT

Thirty studies provided data on the IOP reduction after SLT. Table 8 lists twenty-six of the studies that provided SLT adjunctively with medications, and three[79,80,82] studies that provided SLT sequentially after about a 4-5 weeks wash-out of medications, and one[76] study that provided SLT as primary and sequential treatment. Data were presented on the follow-up time, number of eyes at each follow-up time, the percentage IOP reduction ($IOPR\%$), and the standard error of the percentage IOP reduction ($SE_{IOPR\%}$). In total there were 25[61,76,78–84,87,90–98,100,102,103,105,106] studies that reported data on 6-9 months, 22[76,78,79,82–87,89,90,92,93,95,97,99–103,106] studies on 12 months follow-up, six[83,84,90,95,97,99] studies on 18 months of follow-up, nine[84,86,90,92,95,99,100,104,106] studies on 24 months of follow-up, two[86,90] studies reported data on 36 months, two[86,92] studies reported on 48 months and three[86,89,92] studies reported data on 60 months or greater.

The percentage IOP reduction averaged 21.3% (range: 14.3% to 40.4%) at 6-9 months, 22.4% (range: 11.8% to 43.7%) at 12 months, 17.1% (range: 11% to 20.9%) at 18 months, 17.2% (range: 11% to 23.5%) at 24 months, and 28.3% (range: 17.5% to 34.2%) at 36 months or greater.

Table 8:Intra-ocular Pressure Percentage Reduction Post SLT

Author, Year of Publication	Follow-up (months)	N (eyes)	IOP Percentage Reduction	SE_IOPR%
Abdelrahman et al, 2012[83]	6	65	21.8%	.051
	12	65	23.4%	.052
	18	65	19.6%	.049
Babighian et al, 2010[84]	6	15	19.6%	.102
	9	15	18.4%	.100
	12	15	18.8%	.100
	18	15	20.9%	.104
	24	15	20.9%	.104
Birt, 2007[85]	12	30	22.7%	.076
Bovell et al, 2011[86]	12	78	25.2%	.049
	24	79	23.5%	.047
	36	75	28.2%	.052
	48	72	29.4%	.053
	60	64	31.1%	.058
Bruen et al, 2012[87]	6	56	17.67%	.051
	12	51	21.7%	.058
Giocanti-Auregan et al, 2014 (abstract)[89]	12	NR	29.4%	-
	144	NR	34.2%	-
Greninger et al, 2014[106]	6	84	14.5%	.038
	12	80	11.8%	.036
	24	49	15.6%	.051
Habib et al, 2013[90]	8	79	20.5%	.180
	12	75	18%	.180
	18	65	17.7%	.180
	24	24	12.1%	.020
	36	18	17.5%	.030
Hirneib et al, 2013[91]	6 (OAG)	68	19.3%	.048
	6 (POAG)	45	19.3%	.048
Juzych et al, 2004[92]	6	37	14.3%	.057
	12	32	18.1%	.068
	24	29	23.4%	.078
	36	25	23.4%	.078
	48	21	21.2%	.089
	60	20	27.1%	.099
Kara et al, 2013[93]	6 (POAG)	48	19.8%	.057
	12 (POAG)	48	19.3%	.056
	6 (PXG)	37	25.8%	.071
	12(PXG)	37	27.2%	.073
Katz et al, 2012[82]	4-6	38	22.8%	.068
	9-12	29	25.0%	.080
Kent et al, 2015[94]	6	NR	29.8%	-
Khouri et al, 2014a[95]	8	39	21.3%	.065
	12	38	19.2%	.064
	18	36	17.7%	.064
	24	28	12.2%	.062

Table 8: Intra-ocular Pressure Percentage Reduction Post SLT (Continued)

Author, Year of Publication	Follow-up (months)	N (eyes)		IOP Percentage Reduction	SE_IOPR%
Khouri et al, 2014b[96]	8	42		20.8%	.062
	12	43		16.5%	.056
Koucheki & Hashemi, 2012[97]	6	121		20.0%	.036
	12	127		18.2%	.034
	18	78		17.3%	.042
Lai et al, 2004[78]	6	24		29.4%	.084
	12	24		29.4%	.084
	60	24		32.1%	.086
Leon et al, 2005 (abstract)[98]	6	NR		14.6%	-
Lee et al, 2014[77]	6	22		15.1%	.076
Lee et al, 2015[99]	6	34		21.7%	.029
	9	34		18.8%	.026
	12	34		16.0%	.023
	18	34		11.0%	.016
	24	34		11.0%	.016
Lowry et al, 2016[100]	6	100		14.8%	.035
	12	100		12.14%	.032
	24	100		19.16%	.040
McIlraith et al, 2006[76]	12 (Primary SLT)	74		31.0%	.053
	12 (Sequential SLT)	87		25.6%	.046
Nagar et al, 2005[79]	6	90◦	35	18.3%	.065
		180◦	49	25.9%	.062
		360◦	44	40.4%	.073
	12	90◦	35	21.6%	.069
		180◦	49	32.6%	.067
		360◦	44	43.7%	.074
Nagar et al, 2009[80]	4-6	20		23.7%	.067
Rebenitsch et al, 2013[101]	12	NR		19.0%	-
Russo et al, 2009[102]	6	43		26.0%	.066
	12	43		26.5%	.067
Schlote & Kynigopoulos, 2016[103]	6	36		26.2%	.032
	12	36		33.0%	.036
Tan et al, 2015 (abstract)[81]	6	78		14.5%	.039
Zaninetti & Ravinet, 2008 (abstract)	24	36		17.2%	.062
Zhang et al, 2015 (abstract)	6-9 (270◦)	34		NR	-
	6-9 (360◦)	33		NR	-

NR: Not Reported; SLT: Selective laser trabeculoplasty; OAG: Open-angle Glaucoma; POAG: Primary Open-angle Glaucoma; PXG: Pseudoexfoliative Glaucoma; N: Number of eyes; SE: Standard Error; IOP: Intra-ocular pressure; IOPR: Intra-ocular pressure reduction

4.5.2 IOPR comparing SLT versus Medications

Table 9 includes the IOP levels in both the SLT and the pharmacotherapy group. The percentage IOP reduction and the standard error was also calculated and reported in the table. For a follow-up time between 4-6 months, the IOP reduction averaged 24.3% (range: 15.1% to 40.4%) in the SLT group compared to 22.6% (range: 0 to 43.5%) in the pharmacotherapy group.

At 9-12 months of follow-up the average percentage IOP reduction was 31.0% (range: 21.6% to 43.7%) in the SLT group compared to 31.7% (range: 24.4% to 45.2%) in the pharmacotherapy group. There was one study that gathered data up until 60 months and the percentage IOP reduction for the SLT and medications-only group was 32.1% and 33.2%, respectively.

On average, the IOP percentage reduction was similar between the SLT group and the medications-only group. The study by Lee et al (2014)[77] reported a zero percentage reduction at 6 months post initial medication treatment. Possible reasons include that the baseline IOP for the pharmacotherapy group was 14.5 (2.5), which was already low. What did change was the standard deviation (from 2.5 to 2.2), which means that the patients in the 6 months follow-up group had IOP values closer to the mean. Tan et al (2015)[81] also reported a lower than average percentage IOP reduction (3.16%) for the medications-only group. Reasons for this low percentage reduction could not be identified since the full text was written in Chinese.

Table 9:Follow-up of Included Studies Comparing SLT with Medications

Author, Year of Publication	Follow-up (months)	N of SLT Group	Mean Post-Operative IOP for SLT Group (SD)	IOP Percentage Reduction for SLT Group	SE_IOPR% (SLT Group)	N of Medication Group	Mean Post-Operative IOP for Medication Group (SD)	IOP Percentage Reduction for Medication Group	SE_IOPR% (Medication Group)
Katz et al 2012[82]	4-6	38	18.9(2.9)	22.8%	.068	31	17.8(3)	27.9%	.081
	9-12	29	18.2(2.8)	25%	.080	25	17.7(2.5)	26.7%	.082
Lee et al, 2014[77]	6	22	13.4(2.3)	15.1%	.076	19	14.5(2.2)	0	-
Lai et al, 2004[78]	6	24	18.8 (NR)	29.8%	.093	24	19.1 (NR)	29.3%	.092
	12	24	18.8(NR)	29.8%	.093	24	19.8 (NR)	28.6%	.092
	60	24	18.1(NR)	32.1%	.095	24	17.5 (NR)	33.2%	.097
McIlraith et al, 2006[76] [primary]	12	74	17.8(3)	31%	.053	26	16.9(NR)	30.6%	.090
McIlraith et al, 2006[76] [wash-out]	12	87	19.7(5)	25.6%	.046				
Nagar, 2005[79]	6	90◦ 35	20(NR)*	18.3%	.065	39	16.5(NR)*	43.5%	.079
		180◦ 49	22(NR)*	25.9%	.062				
		360◦ 44	18(NR)*	40.4%	.073				
	12	90◦ 35	19.2(NR)*	21.6%	.069	39	16(NR)*	45.2%	.079
		180◦ 49	20(NR)*	32.6%	.067				
		360◦ 44	17(NR)*	43.7%	.074				
Nager, 2009[80]	4-6	20	16.4(NR)	23.7%	.067	20	15(NR)	34.2%	.075
Tan et al, 2015[81]	6	78	17.73(3.4)	14.5%	.039	78	19.9(2.9)	3.16%	.019

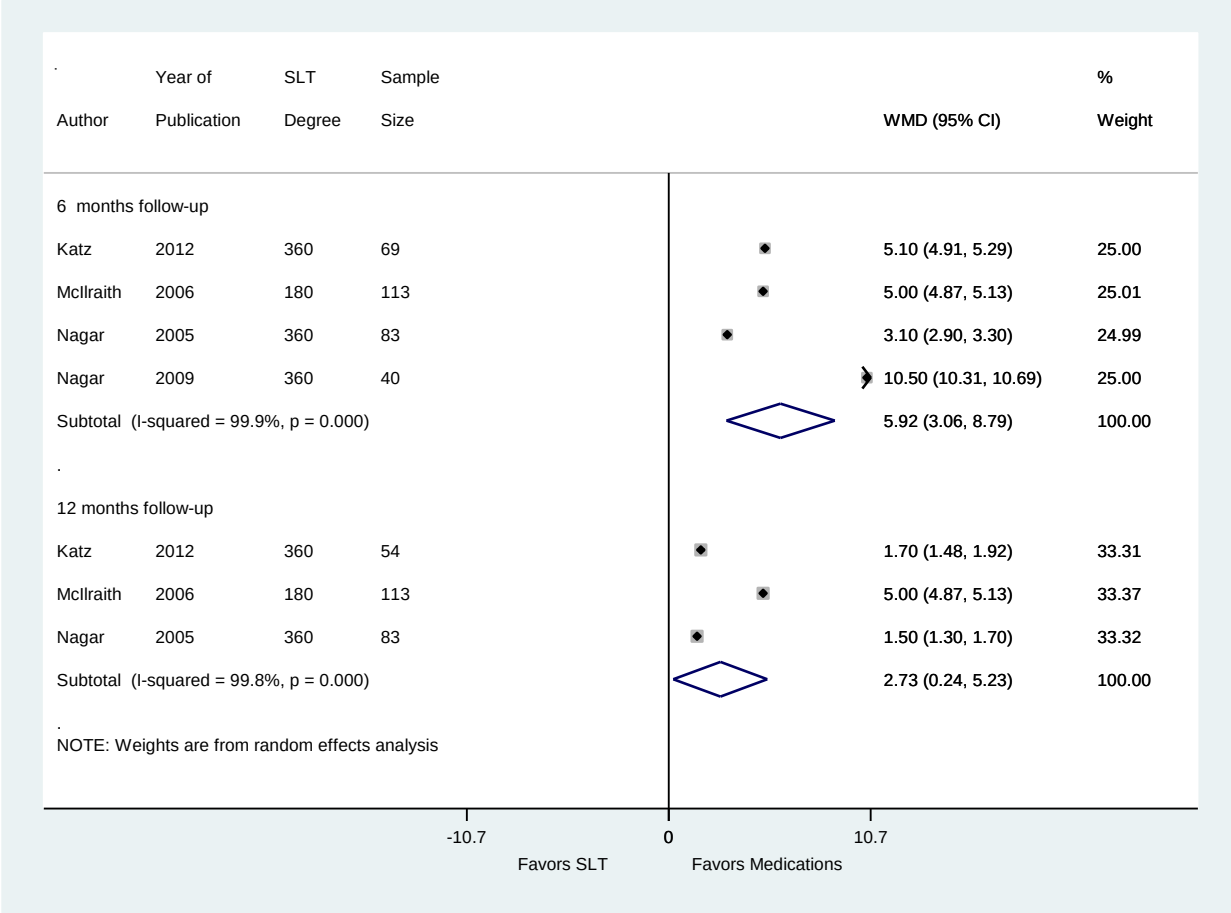
Values with an Asterisk (*) mean that these values have not been provided by the article directly, and have been estimated from a graph
IOP: Intra-ocular pressure; IOPR: Intra-ocular pressure reduction; SD: Standard Deviation; SE: Standard Error; NR: Not reported; N: Number of eyes; SLT: Selective laser trabeculoplasty

