New Modalities of Cycloablation and High-Intensity-Focused Ultrasound

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Natasha Nayak Kolomeyer and Marlene R. Moster

9.1 Introduction

Cycloablative or cyclodestructive procedures aim to lower intraocular pressure (IOP) by decreasing the function of the ciliary body and thereby decreasing the rate of aqueous production. Cycloablative procedures were typically used in refractory glaucoma in eyes with poor visual potential; however, more focused energy and targeted destruction of the ciliary body has led to an increase in cyclodestructive treatment options that are now an important adjunct to our surgical armamentarium.

9.2 Transscleral Diode Cyclophotocoagulation (TSCPC)

Cyclodestructive procedures have evolved since the 1920s, progressing from cyclectomy, cyclodiathermy, cyclocryotherapy, and eventually to cyclophotocoagulation [1–3]. Cyclophotocoagulation was initially performed in 1961 by using light from xenon arc photocoagulation [4] and subsequently using a ruby laser in 1969 [5]. Cyclophotocoagulation established a more widespread application once Nd:YAG (neodymium–yttrium–aluminum garnet) and eventually semiconductor diode lasers were developed. Nd:YAG cyclophotocoagulation (1064 nm wavelength) can be performed with or without ocular surface contact; however, noncontact methods were relinquished due to their higher complication rates. Currently, semiconductor diode lasers are the mainstay of transscleral diode cyclophotocoagulation (TSCPC). They have several advantages including greater uveal melanin absorption, compact size, and minimal maintenance requirements compared to prior lasers. Human cadaveric studies demonstrate epithelial coagulative necrosis and thermal coagulation of the ciliary stroma and vasculature in eyes receiving diode TSCPC [6].

N. N. Kolomeyer (✉) · M. R. Moster
Glaucoma Department, Wills Eye Hospital, Philadelphia, PA, USA

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9.2.1 Procedure

- Typically, local anesthesia or sedation is administered along with regional (retrobulbar/peribulbar/subtenon's) anesthesia.
- Common diode laser settings: Duration is often set at 2–3 s. Power starts at 1250–2500 mW. The power is titrated in 250 mW increments (maximum ~4000 mW) until an audible "pop" is heard; the power is then titrated to 250 mW below the "pop" threshold [3].
- The number of spot treatments varies between 14 and 20, sparing the 3 and 9 o'clock in order to avoid the long posterior ciliary nerves and vessels.
- The G-Probe is placed just posterior to the limbus, perpendicular to the limbus. This places the fiberoptic 1.2 mm posterior to the limbus. Maintain gentle pressure on the G-Probe throughout the treatment duration.
- Some physicians choose to administer a subconjunctival injection of steroids after TSCPC. The eye is patched and a shield is placed over the eye.
- Patients are placed on steroid drops after the laser, with the frequency of topical steroids titrated according to the severity of inflammation. All preoperative glaucoma medications are continued in the immediate postoperative period and can be selectively stopped depending on the IOP response. Patients are typically seen 1 day and 1 week postoperatively and subsequently depending on patient response.

9.2.2 Indications

TSCPC is indicated in patients with refractory glaucoma or a blind painful eye. It is typically used in patients with poor visual acuity (VA). It can also be used earlier in patients where incisional surgery is less ideal, such as those with significant medical conditions, bleeding diathesis, or scarred conjunctiva. The laser power for TSCPC may be reduced when treating eyes with good vision to reduce the risk of sight-threatening complications.

9.2.3 Results

A thorough compilation of the results and complications of TSCPC can be referred to in a recent review article; we have highlighted the most relevant findings below [7]. The treatment effect is often seen around 1 month after TSCPC; it is advisable to wait at least 1 month for retreatment if possible. TSCPC has demonstrated a range of effect on IOP (12.3–66% IOP reduction); post-laser IOP of ≤21 mmHg has been reported in 54–92.7% of eyes. Various studies suggest a correlation between IOP reduction and the amount of energy per treatment session or the number of laser burns. However, there are several studies that could not find a direct correlation. Other factors that influence treatment success include pre-laser IOP and the subtype of glaucoma. Lower success rates have been reported in aphakic, traumatic, and juvenile glaucoma. TSCPC success rates also increase with age and decrease with a

history of prior surgery. More pigmented eyes usually require less energy, but there is no clear relationship with TSCPC success rates.

