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Laser Trabeculoplasty and Aqueous Dynamics

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Abstract

For the past four decades, laser trabeculoplasty has been a staple in the treatment armamentarium against glaucoma. Although the exact mechanism of laser trabeculoplasty has not been fully elucidated, its clinical utility in lowering intraocular pressure has been well established. Aqueous dynamic studies uniformly reveal an increase in aqueous outflow facility at the trabecular meshwork. Accumulating evidence suggests that the mechanism is the result of complex cellular and biochemical processes. Histopathological studies of the trabecular meshwork tissue after argon laser suggest an additional mechanical role. The traditional treatment algorithm for glaucoma placed laser trabeculoplasty as an intermediary between medical therapy and incisional surgery. However, because of the safety profile of selective laser trabeculoplasty, recent studies have challenged this treatment paradigm. One such study was a multicenter trial headed by our department that compared laser trabeculoplasty and medical therapy as initial treatment for glaucoma. We showed a similar efficacy between the two modalities, reinforcing the possibility of using laser as the initial treatment in the right clinical setting.

Keywords: trabeculoplasty, SLT, ALT, outflow facility

1. Introduction

Laser trabeculoplasty entered the treatment armamentarium of glaucoma in 1979 when Wise and Witter showed that application of argon laser to the trabecular meshwork significantly reduces intraocular pressure (IOP) [1]. In an era when medically uncontrolled glaucoma patients underwent incisional surgery, argon laser trabeculoplasty (ALT) was welcomed as a much-needed intermediary treatment that bridged medications to surgery. The Glaucoma Laser Trial (GLT) showed that ALT was as effective as medical therapy as initial treatment for glaucoma [2, 3]. However, post-laser complications due to photocoagulative damage like lack of repeatability were major limitations for initial treatment with

ALT to be widely adopted [4, 5]. In 1995, Latina and Park introduced selective laser trabeculoplasty (SLT), a Q-switched, frequency-doubled, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser [6]. In contrast to its predecessor, SLT delivers a fraction of the energy delivered by ALT, avoiding most of the untoward effects that can arise from thermal damage [7]. Due to its superior safety profile and potential repeatability, SLT has challenged the traditional treatment paradigm [8].

The production and maintenance of IOP is dependent on the balance between the rate of aqueous humor production and outflow. Since the 1950s, this balance was conceptualized by the Goldmann equation, which states IOP equals the rate of aqueous production divided by outflow facility plus the episcleral pressure ($IOP = F/C + P_v$) [9]. This was based on the assumption that aqueous flow in living tissue can be expressed in linear terms. Therefore, at best, this equation is an approximation of the complex physiologic conditions that determine IOP [10]. Laser trabeculoplasty targets the trabecular meshwork, which is the site of the conventional outflow pathway, lowering IOP by increasing outflow facility.

The IOP-lowering effect of laser trabeculoplasty is well established in clinical practice [11]. However, the exact mechanism by which this is achieved is only now being unraveled. In this chapter, we present the current knowledge on the effect of laser trabeculoplasty on aqueous humor dynamics in the anterior chamber. Further, we will discuss the shifting perspectives in the use of laser trabeculoplasty in the clinical setting.

2. Mechanisms of action of laser trabeculoplasty

2.1. The mechanical theory of laser trabeculoplasty

The settings of the argon laser are 50- μm spot size, 0.1-s pulse duration, and power starting at 600 mW. However, operating parameters are not standardized, and settings are dependent on the operator and an arbitrary tissue end point with blanching and vaporization bubble formation. The laser is applied to the trabecular meshwork and sets in motion a physiologic pathway that may require 1–2 months before its IOP-lowering effect can be appreciated [12]. In the original pilot study for ALT, Wise and Witter hypothesized the mechanism to be through mechanical tightening of the trabecular meshwork surrounding the laser treatment spots supporting the original mechanical theory [1].

The histopathological changes seen after ALT are the sequelae of photocoagulative thermal energy applied on the surface of the trabecular meshwork. All studies performed in the past several decades showed significant thermal damage associated with treatment spots. The thermal damage was characterized by crater formation and surrounding coagulative changes in the uveal and corneoscleral layers of trabecular meshwork. Crater formation was associated with disruption of collagenous beams, fibrinous exudates, and lysis of trabecular endothelial cells [13, 14]. Recent studies demonstrated a dose-dependent change in the size and depth of the coagulative damage with increasing laser energy [15, 16]. One study showed the presence of an endothelial membrane overlying the trabecular meshwork

in patients who experienced failure after ALT, revealing a possible mechanism for IOP rise after trabeculoplasty [17].

