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REVIEW ARTICLE

Selective laser trabeculoplasty: past, present, and future

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Abstract

Over the past two decades, selective laser trabeculoplasty (SLT) has increasingly become an established laser treatment used to lower intraocular pressure in open-angle glaucoma and ocular hypertensive patients. In this review we trace the origins of SLT from previous argon laser trabeculoplasty and review the current role it has in clinical practice. We outline future directions of SLT research and introduce emerging technologies that are further developing this intervention in the treatment paradigm of glaucoma.

Introduction

Glaucoma is a progressive multifactorial disease characterised by damage to the optic nerve. It is strongly associated with elevated intraocular pressure (IOP) but may also occur with IOP in the normal range. Glaucoma results in progressive visual field loss and is a leading cause of blindness worldwide, second only to cataract. It is predicted that by the end of the decade, close to 80 million people will have glaucoma, the majority open-angle glaucoma (OAG) [1].

The mainstay of glaucoma treatment is lowering of IOP to slow or prevent further progression and visual loss. This may be achieved by either medical, laser, or surgical means.

Over the past two decades, selective laser trabeculoplasty (SLT) has increasingly become an established treatment to lower IOP in OAG and ocular hypertensive patients.

In this review, we trace the origins of SLT from argon laser trabeculoplasty, review the current role of SLT, and outline both future directions of research and emerging technologies.

Past

Lasers were first used to lower IOP in the 1970s with early attempts meeting limited success. Goniopuncture using the Q-switched ruby laser produced a temporary IOP reduction, whilst high-energy argon laser photocoagulation of the trabecular meshwork (TM) caused acute post-laser IOP spikes [2]. Wise and Witter [3] used argon laser at lower energy levels and reported successful short-term IOP reduction by ~10 mm Hg in 40 phakic eyes, despite 65% of these eyes eventually requiring additional medication.

Anderson and Parrish [4] found that applied radiation energy could be selectively absorbed by a pigmented cell population within a tissue to cause localised damage; a process known as selective photothermolysis (SP). The inherent properties of the tissue provided target selectivity, reducing collateral damage.

SP had two principle requirements; the desired target needed an intracellular chromophore with greater optic absorption at the laser wavelength than surrounding tissue. Second, laser duration could not exceed the time required for thermal diffusion into the tissue (thermal relaxation time) [5].

ALT fulfilled the first requirement of SP, as melanin within the pigmented TM acted as the chromophore. However, the laser duration of ALT (~0.1 s) was longer than the thermal relaxation time of melanin (1 μs) allowing heat generated within pigmented cells to dissipate and damage surrounding TM [5].

ALT: mechanism of action

IOP reduction seen in ALT was mediated by an increase in aqueous outflow, confirmed by both tonographic and aqueous dynamic studies [6, 7]. A mechanical mechanism was postulated in which laser-induced thermal burns of the TM caused collagen and tissue contraction. This reduced the diameter of the inner trabecular ring, reversing collapse of

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the meshwork thus maintaining aqueous outflow [3]. Electron microscopy demonstrated focal coagulative TM disruption with connective tissue and cellular debris deposited within the intra-trabecular spaces [8]. Importantly, ultrastructural TM changes occurred before IOP-lowering response, suggesting the mechanism of action was unlikely to be by mechanical means alone. 'Biological' theories were suggested once ALT was found to modify local cellular signalling pathways to enable increased aqueous outflow [9].

ALT: efficacy

ALT induced an initial 30% reduction in IOP. The response seemed related to pre-treatment IOP and thus eyes with normal tension glaucoma (NTG) showed a smaller effect [2]. ALT was successful as both primary treatment [10] and as an adjunct to maximal medical treatment [6] with IOP reductions reported between 6.4 and 9.7 mm Hg (26–33%).

There were limitations: the effect of ALT diminished over time. Schwartz et al. [11] performed 360° ALT on 72 patients with uncontrolled OAG on maximal medical treatment and found the 77% success rate at 2 years had fallen to 46% at 5 years. Spaeth and Baez [12] treated 109 eyes with uncontrolled OAG on maximal medical treatment with ALT: 32% needed filtration surgery at 1 year, 65% at 5 years, and 95% at 10 years. Failure was highest in the first year and subsequently occurred at 10% per year [13].

The success of ALT in failed eyes was also less than with initial treatment. Richter et al. [14] performed 180° ALT retreatment to 40 eyes that had previously undergone 360° ALT and found only 32% of eyes demonstrated at least 3 mm Hg reduction in IOP.

Baseline predictors of ALT success were higher pre-treatment IOP and increased age. Race was also relevant: black patients had a lower success rate (32%) at 5 years compared to white (65%) [11]. Pigmentary and exfoliative glaucoma showed similar efficacy to primary OAG (POAG), but the largest IOP reductions and earlier failures were noted in exfoliative glaucoma. Other forms of secondary OAG had limited response to ALT with uveitic and developmental glaucomas often showing little or no useful fall in IOP [15].

ALT: adverse effects

The main adverse events related to ALT were transient acute IOP spikes following laser, development of peripheral anterior synechiae (PAS), corneal endothelial changes, and acute anterior uveitis [2]. In one study of 271 eyes, a rise of more than 5 mm Hg occurred in 34% of patients and of more than 10 mm Hg in 12% after 180° of ALT [16].

The frequency and severity of IOP elevations were positively associated with higher energy levels, 360° treatment, more posterior placement of burns, greater angle pigmentation, and a low preoperative outflow facility. Most post-treatment IOP peaks occurred within 2 h and were postulated to be due to TM swelling or obstruction of the trabecular spaces by debris [17].

Development of PAS was another important complication, noted more frequently with higher powers [18]. One study found a three times higher incidence of encapsulated blebs in eyes previously treated with ALT (15.4%) compared to eyes without laser (4.7%) [19].

