Evolution of Cyclophotocoagulation

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Abstract

Cyclodestructive techniques have been a treatment option for refractory glaucoma since its first use in the 1930s. Over the past nine decades, cyclodestruction has advanced from the initial cyclodiathermy to micropulse transscleral cyclophotocoagulation (MP-TSCPC) which is the current treatment available. Complications associated with cyclodestruction including pain, hyphema, vision loss, hypotony and phthisis have led ophthalmologists to shy away from these techniques when other glaucoma treatment options are available. Recent studies have shown encouraging clinical results with fewer complications following cyclophotocoagulation, contributing greatly to the current increase in the use of cyclophotocoagulation as primary treatment for glaucoma. We performed our literature search on Google Scholar Database, Pubmed, Web of Sciences and Cochrane Library databases published prior to September 2017 using keywords relevant to cyclodestruction, cyclophotocoagulation and treatment of refractory glaucoma.

Keywords: Endocyclophotocoagulation; Glaucoma; Transpupillary Cyclophotocoagulation; Transcleral Cyclophotocoagulation

INTRODUCTION

Certain glaucoma patients with co-morbidities like active inflammation, aphakia, failed filters, and neovascular glaucoma, may respond poorly to standard medical and surgical therapy.[1-3] Since the 1930s, cyclodestruction has been a treatment option offered to such patients to lower intraocular pressure (IOP) and slow the progression of glaucoma.[2,4,5] The aim of ciliary ablation is to selectively destroy the ciliary body epithelium, to reduce but not eliminate aqueous secretion.[6] Reduction of aqueous secretion will decrease IOP and slow the progression of glaucoma.[2] Over the past nine decades, the search for treatment options which would provide better focused energy and targeted destruction of the ciliary processes has led to an increase in cyclodestructive treatment options, decrease in collateral tissue destruction and postoperative outcomes comparable to other glaucoma treatment modalities.

The evolution of laser cyclophotocoagulation (CPC) techniques has been accompanied by increasing evidence supporting a change from the historical use of CPC as a treatment of last resort to the use of CPC for treatment of glaucoma in patients with ambulatory vision. This review gives an overview of the history of cyclodestructive procedures and describes the current laser CPC procedures with reference to published literature. It highlights how the need to preserve the globe, minimize collateral damage to adjacent non-pigmented tissue and halt the progression of

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glaucoma in refractory cases, has driven the evolution of CPC.

Historical Background

Since the 1930s, when non-penetrating and penetrating cyclodiathermy were introduced, ciliary body ablative procedures have been used to treat glaucoma.[4,7,8] In the 1940s and 1950s, various studies reported that cyclodiathermy had a poor safety margin and suboptimal clinical response.[9-12]

In 1950, Bietti demonstrated the use of a freezing technique to lower IOP.[13] Histologically, the cryo-injury leads to the destruction of the ciliary body epithelial cells and capillaries, and this results in the breakdown of blood-aqueous barrier with subsequent decrease in aqueous production.[14] Cyclocryotherapy is considered more effective and less destructive than cyclodiathermy and thus replaced the latter as the cyclodestructive procedure of choice.[15] However, complications associated with cyclocryotherapy including uveitis[16], intense ocular pain,[16] lens subluxation,[17] hyphema,[17] IOP spike,[18] hypotony[16] and vision loss,[16] led ophthalmologists to reserve cyclocryotherapy as a treatment option after other surgical procedures to improve aqueous outflow failed.[19] High-intensity focused ultrasound was briefly used for ciliary ablation before it was abandoned due to scleral ectasia, thinning at treatment site, and decreased visual acuity.[20-22] Studies on the use of ultrasonic circular cyclocoagulation in patients with refractory glaucoma have shown encouraging results.[23,24]