4.5.3 WMD in IOPR Comparing Sequential SLT with Medications

A forest plot was created to examine whether the timing of the SLT procedure had an effect on IOP levels. The timing of the SLT procedure was divided into three separate groups. First, we looked at articles that compared Sequential SLT with pharmacotherapy. Sequential SLT was defined as SLT that was provided after a 'wash-out' period of about 4 weeks. During the "wash-out" time, patients were not receiving any glaucoma medications or treatment.

Figure 4 provides a forest plot depicting the WMD of the IOP percentage reduction in the Sequential SLT group and pharmacotherapy group. A significant IOP percentage reduction was seen in the pharmacotherapy group, WMD= 5.92% (95% CI [3.06, 8.79]) at 6 months follow-up and WMD= 2.73% (95% CI [0.24, 5.23]) at 12 months follow-up. Heterogeneity between studies that investigated the impact of Sequential SLT versus medications-only at 6 months (I^2=99.9%) and at 12 months (I^2=99.8%), was significantly high (p=0.00). Therefore, the random-effects model was computed. Furthermore, all four studies compared the Sequential SLT group with a prostaglandin analog only medication group.

Figure 4: Forest Plot for Studies Evaluating Sequential SLT versus Medications

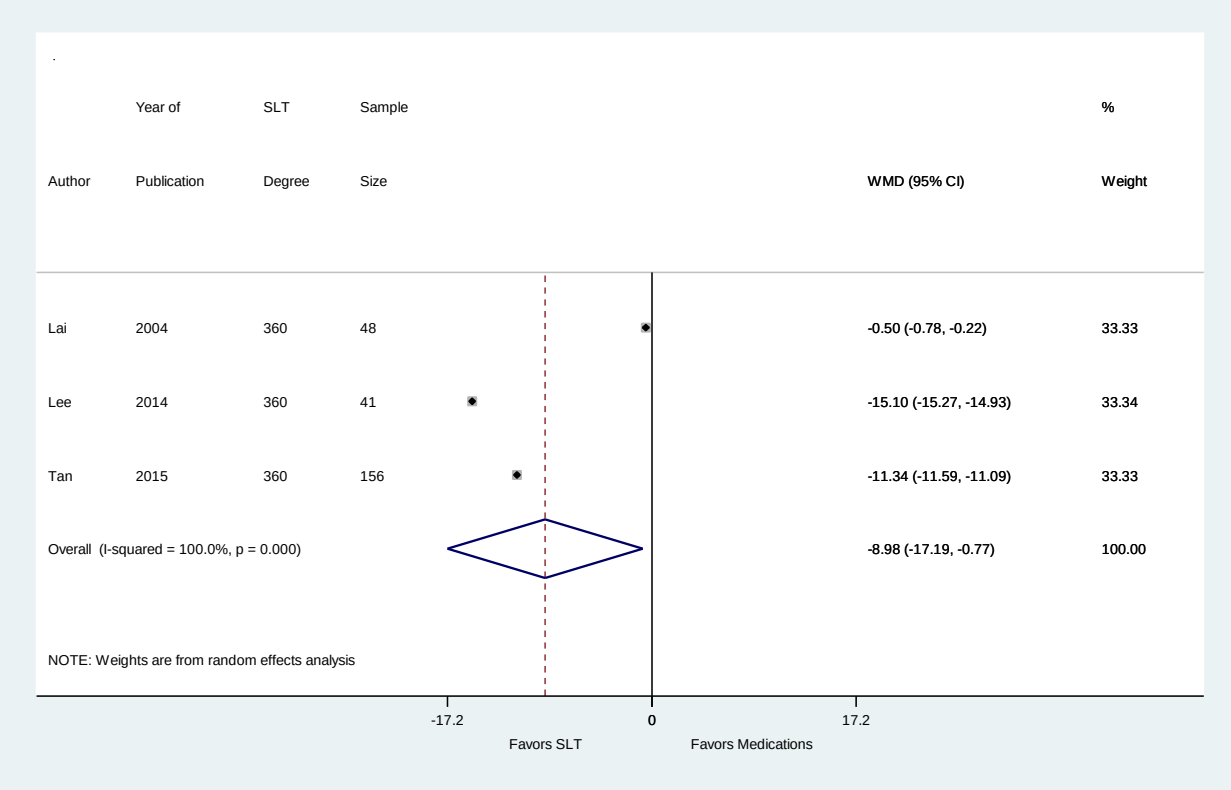


4.5.4 WMD in IOPR Comparing Adjunctive SLT with Medications

A second forest plot was created to examine if the timing of the SLT procedure made a difference on the IOP-lowering effect. This forest plot assessed the IOP-lowering effect comparing Adjunctive SLT with pharmacotherapy. Adjunctive SLT was when a patient was already on topical glaucoma medications and SLT was performed.

Figure 5 provides the forest plot of the IOP percentage reduction comparing Adjunctive SLT with pharmacotherapy at 6 months.Three[77,78,81] studies reported data at 6 months follow-up. Significant percentage reduction in IOP in the Adjunctive SLT group, WMD= -8.98% (95% CI [-17.19, -0.77]) compared to the pharmacotherapy group was seen. One[78] study that had a follow-up of 12 months and there was a 2.3% greater reduction in IOP in Adjunctive SLT group compared to pharmacotherapy group. Because there was only one study with a follow-up time of 12 months, this was not included in the forest plot. Heterogeneity (I^2= 100%) between studies was significantly (p=0.00) high, therefore the random-effects model was computed. All three of the studies compared the Adjunctive SLT group to a mixed class of medications group.

Figure 5: Forest Plot for Studies Evaluating Adjunctive SLT versus Medications at 6 months Follow-up



4.5.5 IOPR comparing Primary SLT with Medications

One[76] study assessed the effect of Primary SLT versus pharmacotherapy on the IOP reduction. Primary SLT was defined as SLT being performed on patients with treatment naïve eyes, meaning the patient did not have any previous medications, lasers or surgical glaucoma treatment. The study[76] found a 31% reduction in IOP in the Primary SLT group compared to a 30.6% reduction in the latanoprost-only group. More studies need to be conducted comparing Primary SLT treatment with pharmacotherapy treatment in order to create a forest plot that illustrates the WMD in percentage IOP reduction between the two groups. Details on this study[76] can be found in Table 9.

4.6 Impact on Medications

4.6.1 Percent Reduction in Number of Medications after SLT

Of the 31 studies, there were 27 studies that looked at post-operative reduction in medications as an outcome. Eighteen[77,81,83,87,88,90–96,99,100,102,103,105,106] studies gathered data at 6-9 months follow-up however, only 13[77,81,83,88,90,92,95,99,100,102,105,106] studies reported this data. An average 19% (range: -4% to 55%) reduction in medications was seen. There were 19[78,83,85–90,92,93,95–97,99–103,106] studies that gathered data at 12-18 months follow-up, but 16[83,85,86,88–90,92,93,95,97,99–103,106,107] studies reported this data. An average 16.1% (range: -3.8% to 64%) reduction in medications was seen. Nine[84,86,90,92,95,99,100,104,106] studies reported data on 24 months follow-up with mean reduction in medications averaging 13.8% (range: -3.8% to 40%). Five[78,86,89,90,92] studies reported data on a follow-up of 36 months or greater with a 6.2% (range:-16.3 to 26.9%) mean reduction in medications. The medication reductions for each study at each follow-up is reported in Table 10.

After assessing the articles, we found the three[83,84,88] studies that reported the highest reduction in medications post SLT treatment included patients with the highest initial medications. Lai et al[78] reported a 16.3% increase in the medications at 60 months follow-up. This increase in medications could be due to worsening patients' conditions, or the effect of SLT wearing off. Studies by Schlote & Kynigopoulos[103], Rebenitsch et al.[101] and Greninger et al.[106] had reported the lowest percentage reduction in medications post SLT in chronic glaucoma patients over the age of 70.

Table 10: Medication Reduction from Baseline in Included Studies

Author, Year of Publication	Follow-up (months)	N (eyes)	Mean Medications (SD)	Mean Reduction in Medications (SD)	Mean Percentage Reduction in Medications
Abdelrahman et al, 2012[83]	6	65	1(NR)	1.25(NR)	55%
	12	65	0.8 (NR)	1.45(NR)	64%
	18	65	1 (1.3)	1.25(1.1)	55%
Babighian et al, 2010[84]	24	15	0.87(0.8)	1.33(0.3)	39.5%
Birt. 2007[85]	12	30	2.2(1.6)	0.7(1.1)	24.1%
Bovell et al, 2011[86]	12	78	2.4(1.3)	0.2 (0.6)	7.7%
	24	79	2.1(1.2)	0.5 (0.5)	19.2%
	36	75	2.3(1.3)	0.3(0.8)	11.5%
	48	72	2.1(1.2)	0.5(0.6)	19.2%
	60	64	1.9(1.3)	0.7(0.8)	26.9%
Bruen et al, 2012[87]	6	56	NR	-	-
	12	51	NR	-	-
Francis et al, 2005[88]	6	66	0.7(0.9)	2.1(0.5)	25%
	12	60	1.5(0.9)	1.3(0.5)	46.4%
Giocanti-Auregan et al, 2014[89] (abstract)	12	NR	1.36(0.8)	0.24(-)	15%
	144	NR	1.3(1.2)	0.3(-)	18.7%
Greninger et al, 2014[106]	6	84	2.7(NR)	-0.1	-3.8%(increase)
	12	80	2.7(NR)	-0.1	-3.8%(increase)
	24	49	2.7(NR)	-0.1	-3.8%(increase)
Habib et al, 2013[90]	8	79	2.10 (1.1)	-0.07	-3.4%(increase)
	12	75	1.97 (1.1)	0.06	2.9%
	18	65	1.70(0.9)	0.33	16.2%
	24	45	1.83(1.1)	0.2	9.8%
	36	18	2.0(1.2)	0.03	1.5%
Hirneib et al, 2013[91]	6 (OAG)	68	NR	-	-
	6 (POAG)	45	NR	-	-
Juzych et al, 2004[92]	6	37	2.6(1.6)	-0.1(0.2)	-4%(increase)
	12	32	2.1(1.4)	0.4 (0.8)	16%
	24	29	2.3(1.4)	0.2 (0.8)	8%
	36	25	2.5(1.5)	0.2(1.1)	8%
	48	21	2.5(1.5)	0.2(1.2)	8%
Kara et al,2013 [93]	6	48	NR	-	-
	12	48	2.4(1.3)	0.5(1.3)	26.3%
Kent et al, 2015[94]	6	NR	NR	0.16(1.2)	-
Khouri et al, 2014a[95]	8	39	1.6(0.9)	0.1 (0.3)	5.1%
	12	38	1.6(0.9)	0.1 (0.3)	5.1%
	18	36	1.5(0.8)	0.2 (0.1)	11.7%
	24	28	1.5(0.8)	0.2 (0.4)	11.7%
Khouri et al, 2014b[96]	8	42	NR	-	-
	12	43	1.45 (0.9)	0.12(0.4)	7.6%
Koucheki & Hashemi. 2012[97]	16.6	78	2.1(0.7)	0.2(0.7)	8.7%