Role of ALT

The benefit of ALT was as an outpatient procedure that was quick, well tolerated, and safe. It avoided the inconvenience and side effects of regular medical treatment and delayed the risks of surgery. However, loss of effect with time and association with bleb encapsulation in drainage surgery meant ALT was considered an adjunct to maximal tolerated medical treatment and a means of delaying surgery.

One pivotal study evaluated ALT's role as a primary treatment: The Glaucoma Laser Trial Research Group found better IOP control with ALT alone compared to a single medication at 6 months, 1 year, and 2 years but inferior control at 5 years or if two medications were used [10]. Compared to surgery, trabeculectomy achieved significantly lower IOPs with reduced diurnal IOP fluctuation [20].

Present

SLT: introduction

Introduced by Latina and Park in 1995, SLT uses a 532 nm Q-switched, frequency-doubled Nd:YAG laser that delivers a shorter pulse duration (3 ns). It satisfies the dual criteria of SP, preventing heat dissipation outside of pigmented TM cells and causing less collateral damage [21].

Since receiving FDA approval in 2001, SLT has increasingly been adopted into practice. In the USA, 75 647 trabeculoplasties were performed in 2001, and this figure had increased to 142 682 procedures in 2012 [22].

The benefits are clear. The procedure is short, outpatient-based with quick recovery and good safety profile.

The role of SLT in the treatment of glaucoma is still not well defined. In this section we review the literature to give current perspectives on aspects related to SLT relevant to its role in clinical practice.

SLT: mechanism of action

Tonographic and aqueous dynamic studies have demonstrated that SLT increases aqueous outflow through the TM [23, 24].

Histopathological comparisons of human eyes that have undergone SLT vs ALT [25] report lesser disruption to the TM in eyes post SLT. Higher power SLT can cause more extensive TM damage than lower power suggesting [26] that damage could be energy dose-dependent.

Since limited structural damage occurs to the TM, the mechanical and structural theories which have been suggested to explain ALT's mechanism of action do not fully apply to SLT. Moreover, SLT has been demonstrated to induce biological changes that modulate increased aqueous outflow through the TM, including changes in gene expression, cytokine secretion, matrix metalloproteinase induction, and TM remodelling [5].

Using microarray analysis, SLT has been shown to modulate expression of genes related to cell motility, extracellular matrix production, membrane repair, and reactive oxygen species production [27]. In vitro studies have demonstrated an increase in pro-inflammatory cytokine expression, including interleukin-1-alpha, interleukin-1-beta, tumour necrosis factor-alpha, and interleukin-8 post SLT [9].

These cytokines increase stromelysin-1 expression (MMP-3), a matrix metalloproteinase implicated in TM extracellular matrix remodelling to increase aqueous outflow through the juxtacanalicular meshwork [28].

Increased TM monocyte recruitment has also been noted post SLT, a result of increased chemokine production [29]. Monocytes increase aqueous outflow in vivo and increase Schlemm's canal permeability in vitro, by further cytokine secretion or directly phagocytosing debris within the TM. Local increases in endothelin-1 are thought to contribute to the acute IOP rise seen post SLT [30] whilst rises in lipid peroxide levels and decrease in antioxidant enzymes may be due to the increased inflammatory response precipitated after laser [31].

In vitro studies demonstrate that SLT and prostaglandin (PGA) analogues may share a common pathway of action by inducing intercellular junction disassembly in Schlemm's canal and TM cells thus increasing aqueous permeability [32].

Clinical technique

Laser treatment

SLT is performed using topical anaesthetic and a gonioscopic lens with coupling medium. The spot size (400 microns) is fixed but number of shots, energy level, and therefore total energy delivered are variable.

In their pilot study, Latina et al. [21] used 50 non-overlapping shots placed over 180° of the TM. The energy level was set at 0.8 mJ and decreased by 0.1 mJ increments until no visible effects or bubbles were observed. In current practice, typical treatment parameters are 50–100 shots applied over 180°–360° with energy adjusted to 0.6–1.4 mJ and an end point of just visible tissue reaction or small microbubbles.

Studies have evaluated whether treating different degrees of the TM with SLT influences IOP lowering. Chen et al. [33] compared OAG patients that received 90° SLT vs 180° SLT and found no significant difference in IOPs at 1, 4, and 7 months between groups (P=0.21). In a RCT comparing 180° SLT vs 360° SLT in patients with untreated POAG/OHT, mean IOP reduction at 1 month was 6.9 and 8.2 mm Hg in the two groups respectively, with no significant difference noted (P=0.35) [24]. Nagar et al. [34] compared IOP lowering of 90°, 180°, and 360° SLT, and found no difference between 180° and 360° SLT treatments at 12 months' follow-up [34]. Both groups were more effective than the 90° SLT group.

Energy settings have also been investigated. Tang et al. [35] compared 39 patients receiving 100 shots of 360° SLT using low energy settings (0.3–0.5 mJ) vs 35 patients who received 100 shots of 360° SLT using standard energy settings (0.6–1.0 mJ). No difference in IOP lowering between groups at all time points up to 1 year was noted. Furthermore, there was reduced incidence of adverse events in the lower energy group. In contrast, Lee et al. [36] found greater total SLT energy was associated with a greater IOP lowering, but this study was limited by small sample size (n=49 eyes, 1 eye per patient analysed from 25 NTG, 24 POAG patients) and short follow-up duration (1 month).

A recent study has evaluated using a shorter laser pulse duration of 1 ns compared to conventional 3–5 ns and found no difference in IOP lowering or adverse events between the two arms in treatment-naive POAG, OHT, and NTG patients with 6-month follow-up [37].