Weekers et al in 1961, used xenon arc photocoagulation over the ciliary body to reduce IOP.[25] In 1969, Smith and Stein reported that ruby and Neodymium: Yttrium-Aluminum-Garnet (Nd:YAG) lasers could be an effective laser source for transscleral CPC.[26,27] Beckman and associates in 1972 reported the first transscleral CPC using ruby laser.[28] The use of Nd:YAG laser for ciliary ablation was reported the following year, and it was found to be more effective than ruby laser for CPC.[29] Pratesi introduced the diode laser in 1984[30], and in 1992, Hennis and Stewart reported on the use of diode laser transscleral CPC to achieve good IOP reduction.[31] The result of clinical use of diode laser endoscopic CPC was first reported by Uram in 1992[32] and it is commonly used in patients undergoing vitreoretinal surgery or phacoemulsification. Recently, the use of micropulse laser delivery was adapted for cyclophotocoagulation. Of the three main types of lasers (Nd:YAG, Argon, and Diode) used for treating glaucoma, diode laser is preferred for CPC owing to its cost, efficiency and portability. During five decades, laser CPC procedures have been used in various ways namely: 1. Transpupillary CPC (TPCPC); 2. Transscleral CPC (TSCPC); and 3. Endoscopic CPC (ECPC).

Laser Cyclophotocoagulative Procedures

Transpupillary cyclophotocoagulation (TPCPC)

This modality entails the transmission of argon laser beam (488 nm) through the pupil to induce photocoagulation of the visible ciliary processes. The clinical application of this procedure has been limited by the need for a clear visual axis and a well-dilated pupil to enable photocoagulation of the entire length of the ciliary processes. When conventional medical and laser treatment fails, argon laser TPCPC offers a treatment option for selected patients with aniridia[33-36] or patients with anterior iris displacement caused by a broad peripheral anterior synechia.[36]

Transscleral cyclophotocoagulation (TSCPC)

During TSCPC, the laser beam transmitted through the overlying sclera is absorbed by melanin in the ciliary processes, leading to selective thermal coagulation of ciliary body tissues. Easy application of this approach, improved energy delivery and focusing system, and reproducibility of outcome is contributory to its widespread use.[37] Historically, because of its high rate of complications, TSCPC has been a treatment of last resort in functional eyes with advanced glaucoma when other treatment options are exhausted.[36] It provides a treatment option for patients who are medically unfit for invasive surgical procedures or patients who have refused incisional surgery.[36] Additionally, TSCPC can be used to mitigate ocular pain in patients who present with a painful blind eye and markedly elevated IOP.[36] Nd:YAG laser (1064 nm) and semiconductor diode laser (810 nm) can be used in contact or non-contact techniques. Moreover, contact semiconductor diode laser is the most popular method of TSCPC in recent times.

Non-contact Nd:YAG Laser

Either retrobulbar or peribulbar anesthesia is given before the onset of the procedure. From a slit lamp delivery system, laser energy is transmitted through the air using a pulsed Nd:YAG laser such as Microruptor II or continuous wave model Microruptor III (H.S. Meridian Inc., Mason, OH).[36] During the procedure, the patients' eyelids may be separated by the surgeon or by using a special contact lens. The contact lens compresses and blanches the conjunctiva and provides land marks which estimate the position of the laser beam from the limbus.

With the eye in primary position, the laser beam is focused on the sclera 1.5 mm posterior to the surgical limbus superiorly and inferiorly, and 1 mm posterior to the surgical limbus nasally and temporally. Preferred focus of the laser beam was determined by postmortem studies on treated eyes.[38,39] This revealed that effective

cycloablation was achieved in eyes treated with the anterior probe edge placed 1.0-1.5 mm posterior to the surgical limbus superiorly and inferiorly, and 1 mm temporally and nasally while using 7-8 J/pulse energy setting.[38,39] In a single session, approximately 30 to 40 laser spots are evenly spaced to cover the entire 360° while sparing 3 and 9 o' clock positions to avoid damaging the long posterior ciliary nerves. After surgery, topical steroids and cycloplegics are applied and the eye is patched.