Table 10: Medication Reduction from Baseline in Included Studies (Continued)

Author, Year of Publication	Follow-up (months)	N (eyes)	Mean Medications (SD)	Mean Reduction in Medications (SD)	Mean Percentage Reduction in Medications
Lai et al, 2004[78]	12	24	0.46 (NR)	0	-
	60	24	0.55 (NR)	-0.09	-16.3%(increase)
Leon et al, 2005[98]	6	NR	NR	NR	-
Lee et al, 2014[77]	6	22	1.5(1.2)	0.8(0.5)	34.7%
Lee et al, 2015[99]	6	34	1.0(1.0)	0.5	33%
	12	34	1.0(0.8)	0.5	33%
	24	34	0.9(0.9)	0.6	40%
Lowry et al, 2016[100]	6	81	2.45(0.3)	.17(1.1)	6.48%
	12	81	2.56(0.9)	0.06(1.1)	2.3%
	24	81	2.76(0.3)	-.14(1.1)	-5.3%(increase)
Rebenitsch et al, 2013[101]	12	NR	1.5(1.1)	0(-)	0
Russo et al, 2009[102]	6	43	2.2(1.2)	0.1 (0.5)	4.3%
	12	43	2.2(1.1)	0.1 (0.5)	4.3%
Schlote & Kynigopoulos, 2016[103]	6	36	1.9(1.0)	0	0
	12	36	1.9(1.0)	0	0
Tan et al, 2015[81]	6	78	2.19(0.3)	1.04(0.3)	47.5%
Zaninetti & Ravinet, 2008[104]	24	36	1.36(NR) drops/patient	.08(-)	5.5%
Zhang et al, 2015[105]	6-9 (270°)	34	1.3(0.5)	1(0.5)	43.5%
	6-9 (360°)	33	1.1(0.3)	1(0.3)	47.6%

NR: Not reported; OAG: Open-angle Glaucoma; POAG: Primary Open-angle Glaucoma; N: Number of eyes; SD: Standard Deviation

*Lai et al, 2004: the baseline number of medications was not provided. The number of medications at 12 months was used as the baseline to calculate the percentage reduction at 60 month

4.6.2 WMD of Pre-and-Post SLT Medications

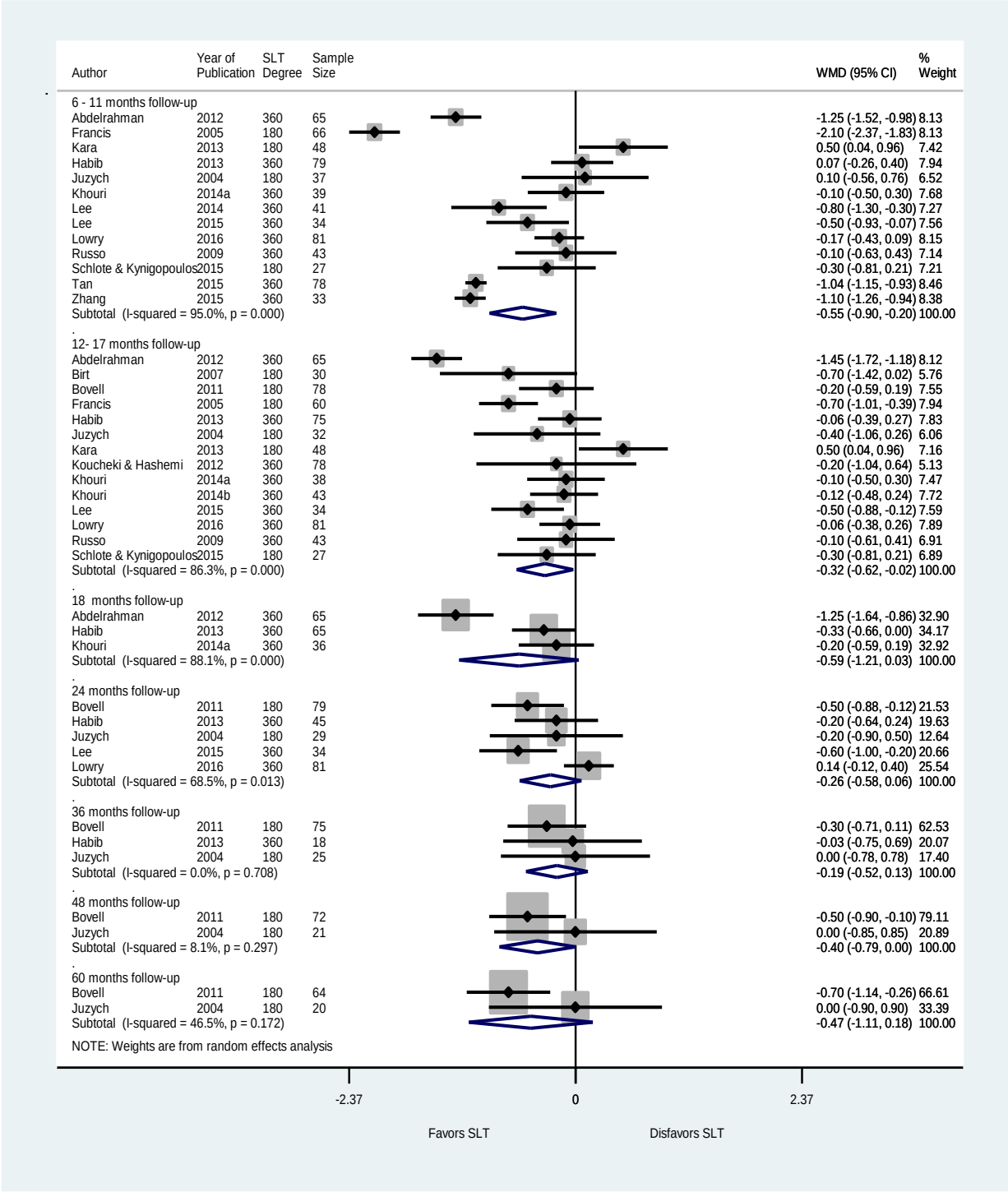
Figure 6 is a forest plot that illustrates the pre-and-post-operative topical glaucoma medications. The data are divided into seven different follow-ups: 6 to 11 months, 12 to 17 months, 18 months, 24 months, 36 months, 48 months, and 60 months.
Thirteen[77,81,83,88,90,92,93,95,99,100,102,103,105] studies reported 6 to 11 months follow-up, 14[83,85,86,88,90,92,93,95–97,99,100,102,103] studies reported 12 to 17 months follow-up, three[83,90,95] studies reported 18 months follow-up, five[86,90,92,99,100] studies reported 24 months follow-up, three[86,90,92] studies reported 36 months follow-up, two[86,92] studies reported 48 and 60 months follow-up. Studies that did not report on a sample size were not included in the forest plot but were included in the tables.

Heterogeneity between studies that reported reduction in medications at 6 to 11 months follow-up (I^2=95%, p=0.00), at 12 to 17 months follow-up (I^2=86.3%, p=0.00), 18 months follow-up (I^2= 88.1%, p=0.00), 24 months follow-up (I^2= 68.5%, p=0.013) was significantly high. At 36 months follow-up (I^2= 0%, p=0.70), 48 months follow-up (I^2= 8.1%, p=0.29), and 60 months follow-up (I^2= 46.5%, p=0.17) there was non-significant between study heterogeneity.

There was a significant reduction in post-operative medications at 6 to 11 months follow-up, WMD= -0.55 medications (95% CI [-0.90, -0.20]), at 12 to 17 months follow-up there was also a significant reduction, WMD= -0.32 medications (95% CI [-0.62, -0.02]). There was a non-significant reduction at 18 months follow-up WMD= -0.59 medications (95% CI [-1.21, 0.03]), at 24 months follow-up WMD= -0.26 medications (95% CI [-0.58, 0.06]), at 36 months follow-up WMD= -0.19 medications (95% CI [-0.52, 0.13]), at 48 months follow-up WMD= -0.40 medications (95% CI [-0.79, 0.00]), and at 60 months follow-up WMD= -0.47 medications (95% CI [-1.11, 0.18]).

Overall, there was a slight lean towards favoring SLT at all follow-up times, and there was a significant reduction in the number of pre-and-post-operative medications at 6 to 11 months and 12 to 17 months of follow-up, however these results should be interpreted with caution as there was high heterogeneity reported in these subgroups.

Figure 6: Forest Plot of Medications Pre-and-Post SLT



4.6.3 Subgroup Analysis by SLT Degree

A subgroup analysis was conducted to determine if the SLT degree, specifically whether SLT was applied over 360 degrees or 180 degrees of TM, made any impact on the reduction in medications. Figure 7 depicts a forest plot of medications pre-and-post SLT at 6 to 11 months follow-up. There were nine[77,81,83,90,95,99,100,102,105] studies that reported data on SLT preformed over 360 degrees of the TM and there was a significant reduction in medications, WMD= -0.58 medications (95% CI [-0.89, -0.29]), with a significant between study heterogeneity (I^2= 92.7%, p=0.00). There were three[88,92,103] studies that performed SLT treatment over 180 degrees of the TM. There was a non-significant reduction in medications, WMD=-0.79 medications (95% CI [-2.29, 0.71]), with significant between study heterogeneity (I^2=96.8%, p=0.00).

Figure 8 depicts a forest plot reporting the WMD of the medications reduction before and after SLT for studies that reported follow-up times from 12 to 17 months. Eight[83,90,95–97,99,100,102] studies reported data for 360 degrees of SLT treatment, and there was a non-significant reduction in medications pre-and-post SLT, WMD= -0.34 medications (95% CI [-0.77, 0.10]), with significant between study heterogeneity (I^2= 90.5%, p=0.00). Six[85,86,88,92,93,103] studies reported data for SLT preformed over 180 degrees of the TM. There was a non-significant reduction in medications post SLT, WMD= -0.29 medications (95%CI [-0.67, 0.09]), with significant between study heterogeneity (I^2=74.2%, p=0.00).

Overall, based on the forest plots, there appeared to be a significant reduction in medications at 6 months post SLT when a patient received 360 degrees of treatment over the TM. However, by 12 months follow-up, the significant effect may ware off. Providing SLT at 180 degrees did not appear to significantly reduce the medications at 6 months or 12 months post SLT treatment. Due to high heterogeneity, the random effects model was used.

