Micropulsed laser trabeculoplasty *vs.* selective laser trabeculoplasty: understanding how these lasers are useful to control intra-ocular pressure in primary open angle glaucoma.

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Received: *25-May-2023, Manuscript No. AACOVS-23-99600;* ***Editor assigned:*** *29-May-2023, AACOVS-23-99600 (PQ);* ***Reviewed:*** *12-Jun-2023, QC No. AACOVS-23-99600;* ***Revised:*** *24-Jul-2023, Manuscript No. AACOVS-23-99600 (R);* ***Published:*** *31-Jul-2023, DOI:10.35841/aacovs.7.5.669-672*

Abstract

Selective Laser Trabeculoplasty (SLT) has been used to lower intra-ocular pressure of Primary Open Angle Glaucoma (POAG) patients, both as an initial or as adjunctive treatment, and proven to be safe and effective. Micropulse Laser Trabeculoplasty (MLT) has also been used for the same purpose, with similar efficiency. In this mini-review, we briefly describe some aspects of how these lasers work, what ultra-structural changes are induced by them, their biological effects, clinical usefulness, compare the two technologies and try to correlate them to trabecular meshwork function restoration.

Keywords: Glaucoma, Intraocular pressure, Treatment lasers, Selective laser trabeculoplasty, Micropulse laser trabeculoplasty.

Introduction

Glaucoma is classically defined as a progressive optic nerve neuropathy that may affect the visual field and result in blindness if not treated. Intra-Ocular Pressure (IOP) is the only known risk factor that we can control medically, with laser therapy or surgery. The Ocular Hypertensive Treatment Trial (OHTS) has showed us a clear time relation, meaning that IOP rises first and glaucoma may result subsequently [1]. Topical drops remain the most popular treatment worldwide, however, laser is taking a major lead on the daily management of POAG, as pivotal clinical trials demonstrate its effectiveness and safety profile [2,3].

Literature Review

First attempts to use lasers in glaucoma were done in 1970, with ruby-lasers goniopuncture, with limited results. ALT has been introduced in 1979, used argon green laser, as a new method of lowering IOP and has been shown to effective and safe. The glaucoma laser trial, performed in 1990, demonstrated that argon laser trabeculoplasty had a superior IOP lowering effect as compared to timolol [4].

As an evolution of ALT, the initial studies with SLT were performed by Latina, in 1995, targeting *in vitro* cells [5]. This laser is a Q-switched Neodymium-Doped Yttrium Aluminium Garnet (Nd:Yag) ion crystal, with a green (532 nm) light source. The principle of this laser application (Q-switching) is based on a pulse formation that allows the production of high peak power of energy, much higher than a continuous laser mode. In the case of SLT laser, the attenuator (or the saturable absorber) inside the laser's optical resonator is the Nd:Yag, that stores the light energy and deploys it very quickly after reaching a threshold point. The net result is a short pulse (nanoseconds) of laser light which may have a high peak of energy. This new approach, described to induce less tissue destruction *in vitro*, was also clinically explored by Latina, et al., and shown to be efficient, practically painless and safe [6]. Subsequently, several clinical reports demonstrated that SLT was effective in ocular hypertensive and POAG patients. Other studies reported it to reduce IOP equivalently to ALT treatment, comparable with prostaglandin monotheraphy, and that it may obviate or decrease the use of glaucoma drops [7,8]. More recently, the light trial demonstrated a high success rate of IOP control in treatment naive patients and latter reinforced that such success could be improved with repeated laser application, remarking that the SLT's effect may even last longer and better than previously thought [9].

MLT was initially used for retinal photocoagulation. This modality of laser demonstrated stimulation of retinal pigment epithelium and no thermal damage to surrounding tissue. The use of this laser to the TM confirmed the lack of destruction of tissue [10]. This laser may be delivered with several wavelengths and works with the principle of extremely fast duty cycles of laser activity. The duty cycle is period in which the laser is active during one shot [11]. The short microburst in repetitive microsecond pulses are delivered to the TM, spaced by an intermittent cooling period, what makes the actual power delivered to the targeted tissue much less than a continuous laser, and thus, reducing substantially the coagulation energy. The duty cycles may vary, but for MLT this is ordinarily set at 15% (meaning 15% active and 85% inactive period of laser bursts in one single shot).