Contact Nd:YAG Laser

This requires the use of retrobulbar or peribulbar anesthesia and the patient lying supine. An Nd:YAG laser system such as Microruptor III (H.S. Meridian, Inc., Mason, OH) is used. The anterior edge of the sapphire probe connected to a fiberoptic handpiece is placed on the conjunctiva about 0.5 to 1.0 mm posterior to the limbus, hence, focusing the laser beam over the pars plicata.[40] The probe should apply gentle pressure to the eye to control eye movement. Angle and orientation of the probe relative to the sclera has been shown to affect the area of destruction. Orientation of the probe at an angle greater than 15° can reduce the number of ciliary processes destroyed, thereby reducing efficacy of the procedure.[41] Power setting at 4-7 watts, for 0.5-0.7 seconds, with approximately 16- 40 spots applied over 360°, sparing 3 and 9 o' clock positions prevents damaging the long posterior ciliary nerves.[36] Eyes can be re-treated if there is an inadequate response after 1 to 4 weeks of initial treatment. During retreatment, to reduce the risk of hypotony and phthisis, half the number of primary laser applications have been advocated.[42]

Semiconductor diode laser

Light energy is generated from a semiconductor solid state diode laser system such as (IRIS Oculight SLx, IRIS Medical Inc., Mountain View, CA). This emits light near the infrared spectrum at 810 nm, which is strongly absorbed by melanin in the pigmented ciliary body epithelium, thereby inducing coagulative necrosis of the ciliary body epithelium and stroma. The G-probe centers the fiberoptic pit and is designed such that when placed approximately 1.2 mm from the corneoscleral limbus, it directs the laser beam posteriorly to ablate the ciliary processes. The design of the G-probe encourages orientation of the fiberoptic parallel to the visual axis for efficient delivery of laser energy to the ciliary processes.

Before starting this procedure, retrobulbar or peribulbar anesthesia is given and a lid speculum is secured. Initial power is typically set at 1750 mW and titrated in 250 mW increments to a maximum of 2500 mW. An audible pop signifies an intraocular uveal micro-explosion[43] and can indicate the need to reduce power by 250 mW and complete treatment at the reduced power. Duration is set at 2000 msec for a total of 16 to 20 spots applied over 360 degrees, sparing the 3 and 9 o'clock positions.

Micropulse transscleral CPC (MP-TSCPC)

The micropulse diode laser system (MP-TSCPC, IRIDEX IQ810 Laser systems, Mountain View, CA) is the most recent form of transscleral diode CPC. The device is designed to operate in an "on" and "off" cycle mode. During the "on" cycle, multiple (microsecond) repetitive bursts of laser are emitted by the device and absorbed by pigmented tissues. This causes an increase of thermal energy in pigmented tissues, inducing coagulative necrosis.[44] However, the non-pigmented tissues never attain coagulative threshold because of their lower rate of absorption of thermal energy and also have some time to cool off during the "off" cycle.[44]

This procedure is performed under local anesthesia or sedation, laser settings are usually programmed as follows: power–2000 mW, duty cycle- 31.33%, micropulse "on" time-0.5 ms, and micropulse "off" time-1.1 ms.[44] At the surgeon's discretion, the laser is delivered over 360° for 100-240 seconds, while sparing 3 and 9 o' clock positions to preserve ciliary neurovascular structures. Topical prednisolone acetate 1% applied 4 times daily can be used post-surgery to control inflammation and tapered when inflammatory response decreases.

Endoscopic cyclophotocoagulation (ECPC)

This is a cilioablative procedure whereby the ciliary processes are photocoagulated under endoscopic guidance. ECPC is done using a system (Endo Optiks Inc, Little Silver, NJ) which provides a 110–160° field of view endoscopic video camera, a 175-watt xenon light source, a helium neon laser aiming beam, and an ophthalmic continuous-wave pulsed 810 nm diode laser. All four components are combined into a triple-function hand-held probe connected to a portable unit consisting of a high-resolution monitor, a VHS recorder and a control panel. The laser focuses optimally at a distance of 0.75 mm from the probe tip. Typically, ECPC is done with power setting of 200-300 mW for 1-2 seconds.