Figure 7: Forest Plot of Medications Pre-and-Post SLT by SLT Degree at 6-11 Months Follow-up

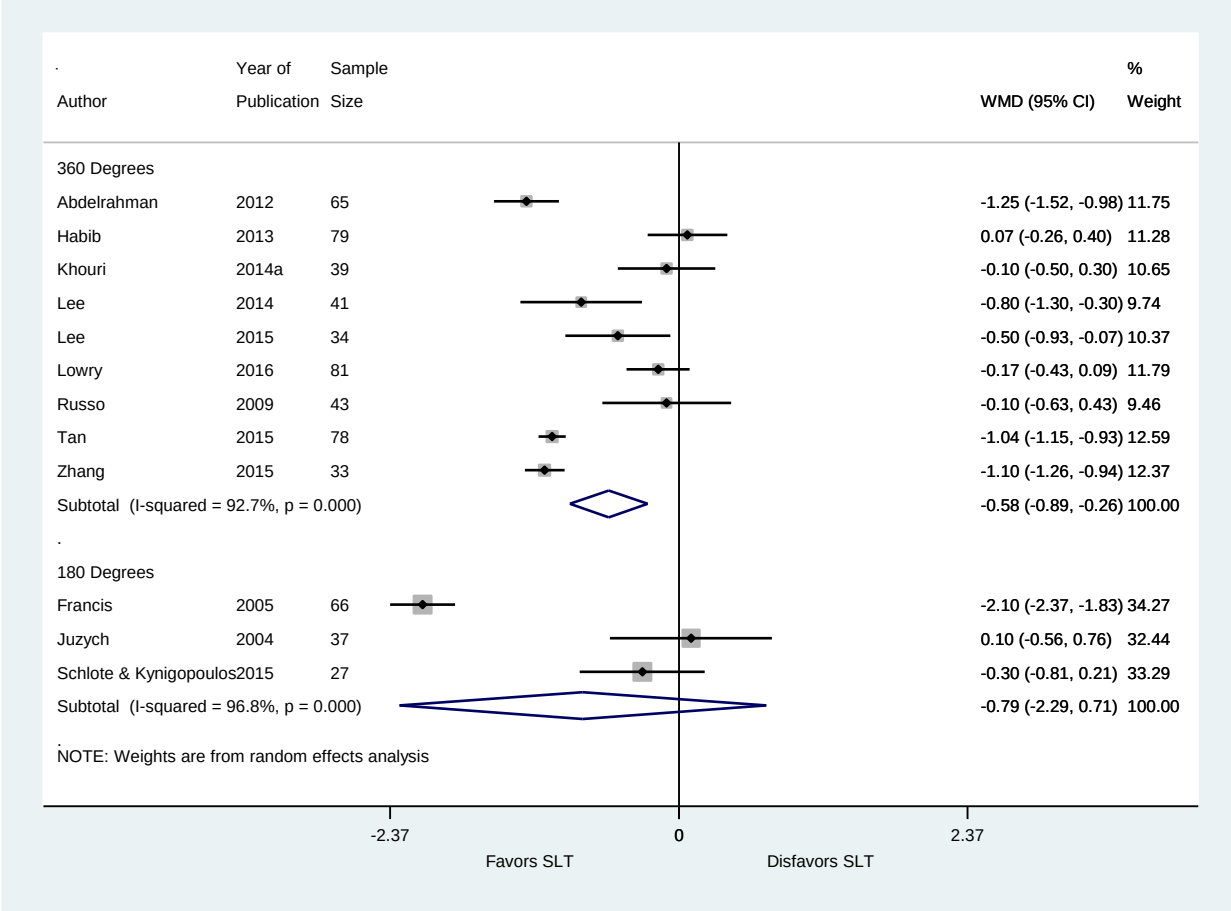
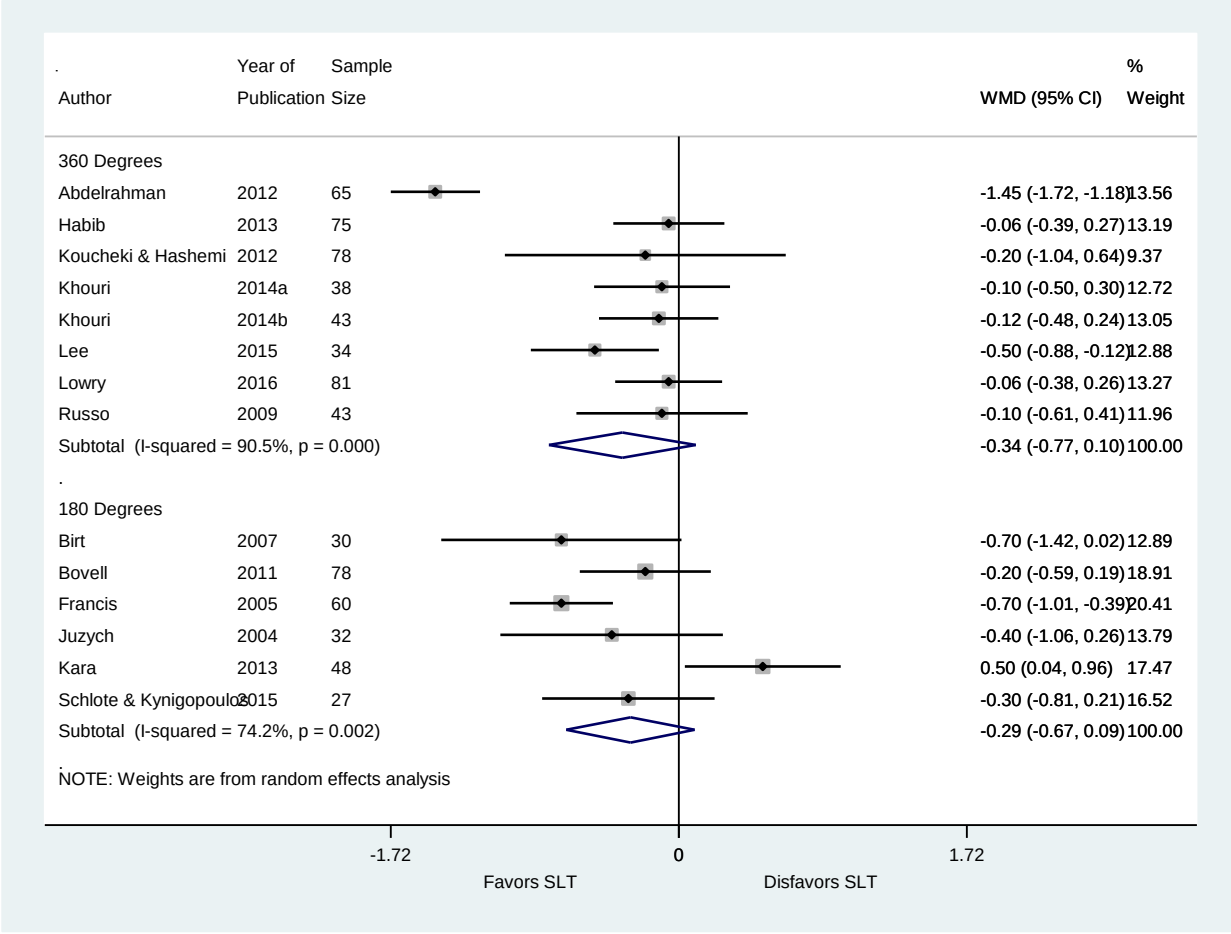


Figure 8: Forest Plot of Medications Pre-and-Post SLT by SLT Degree at 12-17 Months Follow-up



4.6.4 Subgroup Analysis by Study Design

A subgroup analysis was conducted by study design. Figure 9 reports data for 6 to 11 months follow-up post SLT treatment. Eight[83,88,90,92,95,99,100,103] studies reported data from non-RCT studies. The non-RCT studies showed a non-significant reduction in medications, WMD= -0.54 medications (95% CI [-1.16, 0.07]), and a significant between study heterogeneity (I^2= 96%, p=0.00). Four[77,81,102,105] RCTs showed a significant reduction in medications, WMD= -0.89 medications (95% CI [-1.14, -0.63]). Heterogeneity (I^2= 77.6%, p=0.00) between RCTs was significantly high.

Figure 10 reports data for 12 to 17 months follow-up post SLT treatment. Twelve[83,85,88,90,92,93,95–97,99,100,103]studies reported data from non-RCT studies. There was a significant reduction in medications, WMD= -0.35 medications (95% CI [-0.68, -0.01]). Heterogeneity (I^2=88%, p=0.00) between studies was significant. There were two[86,102] studies that reported data from RCTs, and there was a non-significant reduction in medications, WMD= -0.16 medications (95% CI [-0.47, 0.15]). Non-significant heterogeneity (I^2=0%, p=0.76) existed between these two studies.

Based on Figures 9 and 10, RCT study results suggest a significant reduction in medications at 6 to 11 months follow-up. However, a non-significant reduction was observed at 12 to 17 months. This conclusion is based off of two RCTs and thus more RCTs are required to make concrete conclusions. With the non-RCT studies, a non- significant reduction in medications was observed at 6 to 11 months follow-up, and there was a significant reduction at 12 to 17 months follow-up.

These results should not be viewed as definitive because of high heterogeneity. However, it is important to note that the heterogeneity was lower in the RCT studies, which suggested that the non-RCT studies may have a higher heterogeneity due to high confounding within the studies, which the RCT studies have controlled for through randomization of participants.

Figure 9: Forest Plot of Medications Pre-and-Post SLT by Study Design at 6-11 Months Follow-up