SLT is a frequency-doubled 532-nm Nd:YAG laser with a fixed setting of 400 μm spot size and pulse duration of 3 ns. The power is variable and dependent on the operator. Its main advantages compared to ALT are its superior specificity to pigmented trabecular cells and reduced photocoagulative and collateral damage [18]. Selective killing of pigmented trabecular cells has been demonstrated in cultured trabecular cells [19]. This is owed mostly to the short pulse duration, which is shorter than the thermal relaxation time of most tissues. Thermal relaxation time is the time needed for a chromophore to cool down by converting electromagnetic energy into thermal energy. The rapid pulse of energy delivered by SLT prevents excessive thermal diffusion and damage to the adjacent tissue.

Studies uniformly show less structural damage in trabecular meshwork treated with SLT compared to those treated with ALT. The ultrastructural changes arising from SLT are not visible with light microscopy and scanning electron microscopy (SEM), where trabecular beams appear intact and similar in appearance to the adjacent, untreated tissue. However, significantly damaged trabecular beams have been reported in the tissue treated with energy levels higher than those used in the usual clinical setting, one study at 2.0 mJ and another at 1.0–4.6 mJ [16, 17]. Transmission electron microscopy (TEM) of SLT-treated regions show extracellular pigment granules with a characteristic “cracked” appearance [13, 16]. Of note, this characteristic change was seen even at lower energy settings (0.4 mJ). This finding aligns with a study that showed SLT using low energy (0.3–0.5 mJ) had comparable success with treatments using conventional energy (0.6–1.0 mJ) [20].

The mechanical theory of trabeculoplasty states that laser-induced thermal burns to the trabecular meshwork cause tissue contraction and tightening of the trabecular ring. A mechanical stretch is applied to the intervening tissue, effectively opening the untreated portions of trabecular meshwork and widening Schlemm’s canal, leading to increased aqueous outflow [21]. However, the mechanical theory alone does not fully explain the mechanism of laser trabeculoplasty. First, cross-sectional increase of Schlemm’s canal was only noted to increase in eyes with IOP high enough to mechanically collapse the trabecular meshwork (>40 mmHg), not accounting for eyes with lower IOPs [22]. Second, although photocoagulative damage is apparent shortly following treatment, increased aqueous outflow and IOP reduction do not occur until several weeks later [23]. Third, significant IOP lowering is seen in SLT which does not induce the coagulative changes seen in ALT. In the following section, we will highlight the cellular and biochemical pathways leading to increased aqueous outflow and lower IOP (**Figure 1**).

2.2. The cellular theory of laser trabeculoplasty

Attrition of trabecular cells has been observed with normal aging and is correlated with progressive decline in aqueous outflow facility. In glaucoma, the rate of trabecular cell loss is significantly increased compared to non-glaucomatous eyes [24, 25]. Laser-induced trabecular cell division, migration, and repopulation have been observed [26]. These findings suggest that

trabecular cells play a central role in trabecular meshwork function and laser trabeculoplasty lowers IOP by stimulating meshwork cells.