Post laser treatment

Topical IOP-lowering medications are routinely prescribed preoperatively or immediately post SLT to prevent IOP spikes. A meta-analysis of 22 trials involving 2112 patients investigated the efficacy of perioperative medications to prevent increased IOP post laser [38]. Patients receiving medication had a lower risk of the IOP increasing by 10 mm Hg or more within the first 2 h compared with those receiving no medication or placebo (risk ratio (RR) 0.05, 95% confidence interval (CI) 0.01–0.20) and up to 24 h (RR 0.22, 95% CI 0.11–0.42). There was no advantage to

medication being administered before or after laser and no difference in effectiveness between different alpha2-agonists.

Topical anti-inflammatory drops are commonly prescribed post trabeculoplasty to mitigate early inflammation. As SLT's effects are purported to act partly via a biological pathway (including production of pro-inflammatory cytokines), the potential counter-productive nature of prescribing topical anti-inflammatories has been considered.

A prospective RCT of 132 eyes evaluated usage of topical indomethacin 0.1% or dexamethasone 0.1% TDS for 1 week vs control (no treatment) post SLT [39]. No statistically significant difference in anterior chamber reaction, conjunctival redness, reported pain, or IOP lowering between groups at all time points was found. This supports previous studies that have concluded anti-inflammatory drops after SLT do not cause a significant reduction in inflammation or altered IOP-lowering efficacy [40, 41].

Clinical efficacy of SLT in POAG and OHT patients

The first SLT efficacy data reported by Latina et al. [42] who treated 180° of TM demonstrated 6 mm Hg mean IOP reduction in uncontrolled POAG eyes previously treated with ALT and 5.8 mm Hg in eyes without prior ALT. Overall, 70% of eyes exhibited an IOP reduction of ≥3 mm Hg.

Average IOP reduction following SLT is reported to be 21.8-29.4% at 6 months, 16.9–30% at 12 months, 7.7–27.8% at 2 years, 24.5–25.1% at 3 years, 23.1–29.3% at 4 years, 22.6–32.1% at 5 years, and 22.8% at 6 years [43].

The IOP-lowering effect of SLT diminishes with time. On the basis of the commonly adopted success criteria of IOP reduction >20% from baseline IOP, success rates vary from 66.7 to 75% eyes at 6 months, 58 to 94% at 12 months, 40 to 85% at 2 years, 38 to 74% at 3 years, 38 to 68% at 4 years, and 11.1 to 31% at 5 years [43].

SLT vs ALT in OAG/OHT patients

To date, there are at least 10 RCTs comparing SLT vs ALT [44]. All studies have reported no difference in IOP reduction between the two treatments. A meta-analysis [45] evaluated four RCTs comparing efficacy of SLT and ALT [46, 47, 48, 49]. Studies included patients with POAG, pseudoexfoliation (PXF), pigment dispersion syndrome, uveitic glaucoma, and NTG. In all studies, patients had uncontrolled IOP despite maximally tolerated medical treatment or previous ALT. Patients received 180° of treatment in both groups. Overall, there was a pooled total of 150 eyes in the SLT group and 140 eyes in the ALT group. Definition of success varied between the studies. Three out of four studies aimed for >20% IOP lowering without need for further surgery [46, 47, 49], whereas one study was less stringent—opting for 15% IOP reduction [48].

Difference in pooled mean IOP reduction between both groups was not significant at −0.5 mm Hg (95% CI: −1.5 mm Hg, 0.4 mm Hg). Two studies [46, 47] assessing the effect of SLT and ALT on reducing the number of medications required found no significant difference and treatment success for SLT and ALT was similar between both groups (P>0.05). Overall, SLT demonstrated comparable efficacy with ALT in patients on maximally tolerated medical treatment [45].

These findings agree with two previous meta-analyses evaluating SLT vs ALT [50, 51]. A third meta-analysis, comprising of 6 studies reported SLT to have a superior IOP lowering efficacy to ALT [52]. This difference could have arisen as this meta-analysis also included quasi randomised controlled trials as part of their analysis.

SLT vs topical medication in OAG/OHT patients

Multiple trials have compared SLT against topical medication in treating OAG and OHT patients [44]. Within SLT groups, there is often variability in the degree of TM treated. Common parameters used by studies include 90^0, 180^0 or 360^0 SLT.

Nagar et al. [34] performed a RCT comparing 90°, 180°, and 360° SLT vs latanoprost in OAG/OHT patients. Success rates were significantly higher in the latanoprost group compared to the 90° and 180° SLT groups but similar to the 360° SLT group. This was confirmed in a subsequent RCT where 20 patients receiving 360° SLT were compared against 20 patients taking 0.005% latanoprost [53]. SLT decreased IOP by 4.7 mm Hg (95% CI 3.6–5.7 mm Hg; P<0.01) with a similar reduction from latanoprost. Both were found to reduce diurnal IOP fluctuation with no difference in treatment success at last follow-up (4–6 months) between groups (P=0.4).

To date, two meta-analyses comparing SLT with medication have been performed [45, 54]. Both include four RCTs, but Li et al. [54] also included one further prospective non-randomised trial [55]. In four out of five studies, 360° SLT was performed.

In three of the five studies, the medication arm consisted of PGA monotherapy [34, 53, 55], whereas in the other two studies [56, 57], different topical agents, including combination drops were permitted to be used.

Definition of success varied between studies—four studies compared SLT with medication (either PGA monotherapy or different topical medications used in combination) in terms of IOP reduction whilst one study classified success as meeting a target IOP. When using IOP

reduction as a success criterion, one study chose IOP reduction as IOP <21 mm Hg after intervention [56] whilst the remaining three used at least 20% IOP reduction from baseline [34, 53, 55].

Analysis included 492 eyes of 366 patients with OAG. SLT showed no significant difference in IOP reduction compared to medication (either PGA monotherapy or different topical medications used in combination) (weighted mean difference 0.6, 95% CI: −0.24, 1.43). There was no significant difference in achieving target end-point success rates between groups (pooled OR 0.84, 95% CI: 0.42, 1.68). Similar analyses performed by Wong et al. [45] also demonstrated no significant difference between SLT and medication (either PGA monotherapy or different topical medications used in combination).