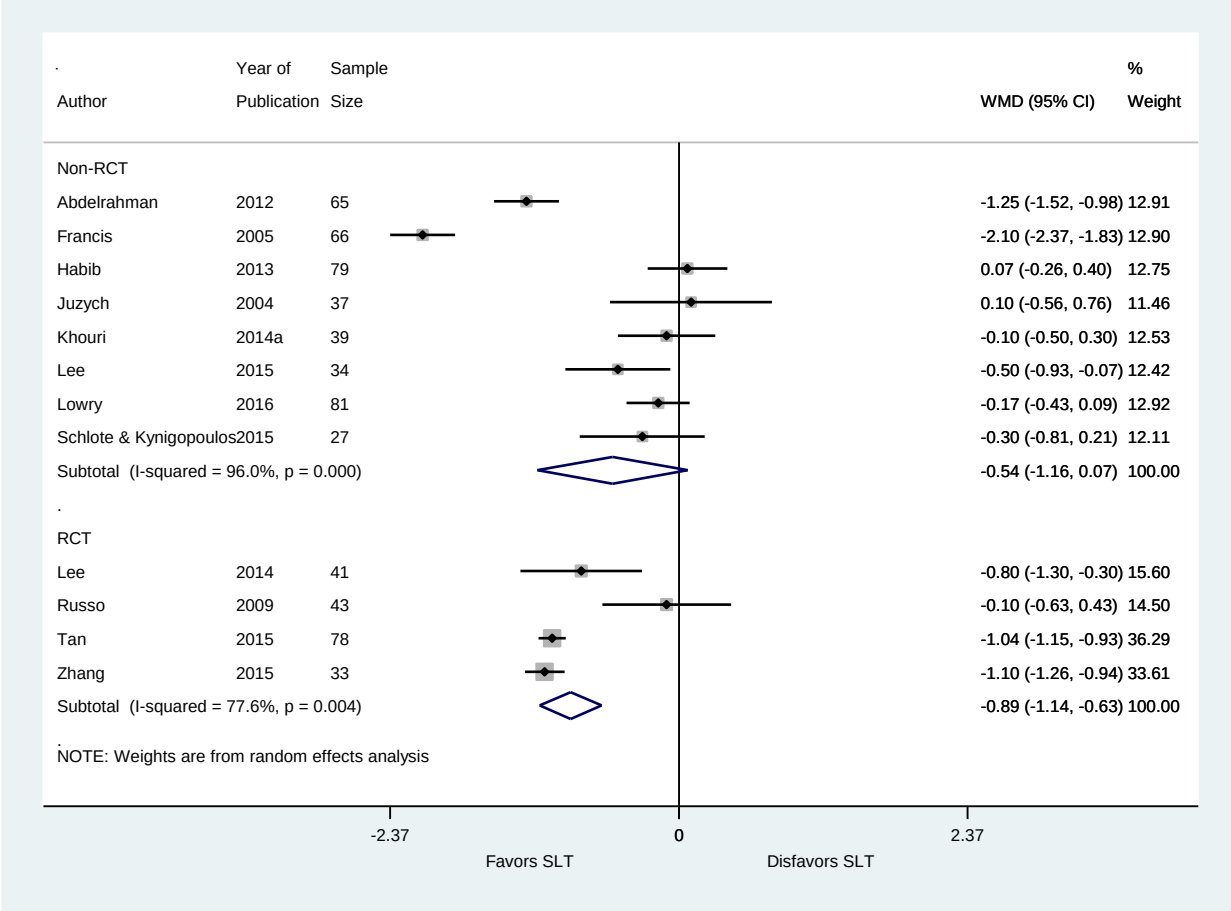
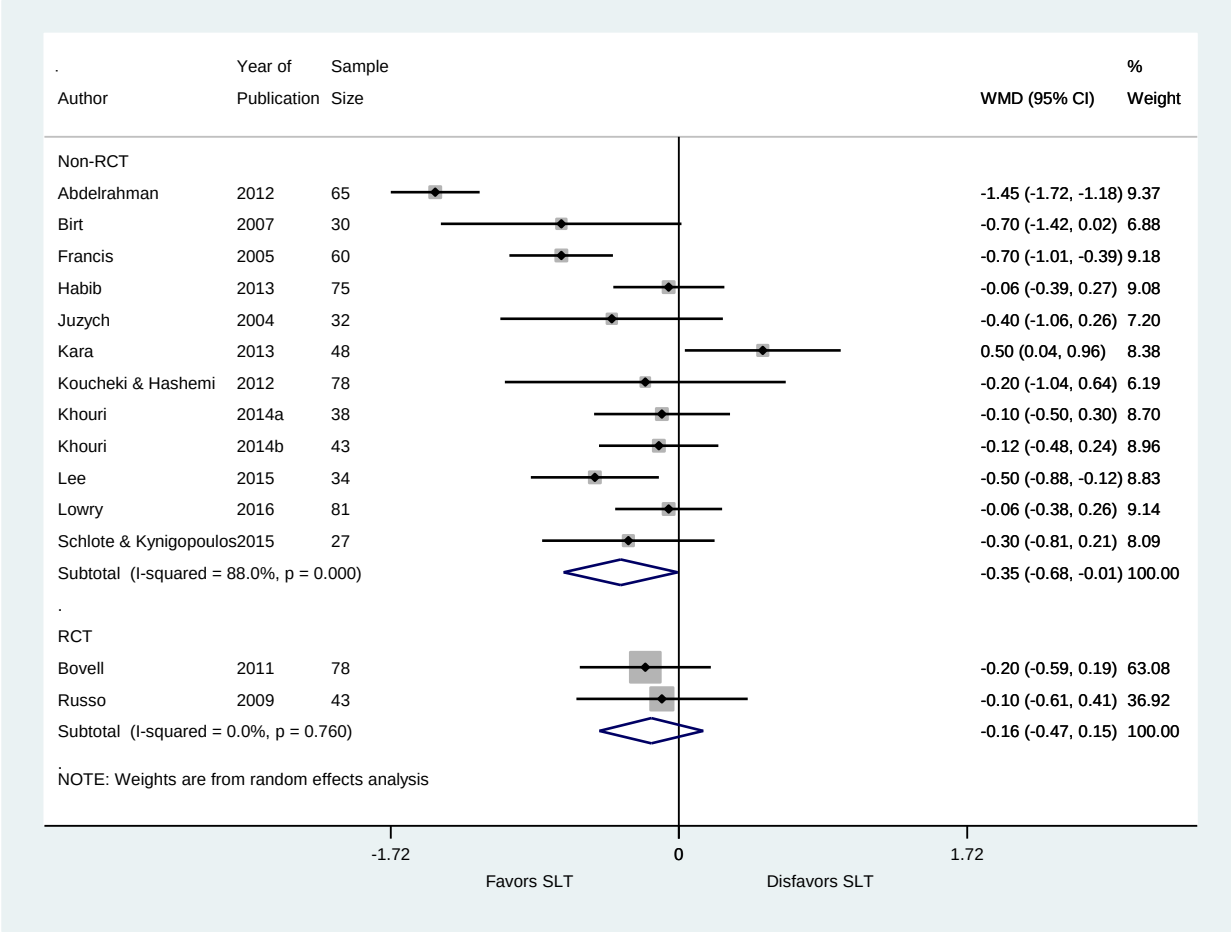


Figure 10: Forest Plot of Medications Pre-and-Post SLT by Study Design at 12-17 Months Follow-up



4.7 Impact on Adverse Events

Of the 31 included studies, 21[76–79,82–86,88,89,91–94,97,100–103,106] reported on adverse events that occurred after SLT treatment. Eleven[78,79,83,84,86,88,93,97,100,102,106] studies reported an IOP spike, ten[78,79,83,86,88,93,97,100,102,106] studies reported on the number of IOP spikes observed. There were at least 72 cases of IOP spikes among 1,742 eyes that underwent SLT, which was approximately 4.13%. All of the studies had a different definition for IOP spike. Four[78,79,83,88] studies defined a spike as an IOP greater than 5mm Hg within 24 hours of operation. Four[86,97,102,106] studies defined an IOP spike as an IOP of greater than or equal to 6mm Hg within 24 hours of operation. Lowry et al[100] defined IOP spike as an IOP greater than 7 mm Hg and Babighian et al[84] stated that the IOP spikes did not exceed 8 mm Hg. Three[79,83,93] studies reported that patients experienced ocular discomfort. The types of ocular discomfort were not described in the articles. A flare or inflammation of the anterior chamber was reported in two[76,84] studies. Five[85,86,97,100,103] studies reported that the patient required additional intervention to stabilize the IOP levels. A detailed list of all reported complications is provided in Table 11.

Table 11: Reported Adverse Events Post SLT Treatment

Author, Year of Publication	Reported Complications Post SLT
Abdelrahman et al, 2012[83]	Ocular discomfort, IOP rise 1 week following SLT (5 cases), IOP spike associated with a mild flare in the anterior chamber
Babighian et al, 2010[84]	Flare of anterior chamber (2 cases), IOP spike (2 cases)
Birt. 2007[85]	Trabeculectomy (5), Further laser therapy (7)
Bovell et al, 2011[86]	IOP spike (3 cases), Additional interventions including Ahmed Valve (5 cases), Repeat SLT (17 cases), ALT (5 cases), Trabeculectomy Mitomycin C (14 cases), Diode cyclophotocoagulation (1 case), Cateract extraction with intraocular lens implant/Trabeculectomy with Mitomycin C (10 cases)
Bruen et al,2012[87]	-
Francis et al, 2005[88]	IOP spike (6 cases)
Giocanti-Auregan et al,2014[89]	No significant complications
Greninger et al, 2014[106]	IOP spike (8 cases), cystic macular edema (1 case), Corneal epithelial defect (1 case)
Habib et al, 2013[90]	-
Hirneib et al, 2013 [91]	No adverse events after SLT
Juzych et al, 2004[92]	Complications treated but not reported
Kara et al, 2013[93]	IOP spike (7 cases), Iritis (5 cases), Ocular discomfort (16 cases)
Katz et al, 2012[82]	No IOP elevation or uveitis, no peripheral anterior synechiae
Kent et al, 2015[94]	Specifically no IOP spikes reported. Defined as an IOP increase of 6 or more mm Hg after 1 hour of SLT
Khouri et al, 2014a[95]	-
Khouri et al, 2014b[96]	-
Koucheki & Hashemi, 2012[97]	Mild pain during SLT (23.5%), Inflammation in eyes (42.6%), IOP spike (6 cases), Further surgical intervention (17.6%)
Lai et al, 2004[78]	IOP spike (3 cases), No persistent anterior chamber reaction beyond 1 week
Leon et al, 2005[98]	-
Lee et al, 2014[77]	No complications from the laser procedure
Lee et al, 2015[99]	-
Lowry et al, 2016[100]	IOP spikes (6 cases), Further surgery (9%)
McIlraith et al, 2006[76]	Minimal inflammatory reaction (33 cases), Flare (+1) (3 cases)
Nagar et al, 2005[79]	IOP spike (24 cases), Ocular discomfort (29 cases), mild uveitis (53 cases)
Nagar et al, 2009[80]	-
Rebenitsch et al, 2013[101]	No adverse effects reported
Russo et al, 2009[102]	Anterior chamber inflammation (12 eyes), IOP spike (6 cases)
Schlote & Kynigopoulos, 2016[103]	1 abnormal wound healing, trabeculecomy because of insufficient IOP reduction (8 eyes), filtration surgery
Tan et al, 2015[81]	-
Zaninetti & Ravinet, 2008[104]	-
Zhang et al, 2015[105]	-
IOP: Intra-ocular pressure; mm Hg: millimeters of mercury; SLT: Selective laser trabeculoplasty; ALT: Argon laser trabeculoplasty	

4.7 Sensitivity Analysis

The sensitivity analysis was conducted to examine the robustness of the results. In Figure 4, we found that Sequential SLT versus pharmacotherapy at 6 months and 12 months follow-up had an IOP-lowering effect that favored pharmacotherapy. We re-ran this forest plot, excluding a study by McIlraith et al.[76], and found that the results remained the same (See Figure 11).Significant reduction in IOP was seen at 6 months in the pharmacotherapy group compared to the Sequential SLT group, WMD= 6.23% (95% CI [1.90, 10.57]). Heterogeneity between studies was found to be significant (I^2=99.9%, p=0.00).At 12 months a significant reduction in IOP occurred in the pharmacotherapy group compared to the Sequential SLT, WMD= 1.60% (95% CI [1.40, 1.79]). Moderate heterogeneity (I^2=42.8%, p=0.18) was observed.

Figure 5 illustrated a forest plot of the WMD comparing Adjunctive SLT with pharmacotherapy. At 6 months follow-up there were two full-text articles and one abstract only, and the IOP-lowering effect favored the SLT group, WMD=-8.98% (95% CI [-17.19, -0.77]). When we re-ran the forest plot, and excluded the abstract[81], we found similar results. (See Figure 12).The WMD of Adjunctive SLT and medications-only group showed no significant difference, WMD=-7.50% (95% CI [-22.20, 7.20]). Heterogeneity (I^2= 100%, p=0.00) was significant between studies.

Figure 6 illustrated a forest plot of the WMD of the medication reduction pre-and-post SLT. At all follow-up times, except for 6 to 11 months and 12 to 17 months post SLT treatment, there was a non- significant reduction in medications after SLT treatment. We re-ran the forest plot eliminating the abstracts: Tan et al[81] and Zhang et al[105]. This strategy produced different results. (See Figure 13). There were 11[77,83,88,90,92,93,95,99,100,102,103] studies included at 6 to11 months follow-up, 14[83,85,86,88,90,92,93,95–97,99,100,102,103] studies included at 12 to 17 months follow-up, three[83,90,95] studies included at 18 months follow-up, five[86,90,92,99,100] studies included at 24 months follow-up, three[86,90,92] studies included at 36 months follow-up, two[86,92] studies included at 48 and 60 months follow-up.