Access to the ciliary process can be gained either through a limbal or a pars plana approach. The pars plana approach is not commonly used due to the need for either a simultaneous or previous vitrectomy and possible associated complications like choroidal and retinal detachment.[45] However, the pars plana approach can be favorable in the presence of an anterior chamber lens or an aphakic eye with posterior synechiae limiting access to the ciliary sulcus.[45,46]

In the limbal approach, after the pupil is dilated with cyclopentolate 1% and phenylephrine 2.5%, a viscoelastic agent is injected into the ciliary sulcus to enlarge the space between iris and lens. Through a

2.0 mm corneal incision, the endoscope can be inserted and oriented posteriorly to visualize ciliary processes on the monitor and treatment can begin. Laser energy is set at 200 mW and titrated until the ciliary process appears blanched or shrunken. A pop sound or bubble is formed when excessive energy is used: this leads to increased inflammation and breakdown of the blood aqueous barrier. Through one corneal incision, the laser can be applied 270° of the ciliary body using a curved probe. The entire 360° of the ciliary body can be treated with two corneal incisions. Typically between 180-360° are treated.[32,47,48] Viscoelastic agent is removed from the anterior chamber before surgical wound closure. Retrobulbar bupivacaine and sub–Tenon's injection of 1 mL of triamcinolone (40 mg/ml) is usually administered at the end of the procedure to minimize postoperative pain and inflammation respectively.

DISCUSSION

Cyclodiathermy and cyclocryotherapy were typically used to treat patients who had poor vision and end-stage glaucoma.[4,7,15,49] However, the suboptimal clinical response and adverse effects including postoperative pain, IOP spikes, hyphema, vitreous hemorrhage, and phthisis, associated with cyclodiathermy and cyclocryotherapy inspired vision scientists and physicians to search for more precise methods of ciliary ablation.[9,12,15,19] In the 1970s and 80s, Nd:YAG laser was considered the laser of choice for ciliary ablation owing to its ability to penetrate the sclera more effectively with less backscatter.[29]

A long-term follow-up of 500 patients treated with noncontact transscleral Nd:YAG CPC found that compared with cyclodiathermy and cyclocryotherapy, transscleral Nd:YAG CPC was associated with less transient IOP elevation, less ocular inflammation and less pain.[3] These findings were attributed to the fact that the laser-induced lesion is more focal and causes less damage to adjacent tissues compared with other cyclodestructive procedures.[3] Histopathology studies revealed that Nd:YAG laser CPC destroyed less adjacent tissue compared with cyclodiathermy or cyclocryotherapy.[38,50]

Compared with noncontact transscleral Nd:YAG CPC, contact transscleral Nd:YAG CPC is more efficient in transmitting focused laser energy to the ciliary body, causes less scleral destruction, more controlled destruction of the ciliary body processes, better IOP control and a lower incidence of vision loss.[3,42,51-53] Consistently, studies have reported that destruction of the ciliary epithelium leads to IOP reduction and lower incidence of vision loss.[3,4,19,31,44,54] With regard to these findings, cyclodestructive techniques available in the 1970s and 80s could preserve the globe by preventing glaucoma from progressing to a painful eye which might necessitate enucleation. Nonetheless, the need to slow or

prevent vision loss associated with end-stage glaucoma or cyclodestruction itself, kept researchers searching for better treatment approaches.