In summary, meta-analysis data suggests SLT is as effective as medication (either PGA monotherapy or different topical medications used in combination) for IOP control, with similar success rates. Limitations to consider include data being derived and pooled from trials of different durations with missing data during follow-up, as well as different definitions being used to define success.

SLT vs surgical treatments in OAG/OHT patients

No studies have evaluated SLT against glaucoma surgery. ALT has previously been evaluated against trabeculectomy and found to be inferior at IOP lowering [20]. Similar comparisons with SLT would be expected to yield similar results. The AGIS study looked at the impact of timing of ALT before versus after trabeculectomy and found no difference for white patients, but a small adverse impact of prior laser on trabeculectomy function for black patients [58].

More recently, Fea et al. [59] compared 25 eyes receiving SLT vs 31 eyes receiving placement of Hydrus microstent, a microinvasive glaucoma surgery (MIGS) device. At 12 months, a significant decrease in IOP was noted in both groups. Comparison between groups revealed no significant difference in mean IOP reduction but a threefold greater reduction in medication use in the hydrus group compared with SLT was found (−1.4±0.97 vs −0.5 ±1.05, P=0.001). Forty-seven percent of patients were medication-free at 12 months in the hydrus group vs only 4% in the SLT group.

A higher frequency of postoperative complications were seen in the hydrus group—three patients experienced a temporary reduction of visual acuity post-operatively and two patients had postoperative IOP spikes vs no complications noted in the SLT group.

These results suggest MIGS devices have a similar IOP-lowering efficacy to SLT and can reduce the number of medications that patients take. However, MIGS insertion is a surgical procedure performed in theatre associated with an increased adverse event profile. Further studies are needed to fully compare MIGS with SLT to evaluate effectiveness, safety, and cost.

SLT as primary treatment in OAG/OHT patients

Most studies investigating primary SLT have compared efficacy against topical medication. They have found 'primary' SLT to have a similar IOP-lowering efficacy and success rate to topical medication using a variety of success criteria.

Many of these studies have included patients taking topical medications stopped for a variable duration (4 weeks to 3 months) before SLT [34, 47, 55]. Such patients are not truly treatment-naive. Despite a washout period to mitigate against residual effects of prior topical treatment, some studies have shown SLT to be less effective when used following topical treatment. McIlraith et al. [55] reported clinical outcomes in 87 eyes on topical glaucoma medication discontinued 4 weeks before SLT. IOP reduction was significantly less compared to the treatment-naive group (8.1 vs 6.4 mm Hg, P<0.001). Explanations include inadequate washout time or simply that SLT is more effective as a primary treatment.

SLT as adjunct treatment in OAG/OHT patients

Similar to ALT, SLT has also been investigated as an adjunct treatment for patients on concurrent topical therapy as a means of further IOP reduction. Weinand et al. [60] reported clinical outcomes of 52 POAG eyes that received adjunct SLT whilst on topical medical treatment. Average IOP reduction from baseline was 24.3% (6.0 mm Hg) at 1 year, 27.8% (6.12 mm Hg) at 2 years, 24.5% (5.53 mm Hg) at 3 years, and 29.3% (6.33 mm Hg) at 4 years. In a RCT of 41 medically controlled POAG patients evaluating the effect of adjuvant SLT vs medication alone [61], at 6 months, average IOP post SLT was 7.6% lower than the medication group (P=0.03) with the SLT group requiring significantly fewer anti-glaucoma medications compared with the medication group (P=0.02). Adjunct SLT in POAG patients with uncontrolled IOPs despite medical therapy has also been shown to be effective [62, 63], whilst other studies have demonstrated a reduction in number of concurrent glaucoma medications needed to control IOP following SLT [62, 64].

Woo et al. [65] investigated the effects of concurrent topical medication on efficacy of first-time adjunct SLT. Patients were grouped into different groups (0–3) based on the number of medications they were taking before SLT and then followed for up to 5 years. Average IOP reduction following SLT varied between 21.8 and 29% across all

groups at 6 months, and between 23.6 and 25.6% at 5 years with no statistically significant difference noted between groups. Mixed model analysis demonstrated no significant interactions between number of medications and post-treatment IOP response over time and was in agreement with previous studies demonstrating this. Importantly however, of the 206 patients initially in the study, only 55 patients remained at 5 years due to loss to follow-up and patients requiring additional intervention. This makes interpretation of the longer-term outcomes difficult and reiterates that the effect of SLT is largely temporary.

SLT following other treatment interventions

SLT is effective as an adjunct in patients who have previously undergone ALT. Mean IOP reduction at 1 year in 30 OAG patients receiving primary SLT (23%) was no different to 27 OAG patients receiving SLT after prior ALT (19.3%) [66].

Zhang et al. [67] investigated the efficacy of SLT in advanced POAG patients who despite previous trabeculectomy had uncontrolled IOPs requiring additional topical treatment. In 18 eyes, mean IOP was reduced from 21.3 to 16.2 mm Hg at last follow-up with 77.7% of patients achieving a reduction of >20% from pre-treatment IOP. The study was small with a short follow-up (9 months) limiting the conclusions that can be made.

In conclusion, SLT is effective as an adjunct in OAG patients on medical treatment. It is effective at delaying the need for surgery in uncontrolled OAG patients but also may have a role in post-surgical patients as a means of further IOP reduction.

IOP fluctuation reduction with SLT

Large diurnal IOP fluctuations are considered by some to be an independent risk factor for glaucoma progression [68]. Nagar et al. [53] reported that SLT and PGAs are successful at reducing IOP variation in POAG patients over the whole follow-up period, but PGAs are more effective (3.6 mm Hg, 95% CI 3.2–3.9 vs 2.5 mm Hg, 95% CI 2.2–2.9 mm Hg, P=0.04). Kiddee et al. [69] confirmed this in POAG and NTG patients, and also demonstrated that PGAs reduce IOP fluctuation throughout a 24 h period, whereas SLT's effect is pronounced at night. The extent of SLT treatment may also influence IOP fluctuation [70] with 360° SLT being shown to reduce IOP fluctuation >180° treatment.