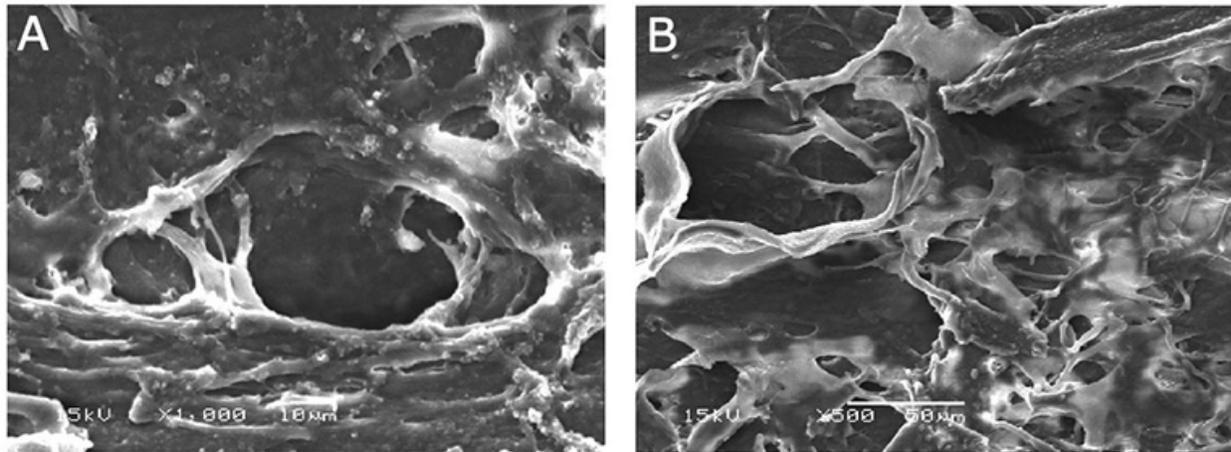


Figure 1. (A) Electron microscopy of trabecular meshwork treated with ALT showing characteristic crater formation and coagulative damage. (B) SLT-treated trabecular meshwork at high energy levels (2.0 mJ/pulse) shows tissue scrolling near treatment areas. These changes are not observed in therapeutic levels (<1.0 mJ/pulse) [13]. Modified with permission from [16].

ALT on human corneoscleral explants stimulated a nearly twofold increase in DNA replication and fourfold increase in cell division in the early post-laser period [26, 27]. During the first 2 days following ALT, the increased cell division was noted predominantly in the anterior meshwork near Schwalbe's line. After 2 weeks, the laser burn sites displayed migration of and repopulation of new trabecular cells. Interestingly, the replicative effect of the laser was widespread with the untreated 180° of the meshwork showing evidence of cell division as well, raising the possibility of cellular signaling as a potential mechanism. A similar study performed *in vivo* on cynomolgus monkeys compared the effect of ALT and SLT on trabecular cell division [28]. SLT-treated eyes had a significantly greater rate of cell division compared to ALT.

Trabeculoplasty with both ALT and SLT has been demonstrated to recruit monocytes to the trabecular meshwork. In one study, SLT was demonstrated to induce a fivefold increase of monocytes [29]. This is thought to occur through an upregulation of several cytokines and chemotactic factors, which will be discussed in more detail in the following section. Autologous monocytes introduced in the anterior chamber of rabbit eyes resulted in a significant reduction in outflow facility and IOP [30].

2.3. The biochemical theory of laser trabeculoplasty

Trabecular cells synthesize and are surrounded by extracellular matrix (ECM) products such as collagen, glycosaminoglycans (GAGs), proteoglycans (PG), fibronectin, and other structural elements [31, 32]. There is mounting evidence that ECM of trabecular meshwork plays an important role in the regulation of aqueous outflow [24]. It is a major component of the juxtacanalicular meshwork (JCM), which is thought to be the site of greatest aqueous flow

resistance [33]. Along with trabecular cell loss, increased fibrillar ECM deposition around elastic-like fibers, or sheath-derived plaques, has been identified as a common feature in various forms of open-angle glaucoma [25, 34]. Alterations in ECM components have been observed following laser trabeculoplasty.

GAGs, a major component of ECM, are large carbohydrate polymers composed of repeating disaccharide units. They are thought to fill the intertrabecular spaces of the JCM, regulating aqueous flow by forming viscoelastic gel-like solutions [35]. Trabecular meshwork GAGs are abundant and exist in the form of hyaluronic acid, keratan sulfate, chondroitin sulfate, and heparan sulfate [36]. Chondroitin sulfate forms a sheath surrounding the elastic-like fibers in the JCM, and increased levels seem to correlate with elevated IOPs. Rabbit eyes with dexamethasone-induced ocular hypertension (OHTN) showed an increase in chondroitin sulfate and decrease in hyaluronate levels [37, 38]. Later, the same group discovered elevated chondroitin sulfate levels and decreased hyaluronate and heparan sulfate levels in human eyes with glaucoma [39]. Hyaluronic acid levels were noted to be 77% reduced and chondroitin levels were elevated 24% in glaucomatous trabecular meshwork [40]. Trabeculoplasty has been shown to modulate GAG synthesis patterns by trabecular cells. Argon laser treatment of organ cultures reverted the composition to a normal GAG expression pattern in 7–10 days [22].

Proteoglycans (PG) are another major component of ECM and are composed of a protein core bound to several GAG chains. Diminished ECM turnover at the JCM is associated with aqueous flow resistance. Several lines of evidence point to the role of proteoglycans as important modulators of trabecular meshwork ECM turnover. SLT treatment of cat eyes revealed an elevated presence of biglycan, prolargin, keratocan, and fibromodulin compared to non-lasered controls [31]. The laser-induced change in GAG and PG may offer new insight into the biologic mechanism of laser trabeculoplasty. The exact role of the increased expression of glycoproteins with trabeculoplasty is still not known and further research is warranted.