Selective photothermolysis is a concept of laser application which makes light more selectively absorbed by specific tissues

and intracellular chromophores, not exceeding their thermal relaxation time and therefore not diffusing heat to nearby tissue [12]. Simply put, ALT, SLT and MLT can interact with melanin chromophores in the trabecular tissue, but only SLT (*via* nanosecond pulses) and MLT (*via* its ultrafast and low duty cycles of microbursts) are capable not to excite melanin, which thermal relaxing time is around 1 millisecond. In other words, only SLT and MLT are truly selective, in theory. Electronic microscopy has shown that the 100% duty cycle, of the continuous wave pulsed laser as used in ALT, produces vaporization on the centre of its shot, followed by concentric circles of carbonization, coagulation and hyperthermia of adjacent tissue [13]. Fudemberg, et al., showed on cadaver eyes that the collagen fibres and cells of the TM are distorted, stretched mechanically and destroyed by ALT and, conversely, both SLT and MLT showed no such distortion, nor apparent damage to TM microscopic structure, hence, these lasers are regarded not to induce perceivable structural changes.

Another concept that applies to all lasers is their wavelength on the spectrum of light, a characteristic that defines their depth of penetration. Basically, the longer the wavelength the deeper the laser action on tissue, what is of foremost importance to their comparisons and clinical utility. Therefore, in our opinion, the best way to compare the usefulness of MLT laser to SLT is using the same wavelength (532 nm-green). This, in theory, could lead to the most similar laser interaction with trabecular meshwork tissue so to emulate the clinical advantages reported on pivotal clinical trials, as the light trial, which made green Nd:Yag SLT the current gold standard of POAG treatment (Supplementary Figure 1).

In a recent published study, we compared the efficacy of SLT versus green-532 nm MLT, in POAG patients, requiring additional IOP lowering [14]. Laser treatment was efficient in both groups, with reduction of 24.9% in SLT group and 23.4% in green-532 MLT group in IOP from baseline, with no statistically significant difference in IOP reduction between groups. Nevertheless, at 12 months, the mean number of glaucoma medications was significantly smaller in SLT group as compared to MLT group. Success at 12 months (defined as IOP<21 mmHg and >20% reduction from baseline IOP without need for additional medications, laser or surgery) was 61.5% for SLT and 58.7% for MLT treated eyes, not statistically different. The number of successful patients without medications was somewhat low, but not statistically different in groups, 25% for SLT and 18.5% for SLT. We also discuss in this paper that, MLT with red 810 nm laser was the first modality of MLT laser studied. In 2008, Detry-Morel reported an IOP reduction of 12.2% for MLT and 21.8% for SLT and much higher success rate (IOP reduction >20% from baseline) with SLT (50.0%) as compared to MLT (35.5%) at 3 months follow up. Subsequent non-comparative studies reported IOP reduction ranging from 17.2% to 21.3% with 810 nm-red MLT. Prospective studies with MLT with yellow 577 nm laser showed that yellow MLT had an IOP reduction around 13.0% to 21.6% as compared to around 16.0% to 19.8% of SLT. In a non-comparative studies with yellow-MLT, reported a success rate (IOP reduction >20% from baseline) of 29.6% for yellow-MLT and 36% for SLT in a follow up for 24-52 weeks. A green-532 MLT laser used by other authors, in a retrospective comparative study, showed a reduction of 11.5% for MLT and 10.4% for SLT from baseline IOP. A success rate of 44.0% for MLT and 40.0% for SLT was reported (defined as >20% IOP reduction from baseline).

We highlighted, in our paper, that although SLT and green-MLT had similar performance in IOP reduction, SLT required less medication to achieve target IOP. Furthermore, our successful patients, without medications in both groups (18.5% to 25%, respectively) were much lower than the results of light study after 3 years of follow-up (around 78%). This could be explained by the design in light trial that used SLT as first line, in treatment naïve POAG patients and allowed laser retreatment. We speculated that chronic use of topical medications may interfere with laser performance and if we had retreated both SLT and MLT could achieve better performance without drops. Limitations of this work were its retrospective design and relatively small sample size. We suggested prospective studies to be carried in order to compare these technologies.

Another aspect that we addressed in our paper is a practical perspective of laser acquisition. Although SLT laser have been shown to be extremely useful in glaucoma management, its use is limited to glaucoma treatment only, whereas MLT can be used in glaucoma as well as other retinal diseases. This flexibility may represent a significant advantage to the cost effectiveness of micropulse lasers, especially in ophthalmic clinics with high demand of such sight threatening diseases. Conversely, one may argue that Nd:Yag lasers, combined to SLT are available in the market, ant may be used to do iridotomy and capsulotomy. However, depending on high demand and power settings used in the latter procedures, stress on laser cavity may also be taken in consideration when deciding to purchase combined or separate laser equipments.