Contact lens sensors (CLS; SENSIMED Triggerfish, Sensimed, Switzerland) have been used to continuously measure changes in ocular dimensions over 24 hours which are then interpreted as being related to fluctuations in IOP. At 1 month after laser, in 18 NTG patients treated with 360° SLT [71] who had achieved treatment success (≥20% IOP reduction), there was a 24.6% reduction in 24 h IOP variability, whereas in unsuccessful patients, the IOP variability increased by 19.2%. This differs to a study by Tojo et al. [72] who also investigated 24 h IOP fluctuations using CLS in 10 NTG patients. They found the range of IOP fluctuations was not significantly changed between pre and post SLT over 24 h (P=0.77) or during the daytime diurnal period (P=0.92), but the range of IOP fluctuations during nocturnal periods was significantly decreased (P=0.014). SLT was thus shown to significantly lower IOP and decrease nocturnal IOP fluctuations in NTG patients supporting the findings of Kiddee *et al.* [69]

Repeatibility of SLT

The IOP-lowering effect of SLT diminishes with time. As SLT causes minimal structural TM damage, repeat treatment has been considered feasible in suitable patients requiring further IOP reduction. To date, seven studies report outcomes of repeat 360° SLT.

Ayala et al. [73] performed a RCT to evaluate the effect of repeat SLT in POAG/PXF glaucoma patients. Patients were treated initially with 180° SLT in the lower half of the TM and then randomly received further SLT in the previously treated TM or in the 180° upper untreated TM. In all, 40 patients were included in both groups. The study found no significant differences in IOP between the retreatment groups at all time points but follow-up was only 6 months (P=0.66). This suggests repeat SLT can be applied to any TM area with similar efficacy and supports the theory that SLT retreatment is similarly effective to primary treatment.

Francis et al. [74] retrospectively evaluated 137 eyes with POAG or secondary OAG (excluding uveitic glaucoma) that had undergone two 360° SLT treatments at least 6 months apart. Percentage IOP reduction between the two treatments at 12–15 months was not significantly different (14.5 vs 10.9%, P=0.11). A sub-analysis of 62 patients where baseline IOPs were matched demonstrated 20% success at 12 months following both initial and repeat SLT (success criteria: IOP between 5 and 21 mm Hg and IOP reduction ≥20% from baseline at 12 months).

Hong et al. investigated 44 eyes with uncontrolled OAG on maximum tolerated medical therapy where primary 360° SLT had initially been successful (success criteria: ≥20% peak IOP reduction). Repeat 360° SLT achieved success in 43.2% of eyes at 5–8 months compared to 50% success at initial SLT [75]. There was no statistically significant difference between primary SLT and repeat SLT success rates. These findings are supported by Polat et al. [76], who performed a retrospective review of 38 eyes with OAG uncontrolled on medical therapy that had undergone two

successive 360° SLT treatments. They found a significant IOP reduction from baseline after both treatments up to 24 months' follow-up. Kaplan–Meier survival analysis demonstrated median survival time of 9 months for initial SLT and 12 months for repeat SLT when using a definition of success as ≥20% reduction in IOP from baseline.

In a separate study of newly diagnosed POAG patients, repeat SLT had a similar mean IOP reduction and treatment success rate (IOP reduction ≥20%) compared to primary SLT in 42 eyes [77]. Mean duration of success in repeat treatment (13.1 months) was longer than initial treatment (6.9 months). This difference was not statistically significant.

Repeat SLT can be successful irrespective prior SLT success. Khouri et al. [78] performed repeat 360° SLT after initial SLT in 51 OAG eyes. Eyes were stratified into those that had a successful response to initial SLT (≥20% IOP reduction from baseline) vs a modest response (<20% IOP reduction from baseline). Forty-one per cent of eyes met the success criteria after primary SLT and 43% after repeat SLT. In the 22 eyes with treatment success after repeat SLT, the proportion of eyes with initial successful response (11 eyes) and modest response (11 eyes) was the same. In a different study [79] of longer-term outcomes of repeat 360° SLT, 29% of eyes achieved IOP reduction >20% at 24 months compared to 36% of eyes following initial treatment—this was not statistically significant.

Overall, repeat SLT appears to be comparable to initial SLT. It achieves a similar absolute level of IOP control but mean IOP reductions following repeat SLT appear to be smaller. This could be explained by residual effects of initial SLT not typically wearing off before retreatment. In addition, selection bias may apply with repeat SLT, where patients who respond to initial SLT are offered retreatment. Larger prospective studies investigating repeat SLT are required to investigate this further.

SLT in PACG

SLT is not commonly performed in primary angle-closure glaucoma (PACG) patients. Visualisation of the TM within the angle is required, which can be limited in these patients. Nonetheless, the efficacy of SLT in PAC/PACG patients where some of the angle is open and visible for treatment has been evaluated.

Narayanaswamy et al. [80] performed a prospective RCT to evaluate the effect of SLT in PAC/PACG patients that had previously undergone laser iridotomy. Following iridotomy, the angle was open with atleast 180° visible posterior TM on gonioscopy, but IOPs were still >21 mm Hg. A total of 96 eyes were randomised to SLT and 99 eyes to PGA therapy. At 6 months, IOP decreased by 4.0 mm Hg (95% CI, 3.2–4.8) in the SLT group (P<0.001) and by 4.2 mm Hg (95% CI, 3.5–4.9) in the PGA group (P<0.001). There were no differences between groups in the absolute mean reduction of IOP (4.0 vs 4.2 mm Hg, P=0.78) or in percentage IOP reduction (16.9 vs 18.5%, P=0.52). The procedure appeared safe in PAC/PACG patients with only one patient suffering from a transient IOP spike.