9.2.4 Complications

Adverse effects associated with treatment include vision loss (8.8–47%), hypotony (0–26%), hyphema (0–2%), anterior uveitis (9–28%), pupillary changes (0.8–50%), phthisis (0–10%), retinal detachment (1%), IOP spike, cataract progression, vitreous hemorrhage, lens subluxation, necrotizing scleritis, and rarely sympathetic ophthalmia [1].

The literature suggests a relationship between the amount of energy delivered and the risk of hypotony and phthisis [8]. It is unclear if this is a nonlinear relationship, but treatment sessions utilizing more than 80 J of energy tend to have higher rates of these complications. Glaucoma subtype (including neovascular glaucoma [NVG]) and high pretreatment IOP are also considered risk factors for hypotony and phthisis. This suggests that lower energy settings in a high-risk patient may be important in minimizing these complications.

Loss of more than two Snellen lines of VA was reported on average in 22.5% of eyes (0–55% range) [7]. Rotchford et al. evaluated the outcomes of TSCPC in patients with VA of at least 20/60. After 5 years, 73.5% of patients had an IOP of 16 mmHg or less and 30.6% had lost two or more Snellen lines of VA [9]. The proportion of patients who lost vision is consistent with that reported after incisional surgery, suggesting that TSCPC can be considered as an option in selected eyes with good visual potential.

Concerns regarding postoperative complications must be balanced against overall efficacy for each individual patient, as studies suggest a relationship between the amount of laser energy delivered and IOP reduction, as well as the risk of hypotony and phthisis.

9.3 Micropulse Transscleral Cyclophotocoagulation (MP-TSCPC)

The micropulse delivery mode of diode laser (MP-TSCPC, MicroPulse P3, IRIDEX IQ810 Laser System, Mountain View, CA, USA) is a more recent form of TSCPC. MP-TSCPC operates in an “on” and “off” cycle mode, delivering 810 nm infrared radiation from a diode source. During the “on” cycle, multiple bursts of laser are emitted by the device resulting in an increase in thermal energy absorption in pigmented tissues and induction of coagulative necrosis. Theoretically, the nonpigmented tissues do not cross the coagulative threshold because they have a lower rate of thermal energy absorption and are able to cool off during the “off” cycle. The MP-TSCPC also employs a novel probe that: (a) allows sweeping, continuous applications compared to individual spot treatments and (b) targets the pars plana rather than the pars plicata.

9.3.1 Procedure

- MP-TSCPC can be performed under topical, regional (peribulbar/subtenon's/retrobulbar), or general anesthesia. Some physicians find that topical or local anesthesia with a short burst of heavy sedation can be used without a need for retrobulbar anesthesia when in the operating room. However, if done in an office setting, regional (retrobulbar/peribulbar/subtenon's) anesthesia is commonly employed.
- Default laser settings are: micropulse mode, 2000 mW power, duty cycle of 31.33%, micropulse "on" time of 0.5 ms, and micropulse "off" time of 1.1 ms. At the surgeon's discretion, the laser is delivered over 360° for 100–360 s, while sparing the 3 and 9 o'clock positions as above for TSCPC. The duration of treatment is often titrated based on the patient's history. While the default laser settings are 2000 mW, more recently surgeons have titrated the power settings in the 2000–2500 mW range based on the patient's history as well.
- The MP-TSCPC probe is placed along the limbus perpendicular to the sclera. The probe is then moved in a continuous, sliding, slow motion around the limbus, sparing 3 and 9 o'clock, while applying firm pressure. The rate of movement is encouraged to be around 10–20 s per quadrant. The probe tip is designed to position the fiberoptic tip 3 mm posterior to the limbus (Fig. 9.1).
- Some physicians choose to administer a subconjunctival injection of steroids after MP-TSCPC.
- Topical steroid drops are typically applied four times daily post-surgery to control the inflammation and subsequently tapered as inflammatory response decreases.