Diode laser provides a wavelength that is mostly absorbed by the melanin pigment of the ciliary epithelium, causing thermal destruction of the ciliary body tissues and less damage to surrounding ocular tissues.[30,46] Transscleral diode CPC was first used to control IOP in 1992 and it is typically performed using a continuous delivery of laser energy.[31,44] Both contact and non-contact transscleral diode CPC are effective for treating refractory glaucoma: however, contact transscleral diode CPC is preferred due to a more efficient ablation of the ciliary body epithelium.[55,56] Although accurate comparison of results of transscleral diode CPC is difficult, studies on refractory eyes have reported between 63 and 89% success in reducing IOP to 22 mmHg or less.[57,58] Retreatment tends to occur more often in posttraumatic cases, younger patients, and patients who have secondary glaucoma after vitreoretinal surgery.[59,60] A recent study of transscleral diode CPC on 17 eyes with refractory glaucoma suggested that a higher success rate with less postoperative complications after one treatment can be achieved if CPC was performed in the operating room as opposed to being done in the clinic.[61] The team further explained that the operating room allows for well monitored anesthesia, better tolerability during the procedure and more accurate laser applications.[61]

Typically, transscleral diode CPC is used for refractory glaucoma. Studies on transscleral diode CPC as a primary or secondary surgical procedure have shown good results.[60,62-64] Grueb and associates compared the use of transscleral diode CPC as a primary or secondary procedure in patients with POAG and exfoliative glaucoma, and found a higher success rate of achieving IOP less than 21 mmHg in eyes treated primarily with transscleral diode CPC.[65] Rotchford et al evaluated the effects of transscleral diode CPC in patients with good (≥ 20/60) visual acuity. At 5-year follow-up, the investigators found that 73.5% of patients had a final IOP of 16 mmHg or less and 30.6% lost 2 or more Snellen lines of visual acuity.[66] The proportion of patients who lost vision is consistent with that reported after trabeculectomy or tube surgery.[66] These results suggest a possible role for transscleral diode CPC in selected eyes with significant visual potential.

Adverse effects associated with treatment include vision loss, hyphema, cataract progression, anterior uveitis, phthisis and rarely sympathetic ophthalmia.[60,62,63,66,67] While some studies found a positive correlation between total treatment energy used and surgical success,[68,69] several other studies found no correlation between the two.[57,62,70] Although transscleral diode CPC has successfully been used to lower IOP in patients with advanced glaucoma or in glaucoma patients with ambulatory vision, the damage to adjacent tissues and

occurrence of adverse effects made most ophthalmologists reserve it as a last resort in refractory eyes. However in 2011, the United Kingdom National Cyclodiode Laser Survey of consultant ophthalmologists (47% of respondents were glaucoma subspecialists revealed that 60% of the respondents performed diode laser CPC at any level of vision, while 22% performed diode CPC simultaneously with cataract surgery.[71]

One of the limitations of transscleral diode CPC is the inability to directly visualize the ciliary processes; instead, the position of the laser beam from the limbus has been derived by postmortem experiments.[38,39] The inability to visualize the ciliary body during transscleral diode CPC limits the surgeon's ability to directly observe and control ciliary ablation. Transpupillary argon laser CPC and ECPC were designed to allow direct visualization of ciliary processes. The need for a clear visual axis and a dilated pupil made the use of argon laser transpupillary CPC less adaptable in many patients. Additionally, the clinical outcome of argon laser TPCPC has been unpredictable.[35,36,72,73] Shields et al reported a series of 27 patients who underwent argon laser TPCPC, and showed that only 6 patients (22.3%) had a successful outcome.[74] Postoperatively, a sustained increase in IOP was noted in many cases.[74]