In a retrospective study comparing SLT in 59 eyes with PAC/PACG post PI vs 59 eyes with POAG [81], SLT achieved an average IOP reduction of 38% from baseline in the PAC/PACG group vs 32.7% in the POAG group (P=0.08). Treatment criteria in the PAC/PACG group required at least 180° of visible TM. In both groups, SLT was performed as either a primary treatment for uncontrolled IOP, as an adjunct for patients with uncontrolled IOP on maximal tolerated medical therapy or for those intolerant to medical therapy. Average postoperative follow was 10–11 months. In both groups, SLT permitted reduction of glaucoma medication (1.6 medications in PAC/PACG vs 1.5 medications in POAG, P=0.40). There was no significant difference in frequency of post laser IOP spike between groups.

SLT in NTG

SLT can be of benefit in NTG patients. Patients have lower pre-treatment baseline IOPs compared to POAG patients, so the absolute IOP reduction is often less. Moreover, when using commonly used success criteria (IOP reduction >20% from baseline), the success rates in NTG patients appear lower.

Lee et al. [82, 83] performed a prospective study of 41 eyes with NTG patients evaluating 360° SLT efficacy. At 12 months, average IOP reduction was 14.7% from baseline levels. Absolute success (IOP reduction of >20% from baseline washout IOP without addition of additional medication) was 22% at 12 months and 11.1% at 24 months.

SLT in pseudoexoliation glaucoma

SLT in PXF patients demonstrates comparable IOP lowering to OAG patients [84, 85]. In their review, Kennedy et al. reported a mean IOP reduction for PXF eyes of ~31.5% at 12 months and 31.4% at 18 months. Sixty-four per cent of patients maintained ≥20% IOP reduction at 18 months and 47% at 36 months [86]. PXF also does not appear to be a risk factor for post-laser complications including inflammation.

SLT in pigmentary glaucoma

Koucheki et al. [87] assessed the efficacy of 360° SLT in a cohort of patients with pigmentary glaucoma (PG), POAG, and PXFG. At ~16 months, mean IOP reduction was 16.7%

in POAG, 16.6% with PEX, and 14.5% in the PG group. Percentage of IOP reduction was not significantly different between groups (P=0.696) and no significant difference in success rates were noted (P=0.597).

Interestingly, increased frequency of post-procedure pain, inflammation and IOP spikes were noted in the PG group. A higher rate of further interventions, eg, repeat SLT or trabeculectomy was also observed in the PG group (26.1%) vs the other two groups (POAG 16.5%, PXF 13.6%, P<0.001). Similar associations have been found previously where increased post-laser IOP spikes were noted in patients with heavily pigmented TM [88]. Increased TM pigmentation in PG could cause more energy absorption following SLT resulting in increased pain. This has led to suggestions that lower energy settings be used in PG patients.

In a different study assessing time to failure in 30 PG eyes that had received 180° SLT [89], average time to failure was 27.4 months. Two eyes experienced a post-laser IOP spike however only 180° of TM was treated in this study and lower energy was used limiting comparisons with other studies.

SLT in secondary glaucoma

Few studies have investigated SLT efficacy in secondary glaucoma. Rubin et al. [90] reported the results of seven secondary steroid-induced glaucoma eyes that underwent SLT after intravitreal triamcinolone injections for macular oedema (six eyes) or post central retinal vein occlusion (one eye). Patients had elevated IOP despite maximum tolerated medical therapy (mean preoperative IOP 38.4 mm Hg±7.3) but following SLT, IOP decreased to 25.9 mm Hg±8.8 at 1 month (P<0.007), 23.9 mm Hg±10.6 at 3 months (P<0.006), and 15.7 mm Hg±2.2 at 6 months (P<0.001). Four patients required repeat SLT and two patients failed after the 3-month visit.

Bozkurt et al. [91] investigated whether prophylactic SLT could reduce or prevent the IOP rise often seen following intravitreal steroid injection. In their prospective study, 15 eyes underwent 360° SLT ~8 days before intravitreal triamcinolone injection for diabetic macular oedema. IOP rise from 1 to 3 months was reduced and this effect was maintained up to 6 months.

In a study of 15 uveitic eyes that had received intravitreal steroid to control inflammation, the efficacy of SLT to reduce IOP was evaluated [92]. Mean IOP before SLT was 30.57 mm Hg and was lowered to 14.85 mm Hg (51.4% reduction) at 1 month, 13.42 mm Hg (55.7% reduction) at 6 months, and 15.14 mm Hg (50.4% reduction) at 12 months. Seven eyes (46.7%) achieved success criteria (IOP <22 mm Hg and/or a 20% or more reduction in IOP from the pre-SLT IOP) at 1-month, 6-month, and 12-month follow-up visits. One treated eye developed a prolonged IOP spike but there were no other adverse events.

Zhang et al. [93] evaluated the efficacy of SLT in 42 eyes with silicone oil-induced secondary glaucoma. 360° SLT was performed and mean IOP decreased from 23.1±1.9 mm Hg pre-treatment to 18.4±3.7 mm Hg after treatment (P<0.05). Mean number of anti-glaucoma medications used for IOP control also decreased from 2.17±1.21 to 1.25±0.89 (P<0.05).

Overall, SLT appears to have some clinical efficacy in secondary glaucoma patients. Further large-scale studies are required to fully investigate this further.

Predictors of success: SLT

SLT is not successful in all treated eyes. Studies have analysed baseline patient factors that may predict success, frequently by performing univariate and multivariate regression analyses to seek associations.

Predictors of success comparisons between studies is difficult as multiple variations exist within studies, including study size, patient demographics, glaucoma subtype treated, SLT parameters, follow-up length, and definition of 'success' itself. This creates difficulty in establishing 'definite' robust predictors of SLT success which is reflected in the literature, where multiple studies have varying results.