In order to understand the mechanical and biological effects of laser in TM, one needs to know that ALT make a definitive mark on trabecular meshwork, resulting in increase in aqueous outflow, confirmed by both tonographic and aqueous dynamic studies [15]. A mechanical theory has been described as the major IOP lowering effect of this laser, based on tissue vaporization and a circle of collagen contraction induced by it. This is thought to reduce the diameter of the inner trabecular ring, reversing collapse of the meshwork thus maintaining aqueous outflow [16]. Both SLT and MLT make almost unperceivable tissue contraction, so we may expect that biological effects are more likely to explain their clinical effects, although this has been proven only in SLT studies so far. These include matrix metalloproteinase induction, cytokine expression TM remodelling and some interesting gene expression. Alvarado, et al., found intercellular junction disassembly in Sclemm's canal and TM with SLT similar to the mechanism of prostaglandins analogues, thus increasing TM permeability [17].

Pro-inflammatory cytokine are increased after SLT. These include interleukins and tumour necrosis factors that increase

matrix metalloproteinase related to TM remodelling, inducing increased aqueous outflow [18]. Increased TM monocyte recruitment has also been noted post SLT, leading to increased aqueous outflow *in vivo* and increased Schlemm's canal permeability *in vitro*, by more cytokine secretion or/and directly phagocytosing debris within the TM [19].

Discussion

Scanning electron microscopy and gene expression evaluated by hybridization of RNA showed that SLT is capable to induce genes expressions on TM cells, related to production of reactive oxygen species, cell motility, intercellular connections, extracellular matrix production, membrane repair, glutamate toxicity, antioxidant activities, and inflammation. On microarray analysis, no genes were related to apoptosis or necrosis, thus indicating that SLT does not induce cell damage *in vitro*. Up regulated genes modulated by SLT, correlated with cell motility and contraction indicate that SLT may enhance TM contracting and relaxation capacity. Relaxation of TM is related to increased outflow [20]. Genes involved with TM tissue integrity, adherence, extracellular matrix removal were also up regulated. This indicates that SLT induce repairing and removing of damaged proteins and indicate that SLT may increase removal of oxidized proteins that typically accumulate in degenerating and ageing tissues [21].

This regeneration TM concept induced by SLT and MLT also tangles with new concepts of TM contractile function, regarding it not just as a passive filter, but rather as an active pump structure as stated by Johnstone, et al., that recently purposed that the TM and Schlemm's canal work together as a highly dynamic lymphatic like pump that control of aqueous exit from the eye, describing that the hinged and mobile SC outlet valves connect the TM, permitting an outward flow of aqueous [22]. The authors report a pulse dependent flow into SC, collector channels and aqueous veins, deriving aqueous into episcleral veins due to transient increases in IOP during systole (due to choroidal blood-expansion) that cause the TM's elastic structural elements to deform, including the TM lamellae, the juxta-canalicular cells, and SC inner wall endothelium. The TM tissues move outward into SC during systole, opening external wall valves that permit aqueous to flow into Collector Channels (CC), intra-scleral channels, and finally, the aqueous veins. During diastole, choroidal volume decreases, and IOP falls. The TM recoils, releasing the potential energy stored during systole. TM recoil reduces pressure in SC, favouring aqueous flow from the AC into SC through SC inlet valves. This pulsatile TM motion was imaged by Johnstone in video and confirmed in by Phase-based OCT (PhS-OCT) studies that can identify TM movements in systole and diastole, and accommodation efforts [23].

Conclusion

Considering these explanations, we conclude that green-MLT and SLT are clinically proven to induce IOP reduction in POAG patients. That effect may occur *via* a significant increase in efficiency of the TM function, making it more porous and flexible, rather than simply diminishing its resistance by mechanical destruction. The Green-SLT Nd:Yag laser is the gold standard in current clinical practice, since it is, by far, the most studied *in vitro* and *in vivo* laser up to this point. It is so reasonable to try achieving micro-structural laser marks as close to SLT as possible (with same wavelength) in order to try to emulate SLT clinical results. This makes, in our opinion, the green-MLT laser a more suitable candidate to achieve such IOP reduction. MLT lasers with other wavelengths and ab-external laser trabeculoplasty need further comparative investigation, in that sense, to be fully incorporated in clinical practice.

Lastly, the classical definition of glaucoma, cited in the beginning of this mini-review, may need to be expanded. POAG may be viewed as a TM dysfunction with subsequent IOP rise that leads to optic nerve damage and visual field changes.

Conflict of interest

None.

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