Matrix metalloproteinases (MMP) are a group of zinc endopeptidases that are involved in ECM degradation and turnover [41]. Trabecular cells maintain ECM homeostasis by expressing several members of the MMP family including, collagenase, gelatinase A (MMP-2), stromelysin-1 (MMP-3), gelatinase B (MMP-9), and MMP-14 [42]. Laser-induced upregulation of MMP-2, MMP-3, and MMP-9 has been demonstrated after ALT and SLT and is thought to play a key role in ECM modulation and IOP reduction [43]. This is mediated through reactive secretion of cytokines interleukin-1 β (IL-1 β) and tumor necrosis factor α (TNF- α) [44]. The same factors are thought to mediate laser-induced recruitment of trabecular meshwork monocytes after SLT [29]. Of note, upregulation of MMP is the basis for mechanism of topical prostaglandin analogs and upcoming adenosine signal-mediated medications.

Although the IOP-lowering effect of laser trabeculoplasty is well established in clinical practice, its precise mechanism is not fully understood. It is likely a complex interaction of mechanical, cellular, and biochemical factors that culminate in increased outflow facility and lowered IOP. In the following section, we will move beyond mechanism of action and discuss the measured effect of laser trabeculoplasty on aqueous humor dynamics.

3. Aqueous dynamics of laser trabeculoplasty

Tonography is performed either by applanation (Goldmann) or indentation (Schiotz) of the cornea, displacing aqueous fluid and temporarily increasing IOP. The elevated IOP can induce a reduction in aqueous production. The reduction of inflow is indistinguishable from increased outflow, causing an overestimation of true outflow facility termed “pseudofacility” [45]. On the other hand, fluorophotometry is a noncontact method that determines aqueous flow by measuring the disappearance of fluorescein from the anterior chamber [46]. It is thought by some to be a more accurate method as it avoids tonographic sources of error such as ocular rigidity and pseudofacility. Despite its drawbacks, tonography yields internally consistent and reproducible results and continues to have value as a clinical and research tool [47–49].

A decrease in outflow facility with age has been reported using tonography, fluorophotometry, and perfusion studies of normal eyes [50–52]. An approximately 30% decline in outflow facility has been observed in eyes <40 years of age (0.33 $\mu\text{l}/\text{min}/\text{mmHg}$) compared to >60 (0.23 $\mu\text{l}/\text{min}/\text{mmHg}$) [50, 53]. The age-related decline in outflow facility in OHTN and glaucoma occurs parallel to non-glaucomatous eyes. However, the absolute value of outflow facility is significantly lower in these entities compared to age-matched controls [54, 55]. This finding was corroborated by a 10-year longitudinal study of tonographic outflow facility in hypertensive eyes which demonstrated a progressive decline with age [56]. Atropine was found to reduce, but not eliminate age-related decline outflow facility, suggesting that intrinsic changes in the trabecular meshwork were likely at play [57]. This declining outflow facility has been correlated with the progressive trabecular cell loss and changing ECM composition, both of which has been demonstrated to reverse following laser trabeculoplasty [24].

The effect of ALT on the tonographic outflow facility has been extensively studied. In previously untreated POAG patients, a 63.5% increase in tonographic outflow facility was measured with a 33% reduction in IOP [58]. A similar study on patients already on topical therapy showed a comparable 64% increase in outflow facility and 29% reduction in IOP [59]. Furthermore, this efficacy of ALT did not change in patients on maximum therapy with 64% increase in tonographic outflow facility and 29% reduction in IOP. Medications prior to laser treatment do not appear to alter the effect of ALT on tonographic outflow facility. Fluorophotometric aqueous outflow increased by 25.9% after ALT [60]. The same study showed no significant increase in outflow until 1 week after laser application. The latency in treatment response is contrary to the mechanical theory where laser-induced structural changes are visible immediately following treatment. Instead, it is in keeping with the timing of trabecular cell activation and ECM remodeling following treatment. A study comparing the effect of ALT on fluorophotometric and tonographic outflow showed an increase in outflow facility using both methods [61]. The fluorophotometric outflow increased from 0.016 to 0.075 $\mu\text{l}/\text{min}/\text{mmHg}$, while tonographic outflow increased from 0.112 to 0.151 $\mu\text{l}/\text{min}/\text{mmHg}$. The difference in outflow facility values highlights the measurement errors inherent in tonography [45, 62].