The most consistently reported patient factor, which predicts SLT success is elevated baseline IOP [86]. This is partly explained by the commonly used definition of success (IOP reduction ≥20% from baseline) tending to favour elevated baseline IOPs, as the magnitude of IOP reduction post treatment is often greater with higher IOPs. This is reflected in NTG studies where baseline IOPs are lower and both absolute IOP reductions and success rates are also lower compared to other subtypes [82, 83]. One recent study suggested that patients with pre-treatment baseline of <14 mm Hg may not benefit from SLT at all [94].

A limitation of such success criteria is that though they are a marker of IOP reduction, they may not reflect real-world clinical practice. Patients may achieve >20% IOP reduction from baseline following SLT, but IOP may still be relatively elevated and too high to prevent glaucoma progression. Few studies have used pragmatic individualised target IOPs and assessed 'pursuit of control' for different treatments to obtain target IOPs [57].

Conversely, higher pre-treatment baseline IOPs may in fact be associated with increased treatment failure post SLT [95]. Patients with higher pre-treatment IOPs are more likely to need repeat SLT or surgery as the magnitude of IOP reduction to control disease progression is larger and unachievable by single SLT treatment alone. Other patient factors including sex, race, age, glaucoma type, TM pigmentation,

lens status, and central corneal thickness have been investigated and found not to be predictive of SLT success [86, 94]. Corneal biomechanical markers such as corneal hysteresis and corneal resistance factor may be useful in helping to model the IOP-lowering effect of SLT [96].

Investigating the effect of pre-existing topical medication on SLT success, Woo et al. [65] found no significant difference in success rate based on number of concurrent topical medications. In contrast, Lee et al. [97] found using multiple topical medications particularly topical carbonic anhydrase inhibitors was associated with SLT treatment success. Bruen et al. [98] found that pre-treatment with PGAs was associated with a decreased IOP-lowering response. This is feasible as both SLT and PGAs have been purported to share a common mechanism of action [32].

Complications & adverse events

SLT is a safe procedure, which is well-tolerated with low complication rates. Complications associated with SLT are usually transient and self-limiting.

IOP spikes immediately post laser can occur, with reported rises of ≥5 mm Hg being reported in up to 28% of eyes [86]. An association between IOP spikes has been noted in patients with PG and heavily pigmented TMs [87].

Anterior chamber inflammation is also common post SLT with up to 83% of eyes demonstrating some degree of inflammation [99]. Considering the biological changes that SLT induces, including release of pro-inflammatory cytokines, some regard acute anterior uveitis as a predictable consequence of treatment. This inflammation is usually transient.

Unlike ALT, the development of PAS is uncommon post SLT. In their meta-analysis, Wong et al. [45] noted only 2.86% of cases developed PAS with increased occurrence after repeat SLT [100]. Retinal changes post SLT are also rare, but those described include cystoid macular oedema (often in patients with predisposing conditions), development of subretinal fluid, and choroidal effusions [99].

Transient corneal endothelial changes are well described post SLT. These can occur acutely, within an hour of treatment and are mostly self-limiting with no lasting changes to visual acuity, central corneal thickness, or endothelial cell count [101]. A few case reports of transient corneal oedema and haze have been reported with and without residual corneal stromal scarring and hyperopic shift [102–104].

Cost-effectiveness of SLT

The treatment of OAG/OHT imposes significant costs on health-care systems. The total annual cost in Australia for 2005 was $1.9 billion, of which $355 million was health system costs [105]. Direct and indirect costs are higher for severe disease states (US$623 for mild POAG to US$2511 for severe POAG) suggesting early effective IOP control could reduce future costs [106].

In the USA, Cantor et al. [107] compared costs of medically uncontrolled glaucoma treated with either further medications vs SLT or surgery if required. Using Markov modelling and cost assumptions based on Medicare fee schedules, they found 5-year cumulative costs per patient were $6571, $4838, and $6363 in the medication, SLT, and surgery arms, respectively. An Australian study modelled the cost benefit of laser trabeculoplasty as primary treatment compared to conventional medical treatment and found a saving of $2.50 for every $1 spent on laser treatment, compared to initial medical therapy [105, 108]. Furthermore, cost savings were projected to continue increasing over time since with an ageing population, the prevalence, burden, and treatment needed for POAG were also going to increase [105].

Seider et al. [109] calculated the time threshold at which bilateral SLT would become less costly than bilateral use of topical medication by dividing total costs of SLT by monthly costs of each medication. They found SLT became less costly than most brand-name medications within 1 year and less costly than generic latanoprost and generic timolol after 13 and 40 months, respectively. This is supported by Lee and Hutnik [110] who compared projected 6-year costs of primary SLT vs primary medical therapy in OAG treatment in a Canadian health-care model. If primary SLT had to repeated between 2 and 3 years, use of primary SLT over mono-, bi-, and tri-drug therapy produced a 6-year cumulative cost-saving between $580.52, $2042.54, and $3366.65 dollars per patient, respectively. Guedes et al. [111] confirmed this using modelling to show primary SLT demonstrated better cost-effectiveness than topical treatment in the management of both mild and moderate glaucoma disease states.

In a separate analysis comparing 5-year costs of initiating OAG patients on three different treatment arms—initial medication, initial SLT, or insertion of × 2 MIGS (iStent) devices [112], the projected average cumulative cost at 5 years was lower in the SLT arm ($4730) vs medications arm ($6217). The iStent arm was projected to be cheapest ($4420) despite highest initial year zero costs.

Cost-effectiveness studies of SLT have yet to be performed in the UK. A large, UK-based NIHR-HTA cost-effectiveness study (the 'LiGHT' Trial) will report its findings from 718 patients in 2018 and will determine whether SLT would be similarly efficacious and cost-effective in an NHS setting.