There was a non-significant reduction in medications at 6 to 11 months follow-up, WMD= -0.43 medications (95% CI [-0.95, 0.08]) post SLT. Significant heterogeneity (I^2=95.2%, p=0.00) was seen. At 12 to 17 months follow-up the WMD remained significant, WMD= -0.32 medications (95% CI [-0.62, -0.02]), with significant between study heterogeneity (I^2=86.3%, p=0.00). There was a non-significant reduction in medications at 18 months follow-up, WMD= -0.59 medications (95% CI [-1.21, 0.03]) with significant between study heterogeneity (I^2= 88.1%, p=0.00), at 24 months follow-up, WMD=-0.26 medications (95% CI [-0.58, 0.06]), with significant heterogeneity (I^2= 68.5%, p=0.01). At 36 months follow-up a non-significant reduction in medications was seen, WMD= -0.19 medications (95% CI [-0.52, 0.13]), with a non-significant heterogeneity (I^2= 0%, p=0.70).A non-significant reduction in medications was seen at 48 months, WMD= -0.40 medications (95% CI [-0.79, 0.00]), with a non-significant heterogeneity (I^2= 8.1%, p=0.29), and WMD= -0.47 medications (95% CI [-1.11, 0.18]) at 60 months with a moderate between study heterogeneity (I^2= 46.5%, p=0.17).

Figure 11: Sensitivity Analysis for Studies Evaluating Sequential SLT versus Medications

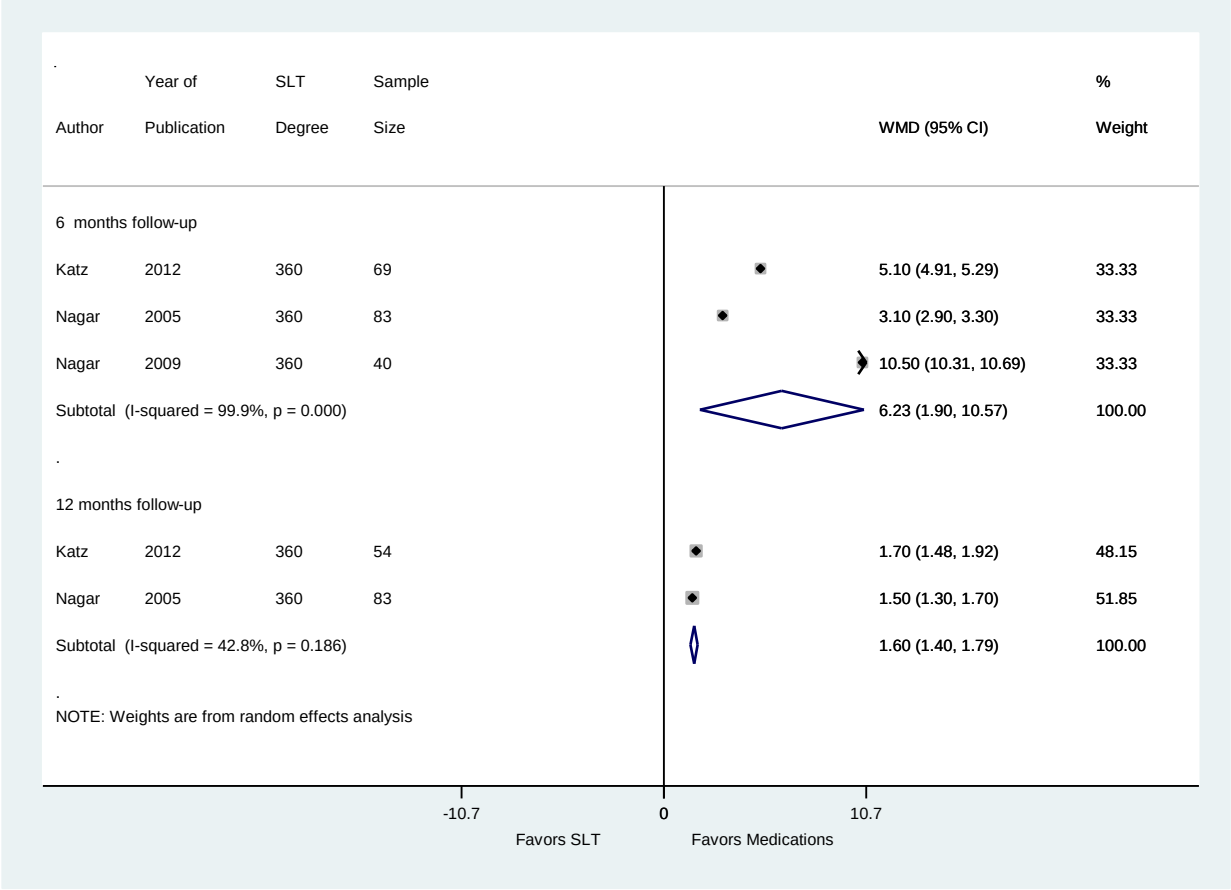


Figure 12: Sensitivity Analysis for Studies Evaluating Adjunctive SLT versus Medications

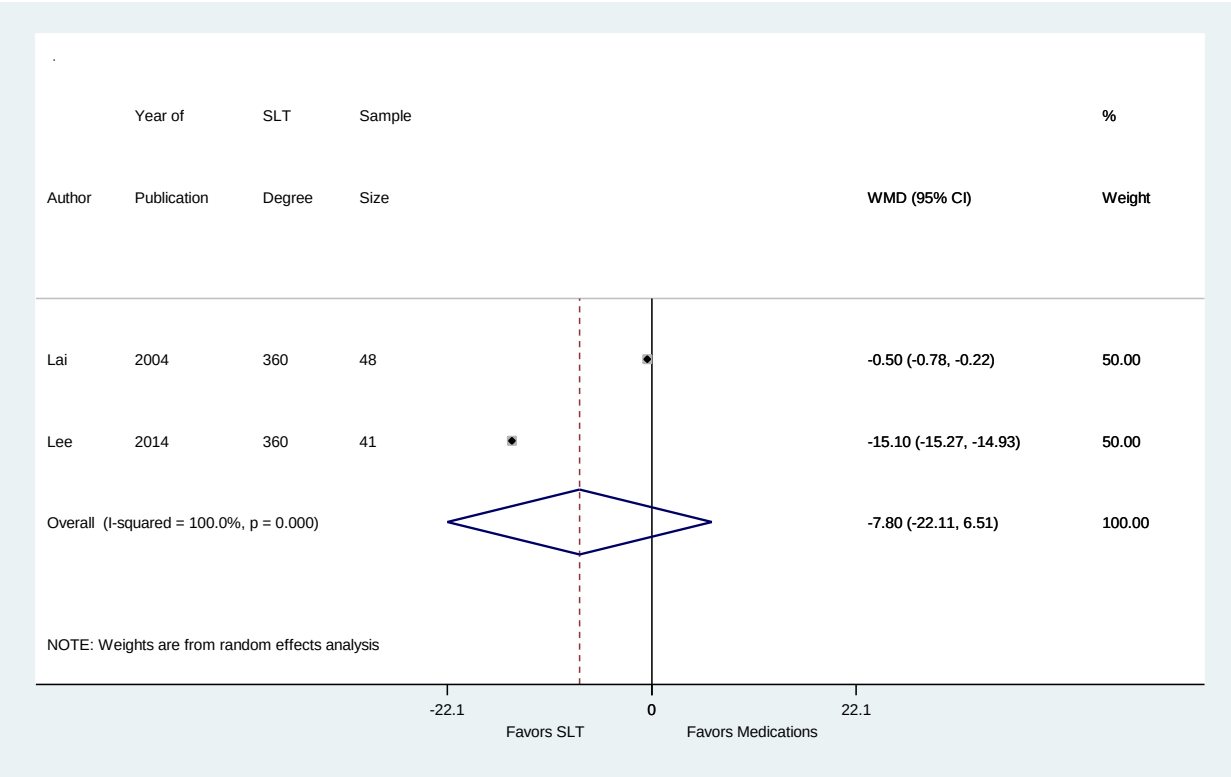
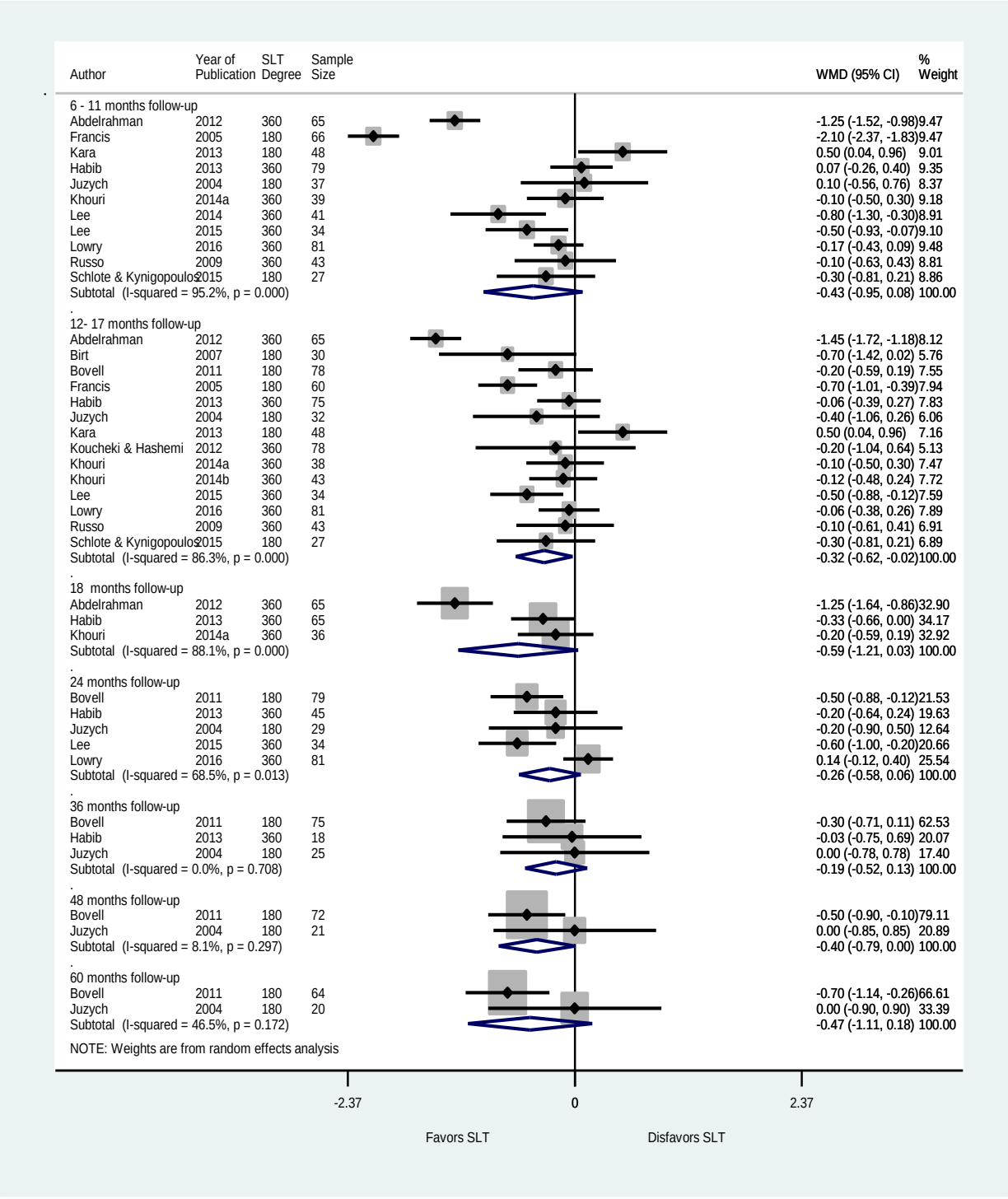


Figure 13: Sensitivity Analysis for Studies Evaluating the Pre-and-Post SLT Number of Medications



4.8 Summary of Findings

Table 12 provides a summary of the main findings reported in the results.