The effect of SLT on tonographic outflow facility is comparable to ALT. In previously untreated OHTN, 360° treatment with SLT caused a 55.5% increase in outflow facility and 21% reduction

in IOP [63]. A study by the same group compared the effect of 180° vs. 360° treatment on tonographic outflow facility [64]. The 180° and 360° groups achieved an increase in outflow facility of 37.5 and 41%, respectively. Although there was a trend favoring the 360° group, there was no statistically significant difference between the two groups. This observation is in concordance with the observation of trabecular cell division even in untreated areas after trabeculoplasty [27]. Fluorophotometric measures showed a 41.2% increase in outflow facility after SLT [65].

4. Selective laser trabeculoplasty as initial treatment

Several retrospective and prospective studies comparing the clinical effectiveness of ALT with SLT showed no demonstrable short-term or long-term difference between the two modalities [23, 66–70]. Although IOP reduction is comparable, the true advantage of SLT over ALT lies in its superior safety profile and repeatability. SLT delivers a fraction of the energy output of ALT resulting in less pain and inflammation associated with treatment [23]. The incidence of iritis, post-laser IOP spikes, and peripheral anterior synechiae is significantly reduced with SLT compared to ALT [71–73]. Furthermore, the lack of trabecular meshwork scarring makes SLT more amenable to repeat treatment [4, 74–77].

The current treatment paradigm for glaucoma starts with medical therapy in the form of eye drops, followed by laser trabeculoplasty, and culminates with surgery. This treatment progression was born from the perceived superior safety profile of medications compared to laser therapy and surgery. As discussed above, the selective laser trabeculoplasty (SLT) has significantly improved the safety of laser therapy and challenges the existing treatment paradigm.

Topical eye drops have long been the initial treatment of choice due to its relative safety in the armamentarium of glaucoma treatments. Medical therapy, however, is not without drawbacks. Medication compliance rates among glaucoma patients are notoriously low with reported nonadherence rates ranging from 30 to 80% [78–80]. Nonadherence is an immense problem and is clearly a significant risk factor for vision loss in glaucoma patients [81]. Difficulty in instilling drops, medication side effects, prohibitively high costs, and complex drop regimens further contribute to this problem [82]. A decline in quality of life has also been reported as a direct result of these challenges associated with medications [83]. Finally, cost studies have revealed significant cumulative savings of SLT over medications and filtering surgery [84, 85].

SLT has shown to have a comparable reduction in IOP compared to single medical therapy. However, SLT has the clear advantage in light of medication compliance, cost, and side effects. This begs the question: Should SLT be offered as the initial treatment for glaucoma? This prompted the evaluation of SLT versus medication as the initial therapy for glaucoma in a multicenter, prospective, randomized clinical trial. Better known as the SLT/MED trial, our study randomized patients to receive SLT (100 applications, 360°) or medication (prostaglandin analog). After 1 year of follow-up, there was a similar IOP reduction between the two groups with a 26.4 and 27% reduction in SLT and medication groups, respectively. There was a trend toward more treatment steps necessary for adequate IOP control in the medication arm with

27% requiring additional drops compared to 11% in the SLT group receiving additional laser [8]. Other prospective studies have been done which corroborate with our findings [86–88].

5. Conclusions

Histopathological findings suggest SLT has mainly a biologic effect while ALT has an additional mechanical effect [13, 16]. However, accumulating evidence seems to favor the cellular and biochemical theory of trabeculoplasty for both ALT and SLT. Aqueous dynamics studies following ALT reveal no significant changes in outflow until 1 week following laser, suggesting the mechanical theory may play a smaller role than previously thought. Nevertheless, the exact mechanism of laser trabeculoplasty is becoming better understood but further studies are needed.

Although the exact mechanism is somewhat uncertain, the clinical utility of laser trabeculoplasty is clearly established. Comparative studies of ALT and SLT do not seem to yield a statistically significant difference in efficacy [66–69]. The SLT/MED study showed a comparable reduction in IOP between patients receiving SLT and medications as initial treatment [8]. In light of low medication adherence rates, drug side effects, and cost of medical therapy, this study reinforces the possibility of using SLT as an initial treatment in the right clinical setting.

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