Quality of life and SLT

The potential benefits of SLT are clear. It is a proven alternative to medication with comparable clinical efficacy, avoiding medication-related side effects and compliance issues. Despite this, there is little evidence to evaluate whether these benefits manifest as a difference in quality of life.

In a RCT of 41 medically controlled POAG patients randomly allocated to receive either additional 360° SLT (n=22) or continue with their usual treatment (n=19), quality-of-life outcomes were measured at baseline and 6 months using the Glaucoma Quality of Life-15 (GQL-15) and Comparison of Ophthalmic Medications for Tolerability (COMTOL) survey scores. No statistically significant difference in the 6-month GQL-15 or COMTOL score as compared to baseline (P≥0.4) or between the two treatment groups (P≥0.2) were noted despite greater IOP reduction and reduction in number of medications in the SLT group. This is different to De Keyser et al. [113] who used a different validated assessment tool for quality of life —the 'Treatment Satisfaction Survey for Intraocular Pressure' and found significant improvement in parameters, including side effects, eye appearance, convenience of use, and ease of administration at 12 months compared to topical treatment.

Further large-scale studies are needed to evaluate whether SLT has a better quality of life compared to topical treatments.

Future

Newer laser trabeculoplasty procedures are emerging and currently under investigation. Pilot studies have compared their efficacy against conventional SLT though further large-scale research is required to establish whether any of these newer modalities could supersede SLT in the future.

Micropulse diode laser trabeculoplasty

Diode laser trabeculoplasty (DLT) was first demonstrated to be effective at IOP lowering in the early 1990s [114] but was noted to cause similar coagulative damage as ALT [115]. Micropulse DLT (MDLT) was first described by Ingvoldstad *et al.* [116] This technique uses trabeculoplasty with subvisible (subthreshold) applications of repetitive short diode (532, 577, or 810 nm) laser pulses spaced by a long relaxation time with spot size of 300 μm. MDLT does not cause coagulative damage to the TM [117] and there is no blanching or bubble formation over the TM during the treatment. Post-treatment inflammation is minimal hence no anti-inflammatory medications are required. MDLT results are variable—some studies report limited IOP lowering success [118] whilst others report better results with mean IOP reduction between 19.5-22% with a good safety profile [119, 120]. In a comparison with ALT, the percentage of eyes with IOP reduction >20% from baseline was lower with MDLT compared with ALT [121]. No large studies exist comparing its use with SLT.

Titanium sapphire laser trabeculoplasty (TLT)

Titanium sapphire laser trabeculoplasty (TLT) uses near-infrared energy (790 nm) in short pulses (5–10 μs) with a spot size of 200 μm. The near-infrared wavelength is believed to penetrate deeper (~200 μm) to the inner and outer walls of Schlemm's canal as well as the collector channels and ciliary body. The laser is believed to be selectively absorbed by pigmented phagocytic cells, preserving the TM tissue [122].

The total radiation energy of TLT is ~250 times that of SLT but is delivered over a longer time period, resulting in a longer thermal relaxation time, causing minimal collateral coagulative damage as a result [123].

In a small RCT comparing TLT vs SLT in OAG/OHT patients, 18 patients received 360° TLT vs 19 patients received 360° SLT. At 12 months, mean IOP reduction was 22% from baseline in TLT group and 20% in SLT group. At 2 years, mean IOP reduction was 35% in TLT group and 25% from baseline. No statistically significant differences in IOP or success rates were noted between groups. Treatments had a similar adverse events profile but despite this, some concerns remain about the long burn duration and deeper penetration of TLT compared to SLT [123].

Pattern scanning laser trabeculoplasty

The PASCAL photocoagulator (OptiMedica Inc., Santa Clara, CA, USA) was introduced in 2006 for semi-automated photocoagulation of the retina [124]. This technology uses short pulse durations (10–20 ms), 100 μm spot size, and computer-guided predetermined pattern of spots. This results in reduction of thermal diffusion and surrounding tissue damage whilst permitting many more shots to be applied per area of TM [117]. In a recent RCT [125], the safety, tolerability, and IOP-lowering efficacy of pattern scanning laser trabeculoplasty (PSLT) were compared against SLT. In all, 29 OAG patients underwent PSLT in one eye and SLT in the fellow eye. There was no significant difference in mean IOP reduction at latest follow-up (6 months).

Trans-scleral SLT without gonioscopy lens

Trans-scleral or direct SLT allows 360° treatment around the perilimbal sclera overlying the TM without a

gonioscopy lens. This eliminates corneal and gonioscopy-related side effects [126, 127]. It utilises similar laser settings to conventional SLT and has similar IOP-lowering efficacy but shots are fired simultaneously in <1 s reducing procedure duration. Direct SLT could potentially enable treatment to lower IOP in angle closure/angle-closure glaucoma patients as visible access to the TM is not required using this technique. If successful, direct SLT could be widely implemented, including in the developing world. Further larger-scale studies are underway to evaluate direct SLT—the GLAUrious trial is a prospective multicentre RCT comparing SLT vs direct SLT. A separate trial evaluating its' use is currently recruiting in Israel.

Conclusions

SLT is as effective as ALT and topical medication in POAG/OHT patients but easier to deliver. It can be used as primary or adjunct treatment and has effect in other glaucoma subtypes. It has been shown to reduce IOP fluctuation but its effect does subside over time. SLT is repeatable, as it causes minimal damage to the TM, and IOP lowering is present even if initial response with primary SLT is limited. Adverse events are uncommon but most of these are transient and self-limiting. SLT has been shown to be a cost-effective option for primary treatment of glaucoma patients and evidence exists to show it is associated with better quality of life. Newer technologies are emerging to further develop SLT but these require further investigation with larger-scale studies.

Methodology

We used the following databases and search terms to research this review: MEDLINE/PubMed: 'Selective Laser Trabeculoplasty; 'SLT; 'Laser Trabeculoplasty; Original research studies; Non-English papers excluded.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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