Table 12: Summary of Main Findings

Research Questions	**Results**	**Interpretation**
What is the IOP-lowering effect between Sequential SLT and medications-only?	*6 months post SLT treatment:* WMD= 5.92% (95% CI [3.06, 8.79]) *12 months post SLT treatment:* WMD= 2.73% (95% CI [0.24, 5.23])	Significant difference favoring the medications-only group
What is the IOP-lowering effect between Adjunctive SLT and medications-only?	*6 months post SLT treatment:* WMD= -8.98% (95% CI [-17.19, -0.77])	Significant difference favoring the Adjunctive SLT group
Does SLT significantly reduce the number post-operative medications?	*6 months post SLT treatment:* WMD= -0.55 medications (95% CI [-0.90, -0.20]) *12 months post SLT treatment:* WMD= -0.32 medications (95% CI [-0.62, -0.02])	Significant reduction in medications at 6 and 12 months follow-up. All other follow-ups showed no significant reduction

Chapter 5

5 Discussion

5.1 Summary of Quantitative Results

The aim of this thesis was to assess the effectiveness of SLT as an intervention in adult patients who were diagnosed with OAG or OHT. The first research question addressed whether SLT was effective at reducing patient's IOP levels compared to traditional pharmacotherapy. This was based on the assessment of 689 eyes. Providing SLT adjunctively was more effective at reducing the IOP levels than medications-only. Further, when the SLT group was 'washed-out' of the medications, the IOP-lowering effect favored the medications-only group both at 6 months and 12 months follow-up. There was only one study that compared Primary SLT with pharmacotherapy and the results showed that when SLT was provided as primary treatment, the IOP reduction favored the SLT group.

The second research question addressed whether SLT would significantly reduce the post-operative medications. We gathered data on 1,742 eyes who underwent Adjunctive SLT treatment. We assessed the WMD in the number of medications from baseline to 6-11, 12-17, 18, 24, 36, 46, and 60 months of follow-up. At all follow-up points, the medication reduction favored SLT treatment; there was a significant reduction in medications post-SLT at 6 to 11 months and 12 to 17 months. However, based on the sensitivity analysis and the high heterogeneity between the studies, concrete conclusions cannot be made.

When we conducted a subgroup analysis based on the SLT degree, we found that providing SLT over 360 degrees of the TM significantly reduced topical glaucoma medications at 6 to 11 months follow-up, but not at 12 to17 months follow-up. Providing SLT over 180 degrees of the TM showed no significant reduction in medications at 6 to 11 months and at 12 to 17 months follow-up. When we conducted a subgroup analysis based on the study design, we found that the RCTs showed a significant reduction in medications post-operatively, at 6 to 11 months follow-up. At 12 to 17 months follow-up the non-RCTs showed a significant reduction in medications. There was high heterogeneity reported in the subgroup analyses and these results should not be viewed as conclusive.

5.2 Interpretation of Results

The majority of clinicians use a 20% IOP reduction from baseline as the determining factor for the success of SLT treatment[39]. The average IOP percentage reduction was 21.3% at 6-9 months follow-up, 22.4% at 12 months follow-up, and approximately 17% at 18-24 months follow-up. In general, SLT provided as an adjunctive treatment, met the definition of a 'successful' treatment option up until approximately 24 months, which corroborates with conclusions made in the literature[22].

A possible reason some studies reported a higher percentage IOP reduction is that their baseline IOPs were higher. As expected, the cumulative IOP-lowering effect of multiple interventions produced a greater IOP reduction. The Adjunctive SLT group, which consisted of patients who were taking medications concurrently with SLT treatment, had a greater IOP reduction compared to the pharmacotherapy group. Furthermore, this study has revealed that the order in which SLT was provided to patients in their treatment regimen may play a role in SLT's success.

When SLT was provided after a wash-out of medications, SLT did not have a stronger effect on lowering IOP levels compared to medications-only group. A study conducted by Ault and Hutnik, (2016)[108] assessed a group of patients who were initially on medications. The patients were randomized to two groups. One group of patients who were washed-out of prostaglandin analog medications for 6 weeks, and then provided SLT, and another group who continued on prostaglandin analog treatment. The baseline IOP was approximately 26.6 (SD: 1.6) mm Hg before the commencement of the study. When all patients took prostaglandin analogs, their IOP reduced to 14.5(SD: 0.6) mm Hg. The patients who were washed-out of prostaglandin analogs for 6 weeks, their IOP rose only to 20.3(SD: 2.6) mm Hg, which was significantly lower than the initial baseline IOP. Results from this study indicated that the impact of the prostaglandin analogs may still be lingering in the eye well after the discontinuation of the medications; this may be a reason why the Sequential SLT group had a smaller IOP-lowering effect. However, more research needs to be conducted to determine the underlying reasons for this observation.

It is important to note that sometimes the intention of SLT as an additional intervention may not be to reduce IOP by a significant amount; sometimes the intention may be to help reduce the patient's dependency on medications. In our analysis, on average, the studies that reported the

greatest number of baseline medications, also reported the greatest percentage reduction in medications, suggesting that SLT was effective at lowering medications when a patient was taking 3 to 4 medications compared to 1 or 2 medications. Furthermore, based on the results of this study, we could not definitively conclude which types of glaucoma medications worked best with SLT because there were only 8[77,84–88,97,99] studies that reported on the type of medications that were prescribed to the patients and the majority of the 8 studies did not provide detailed information on how the medications were taken.

In regard to the exploratory investigation analyzing the adverse events as a result of SLT, we found that out of the 31 studies, 21 studies mentioned adverse events post SLT. The most commonly reported adverse events included post-operative IOP spike within 24 hours, and ocular discomfort. These complications, as well as other complications reported, were treated using steroids or non-steroidal anti-inflammatory eye drops[39]. There are some cases where SLT cannot be performed on a patient. SLT cannot be performed when a patient has closed or very narrow angles, severe kyphosis, ankylosing spondylosis, torticollis or cervical arthritis, head tremors, or eyes that are deeply recessed[109]. With the exception of these cases where SLT cannot be performed, SLT could be considered for OAG or OHT patients. Our results supported previously published conclusions which have stated that there were no extreme complications associated with SLT, suggesting that SLT was a safe procedure.

5.3 Strengths and Limitations

A major strength of this study was the research design. Systematic reviews and meta-analyses help clinicians keep track of current data in a particular subject area by summarizing all previously published results into one paper. This allows clinicians to make evidence-based decisions on the best possible treatment options without having to sift through multiple research studies. Systematic reviews provide a non-biased comprehensive review of the literature that involves creating a search strategy to gather as many relevant articles as possible. The process of systematically reviewing articles reduces the chance of study selection bias[72]. Further, in total, the results were based on 2,431 eyes and follow-up times ranged from 4-6 months to 60 months.

A limitation of this study was the high heterogeneity. The heterogeneity reported in the forest plots ranged from 0% to 100%. High heterogeneity meant that variations in study results were

due to something other than chance. Possible reasons could be that there was no standard way for SLT to be performed on patients. From study to study, SLT differed on the degree, the clock hour the treatment was provided, the number of laser spots applied, whether or not the spots were applied contiguously, the type of medications provided, and the anti-steroidal and anti-inflammatory drugs provided directly before and after SLT treatment. Furthermore, the patients were from differing age groups and differing stages of the disease.

A second limitation was scarce evidence. Four studies evaluated SLT sequentially, three studies evaluated SLT adjunctively and only one study evaluated SLT as primary treatment. Even though patients who underwent Sequential SLT were washed-out of the medications, the lingering effect of the medications persisted, and we wanted to assess whether SLT, by itself, without any previous medications, would result in a greater IOP-lowering effect when compared to medications alone. The small number of relevant studies made this comparison difficult.

A third limitation was the inclusion of studies irrespective of their quality. Data were included from non-randomized clinical trials, various observational studies, and abstracts. Ideally all included studies would be RCTs however, due to the limited amount of studies, we could not eliminate studies based on quality.

A fourth limitation was that we assumed that the pre-and post-operative IOP were independent. Based on this assumption, as well as literature[2], computations were conducted. Further, based on the literature, we computed the SE_IOPR%. Given this limitation in computing the SE_IOPR%, a potential to address this limitation in the future does exist.

5.4 Implications of Practice and Future Research

For future practice, these results suggested that providing SLT concurrently with a combination of drugs may have the potential to reduce the medications in order to diminish non-compliance issues. In a best case scenario, the medical treatment adherence is 75%, and when patients are prescribed two or more medications, the adherence drops[39]. Patients who are non-compliant to their treatment regimen will incur higher medical costs because their disease status will worsen[47].A study conducted by Cate et al[110] found that providing an educational and motivational support package using behavioral change counseling made no difference in

medication adherence. Clements (2012)[109] reported that telephone reminders and tailored printing material also did not help with medication adherence.

Since the majority of the patients that underwent SLT had undergone previous medical treatment, we could not definitively conclude how much of an independent role SLT played in lowering the IOP. For this reason, more studies are required comparing SLT in patients with treatment naïve eyes to SLT in patients on medications. A study conducted by Onakoya et al.[111] compared SLT as primary therapy in treatment naïve eyes to patients who had SLT and medications concurrently (Adjunctive SLT). There were 89 eyes with POAG included in the analysis. They found a similar IOP reduction in both groups. This may suggest that just as the Adjunctive SLT group was more effective at lowering the IOP levels than the pharmacotherapy group in our study, the Primary SLT group may have a greater reduction in IOP compared to the pharmacotherapy group. This could further imply that a patient would not need to take any additional medical treatment, which could save a patient hundreds of dollars per year in medical costs. This was only an inference and a more concrete conclusion could be made if there were more studies comparing Primary SLT treatment with medications-only treatment.

There are currently no standardized procedures for how SLT should be administered to patients. More studies should be conducted comparing different ways of administering SLT. Once an ideal SLT administration is found, this method could be standardized globally. This will make future studies that are included in meta-analysis, which aims to assess the effectiveness of SLT, more comparable and homogenous.

Additionally, future clinical trials should provide a clear description of the types of medications prescribed. In the studies that assessed the pre-and-post-operative medications, most studies did not specify which types of medications were used. This information could have been imperative, because we may have been able to determine whether SLT worked better with certain types of drugs. Also, there need to be more studies to assess steroid or anti-inflammation drug use in the effectiveness of SLT.

5.5 Conclusion

This systematic review and meta-analysis concluded that SLT is an effective and safe treatment option for patients with OAG or OHT. In addition, this study illustrated that SLT's effectiveness depended on when it was provided in the treatment paradigm. Out of all of the treatment strategies that were analyzed, Adjunctive SLT was found to be more effective than pharmacotherapy at lowering IOP levels, as well as lowering medications. Finally, since the majority of medical drug coverage plans only pay for a portion of fees and the patient is left to pay the difference, SLT may be the more cost effective approach since the treatment is covered by OHIP.