Uram first reported the use of ECPC for treatment of glaucoma in 1992.[32] Recently, ECPC has been commonly used in combination with phacoemulsification for treatment of patients with early, moderate or refractory glaucoma. Other documented indications include: (1) poor candidates for filtration surgery, (2) treatment of plateau iris syndrome, and (3) to improve the effect of glaucoma drainage implants.[75] A histopathologic study compared ECPC-treated eyes with transscleral diode CPC-treated eyes and revealed that both led to ciliary body epithelium destruction; however, transscleral diode CPC caused more destruction of the ciliary body stroma, muscles and adjacent tissues.[76] A study on 5,824 eyes treated with ECPC reported the following complications: IOP spikes (14.5%), hemorrhage (3.8%), serous choroidal effusion (0.38%), retinal detachment (0.27%), and vision loss more than 2 lines (1.03%).[77,78] A review of the clinical results and adverse effects of ECPC versus transscleral diode laser CPC concluded that the rates of vision loss, hypotony, and phthisis were higher in transscleral CPC as opposed to ECPC.[67] The author highlighted the need for prospective trials as his review was limited by the case heterogeneity among compared studies.[67] A recent meta-analysis compared the efficacy of ECPC and non-ECPC procedures (transscleral diode CPC, trabeculectomy, drainage implantation and cryotherapy) for treatment of refractory glaucoma, and showed no significant difference in clinical efficacy between these interventions.[79]

As previously mentioned, traditional transscleral diode CPC uses continuous delivery of laser energy to ablate the ciliary body. The continuous mode of laser energy delivered is associated with the occurrence of adjacent non-pigmented tissue damage after transscleral diode CPC.[76] Micropulse diode laser delivery mode interrupts the laser into a series of repetitive segments termed "pulses". It includes an "on" and "off" cycle which permits gradual build-up of thermal energy in the pigmented tissues during the on-cycle, while collateral non-pigmented tissues are permitted to cool during the off-cycle. This mechanism prevents the non-pigmented tissues from reaching coagulative threshold.[54] In 2005, Micropulse laser was first used to treat glaucoma as a trabeculoplasty procedure and was found to cause less severe tissue damage and scar formation.[80]

Tan et al in 2010 published the use of MP-TSCPC for treating refractory glaucoma.[54] The investigators reported an 80% success rate of maintaining IOP between 6-21 mmHg, with no eye developing postoperative hypotony or visual loss after 16.3 ± 4.5 months follow-up.[54] A randomized exploratory study on micropulse versus continuous wave transscleral CPC in patients with refractory glaucoma, reported that 75% of patients in the micropulse group achieved a 45% reduction in IOP while 29% of patients in the continuous wave group achieved similar results after an average of 17.5 months follow-up.[81] Five patients developed hypotony in the continuous wave group while none had hypotony in the micropulse group.[81] Kuchar and associates reported a 73.7% success rate (defined as 20% IOP reduction) in 19 eyes with advanced glaucoma, after 2 months follow-up.[44] A study on 84 eyes with refractory glaucoma treated with MP-TSCPC reported a 41.2% reduction in IOP in all eyes 1 month after surgery. At 3 months post-surgery, inflammation was present in 46% of eyes and at least 1 line of vision loss was noted in 41% of eyes.[82] Lee et al. compared IOP after MP-TSCPC in adult versus pediatric glaucoma patients. They reported a success rate (defined as 5 mmHg ≤ IOP ≤ 21 mmHg and reduced ≥ 20% from baseline at the 12-month follow-up) of 72.22% vs 22.22% at 12 months follow-up. 7 out of 9 pediatric patients required reoperation during the 12 months follow-up, however, no significant complication was noted in both treatment groups.[83]

CONCLUSION

Over the past nine decades, the need to control intraocular pressure in patients with end-stage glaucoma led ophthalmologists and vision scientists to search for the optimum form of cyclodestruction. Recently, CPC procedures have developed and are associated with less postoperative complications. This is contributory to the gradual change in historical application of CPC as treatment of last resort to a treatment modality acceptable for use earlier in the course of glaucoma. Nonetheless, there remains a need for further refinement

that will both decrease complications and maximize utility of CPC.

Literature Search

We performed our literature search on Google Scholar Database, Pubmed, Web of Sciences and Cochrane Library databases published prior to September 2017 using keywords relevant to cyclodestruction, cyclophotocoagulation and treatment of refractory glaucoma.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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