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Appendices

Appendix 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both	i
ABSTRACT			
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	ii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known	15-17
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	17
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	18
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	19
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	18
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	19-20
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	22
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	21-23
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	22-23
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	23-24
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2)for each meta-analysis.	24-26

Appendix 1: PRISMA Checklist (Continued)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	27-28
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	27
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	38-39
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	29-37
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	40-41
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	46-51, 56-58, 66-67
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	51-54
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	43-45
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	68-72
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	74
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	76-77
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	75-76, 77-79
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	103

Appendix 2: Search Strategy

MEDLINE(Ovid)		Search Terms
1	1. Mesh	ocular hypertension/ or glaucoma/ or intraocular pressure/
2	2. Keyword Search	(glaucoma* or ocular hypertension or intraocular pressure or intra-ocular pressure).mp.
3	1 or 2 Total Including Limits	75069
4	1. Mesh	TM/ or trabeculecomy/ or glaucoma/
5	2. Keyword Search	(trabeculoplast* or goniotom* or trabeculotom* or slt or selective laser trabeculoplast*).mp
6	4 or 5 Total Including Limits	36552
7	1. Mesh	prostaglandins/ or prostaglandin/ or synthetic prostaglandin analogs/
8	2. Keyword Search	(Prostaglandin analogs or Prostaglandin* or latanoprost or bimatoprost or travoprost).mp.
9	7 or 8 Total Including Limits	116289
10	1. Mesh	adrenergic beta-agonists/ or levobunolol/ or timolol/ or adrenergic beta-1 receptor agonists/ or betaxolol/
11	2. Keyword Search	(Beta blocker* or B-blocker* or Timolol or Betaxolol or levobutonol).mp.
12	10 or 11 Total Including Limits	55062
13	1. Mesh	Carbonic Anhydrase Inhibitors/ or CAI/
14	2. Keyword Search	(Carbonic anhydrase inhibitor* or Carbonate dehydratase inhibitor* or dorzolamide or brinzolamide).mp.
15	13 or 14 Total Including Limits	5113
16	1. Mesh	Receptors/ or Adrenergic/ or alpha/ or exp Hypertension/ or Adrenergic alpha-Agonists/
17	2. Keyword Search	(Alpha-agonist* or brimonidine or Alphagan).mp.
18	16 or 17 Including Limits	239,978

19	3 AND 6 AND (9 OR 12 OR 15 OR 18)	562 Articles The following Limits were applied: -19 plus years of age -Article published after 1997 -Human Subjects -English Articles

EMBASE (Ovid)		Search Terms
1	1. Emtree	glaucoma/ or intraocular pressure/ or ocular hypertension/
2	2. Keyword Search	(glaucoma* or ocular hypertension or intraocular pressure or intra-ocular pressure).mp.
3	1 or 2	107,631
4	Emtree	Trabeculoplasty/ or laser therapy/ or selective laser trabeculectomy/ or SLT/
5	1. Keyword Search	(Trabeculoplast* or gonotom* or trabeculectom* or slt or selective laser trabeculoplast*).mp.
6	4 or 5	21591
7	Emtree	prostaglandin/ or prostaglandin analog/
8	1. Keyword Search	(Prostaglandin analogs or prostaglandin* or latanoprost or bimatoprost or travoprost).mp.
9	7 or 8	173879
10	1. Emtree	exp beta adrenergic receptor blocking agent/ or exp atenolol/ or exp hypertension/
11	2. Keyword Search	(Beta blocker or b-blockers or timolol or betaxolol or levobutonol).mp.
12	10 or 11	805233
13	1. Emtree	Carbonate Anhydrase inhibitor/ or CAI/ or CAIS/
14	2. Keyword Search	(carbonic anhydrase inhibitor* or carbonate dehydratase inhibitor* or dorxolamide or brinzolamide).mp
15	13 or 14	6195
16	1. Emtree	Alpha agonist/ or adrenergic alpha-agonist/ or alpha-adrenergic agonist/
17	2. Keyword	(Alpha-agonist* or brimonidine or Alphagan).mp.
18	16 OR 17	12518
19	(3 AND 6) AND (9 OR 12 OR 15 OR 18) limit 21 to (human and english language and yr="1997 -Current" and (adult <18 to 64 years> or aged <65+ years>))	550 Articles were extracted from Embase. The following restrictions were applied: -English articles -1997- -Human Adults 18+

CINAHL		Search Terms
1	1.	(MM "Intraocular Pressure") OR (MM "Ocular Hypertension") OR (MM "Glaucoma")
2	2.	(Glaucoma* OR Ocular hypertension OR intraocular pressure OR intra-ocular pressure)
3	1 or 2	
4	1.	(MH "Laser Therapy")
5	2.	(Trabeculoplast* OR Goniotom* OR Trabeculotom* OR SLT)
6	4 or 5	
7	1.	(MH "Prostaglandins, Synthetic+") OR (MH "Prostaglandins I") OR (MH "Prostaglandins E") OR (MH "Prostaglandins")
8	2.	Prostaglandin analogs OR Prostaglandin* OR latanoprost OR bimatoprost OR travoprost
9	7 or 8	
10	1.	(MH "Adrenergic Beta-Agonists") OR (MH "Timolol") OR (MH "Levobunolol Hydrocholoride") OR (MH "Betaxolol Hydrochloride")
11	2.	(Beta blocker OR B-blocker OR Timolol OR Betaxolol OR Levobutonol)
12	10 or 11	
13	1.	(MH "Acetazolamide") OR (MH "Brinzolamide") OR (MH "Methazolamide") OR (MH "Dichlorphenamide") OR (MH "Dorzolamide Hydrochloride")
14	2.	(Carbonic anhydrase inhibitor* OR Carbonate dehydratase inhibitor*OR dorzolamide OR brinzolamide)
15	13 or 14	
16	1.	(MH "Brimonidine Tartrate-Timolol Maleate") OR (MH "Adrenergic Alpha-Agonists")
17	2.	Alpha-agonist* OR brimonidine OR Alphagan
18	16 or 17	
19	[3 AND 6] AND [9 OR 12 OR 15 OR 18]	13 articles were included from this database with the following limits -English only -published 1997- -adult humans 19+

Cochrane Library		Search Terms
Term 1		Glaucoma* OR Ocular hypertension OR intraocular pressure OR intra-ocular pressure
Term 2		Trabeculoplast* OR Goniotom* OR Trabeculotom* OR SLT
Term 3		Prostaglandin analogs OR Prostaglandin* OR latanoprost OR bimatoprost OR travoprost
Term 4		Beta blocker OR B-blocker OR Timolol OR Betaxolol OR Levobutonol
Term 5		Carbonic anhydrase inhibitor* OR Carbonate dehydratase inhibitor*OR dorzolamide OR brinzolamide
Term 6		Alpha-agonist* OR brimonidine OR Alphagan
	Combined (Term 1 OR Term 2) AND (Term 3 OR 4 OR 5 OR 6)	13 articles included from this database using the above search strategy. The following limits were applied: -published 1997- Other limits were not applied because the options were not provided.

Grey Literature Sources	Search Strategy
BIOSIS Previews (67)	#1."TOPIC: (glaucoma* or ocular hypertension or intraocular pressure or intra-ocular pressure) *AND* TOPIC: (trabeculoplast* or goniotom* or trabeculotom* or slt or selective laser trabeculoplast) Indexes=BIOSIS Previews Timespan=1997-2016" (516 articles) #2. "TOPIC: (Prostaglandin analogs or Prostaglandin* or latanoprost or bimatoprost or travoprost) *OR* TOPIC: (Beta blocker* or B-blocker* or Timolol or Betaxolol or levobutonol) *OR* TOPIC: (Carbonic anhydrase inhibitor* or Carbonate dehydratase inhibitor* or dorzolamide or brinzolamide) *OR* TOPIC: (Alpha-agonist* or brimonidine or Alphagan) *Indexes=BIOSIS Previews Timespan=1997-2016"* (82,787 articles) #2 AND #1 Refined by: LANGUAGES: (ENGLISH) *Indexes=BIOSIS Previews Timespan=1997-2016*
Web of Science, Core Collection (115)	#1."TOPIC: ((glaucoma* or ocular hypertension or intraocular pressure or intra-ocular pressure)) *AND* **TOPIC:** ((trabeculoplast* or goniotom* or trabeculotom* or slt or selective laser trabeculoplast*)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1997-2016"* #2."TOPIC: (Prostaglandin analogs OR Prostaglandin* OR latanoprost OR bimatoprost OR travoprost) *OR* TOPIC: ((Beta blocker OR B-blocker OR Timolol OR Betaxolol OR Levobutonol)) *OR* TOPIC: ((Carbonic anhydrase inhibitor* OR Carbonate dehydratase inhibitor*OR dorzolamide OR brinzolamide)) *OR* TOPIC: (Alpha-agonist* OR brimonidine OR Alphagan) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1997-2016"* #2 AND #1 Limits: 1997-present, English Only
Scopus (193)	(SLT AND glaucoma OR (Prostaglandin OR Beta-blockers OR CAIS OR Alpha-agonist))

Appendix 3: Screening Questions

Level 1 (title screening):
Does the article look at Selective Laser Trabeculoplasty (SLT) OR SLT AND Beta-Blockers OR Prostaglandin analogs OR Carbonic anhydrase Inhibitors, Alpha-agonist and or Open-angle glaucoma?
Yes
No
Unclear

Level 2 (abstract screening):
Are there 20 or more patients/eyes included in the study?
Yes
No
Unclear

Is there a follow-up time of greater than 6 months?
Yes
No
Unclear

Is it a research article (exclude systematic reviews and meta-analyses)? (Not an editorial, pilot study, or opinion)?
Yes
No
Unclear

Level 3 (full article screening):
Does the study look at SLT compared with medical therapy or does it look at the effect of SLT on number of medications?
Yes
No
Unclear

Appendix 4: Data Extraction Sheet for Studies Evaluating SLT versus Medications

Author	year	Slttime	Followuptime	sltdegree	n	M_siopr	Sd_siopr	n	m_miopr	Sd_miopr

Appendix 5: Data Extraction Sheet for Studies Evaluating SLT as an Adjunctive Treatment

Author	year	sltdegree	Followuptime	n	m_mpre	sd_mpre	m_mpost	sd_mpost

Appendix 6: Downs and Black Checklist

		Description of Criteria	Possible Answers
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?	Yes/No
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes/No
	3	Are the characteristics of the patients included in the study clearly described?	Yes/No
	4	Are the interventions of interest clearly described?	Yes/No
	5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?	
	6	Are the main findings of the study clearly described?	Yes/No
	7	Does the study provide estimates of the random variability in the data for the main outcomes?	Yes/No
	8	Have all important adverse events that may be a consequence of the intervention been reported?	Yes/No
	9	Have the characteristics of patients lost to follow-up been described?	Yes/No
	10	Have actual probability values been reported (e.g. 0.035 rather than rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes/No
External Validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes/No/UTD
	12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes/No/UTD
	13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes/No/UTD
Internal Validity-Bias	14	Was an attempt made to blind study subjects to the intervention they have received?	Yes/No/UTD
	15	Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes/No/UTD
	16	If any of the results of the study were based on “data dredging”, was this made clear?	Yes/No/UTD
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes/No/UTD

Appendix 6: Downs and Black Quality Checklist (Continued)

	18	Were the statistical tests used to assess the main outcomes appropriate?	Yes/No/UTD
	19	Was compliance with the intervention/s reliable?	Yes/No/UTD
	20	Were the main outcome measures used accurate (valid and reliable)?	Yes/No/UTD
Internal Validity-Confounding (selection bias)	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes/No/UTD
	22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes/No/UTD
	23	Were study subjects randomised to intervention groups?	Yes/No/UTD
	24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Yes/No/UTD
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes/No/UTD
	26	Were losses of patients to follow-up taken into account?	Yes/No/UTD
	27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance	1-5
UTD: Unable to Determine			

Curriculum Vitae

Name:	Muna Hassan
Post-secondary Education and Degrees:	York University Toronto, Ontario, Canada 2008-2012 BHS The University of Western Ontario London, Ontario, Canada 2014- 2017 MSc
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