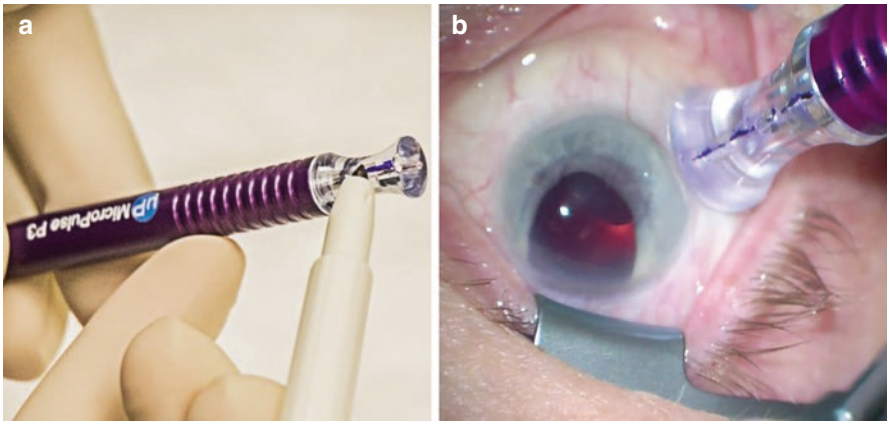

Fig. 9.1 Micropulse transscleral cyclophotocoagulation (MP-TSCPC). (**a**) The notch on the probe is to be placed toward the limbus. The notch is located on the rounder half of the probe and can be marked for easier visibility with a marker. (**b**) The probe is then placed with the marked notch perpendicular to the limbus. (Copyright Marlene Moster, MD; Bill Romano; and Natasha Nayak Kolomeyer, MD; reproduced with permission)

9.3.2 Indications

Indications for MP-TSCPC are broad, spanning noninvasive early interventions as well as refractory primary and secondary glaucomas. We recommend reviewing possible complications with the patient if using MP-TSCPC as an earlier intervention.

9.3.3 MP-TSCPC vs. TSCPC

MP-TSCPC versus TSCPC: A randomized exploratory study compared results of MP-TSCPC (with 100 s treatment duration) and continuous TSCPC in 48 patients with refractory end-stage glaucoma [10]. A successful primary outcome measure (IOP 6–21 mmHg and at least a 30% reduction with or without antiglaucoma medications after 18 months) was achieved after MP-TSCPC and continuous TSCPC in 52% and 30% ($p = 0.13$), respectively. There was a significant difference at 1 year (75% vs. 29%) that reached statistical significance ($p < 0.01$). Mean IOP was reduced by 45% in both groups from a baseline of 36.5 and 35 mmHg after 17.5 ± 1.6 months of follow-up. There was no significant difference in the number of IOP-lowering medications, while the complication rate was higher in the continuous TSCPC ($p = 0.01$) group including prolonged anterior chamber (A/C) inflammation, hypotony, and phthisis bulbi. There was a greater degree of IOP variance in the continuous TSCPC group, but the treatment settings were also more variable.

9.3.4 Results

Tan et al. [11] conducted a prospective case series of 40 eyes with refractory glaucoma that received a mean of 1.4 treatments of 100 s of MP-TSCPC. Eighty percent of eyes achieved relative success (IOP < 21 mmHg or reduction of 30% from baseline) with or without supplemental glaucoma medication, with 65% of eyes achieving successful IOP after one treatment. The average follow-up period of 17.3 ± 2.0 months was significantly longer than most other studies.

A retrospective review of 79 refractory glaucoma patients who received 120–360 s of MP-TSCPC demonstrated a treatment success rate of 75% at 3 months (IOP of 6–21 mmHg or a reduction of IOP by 20%), with an additional 10% of patients meeting the success criteria after the addition of IOP-lowering medications [12]. At 6 months, the treatment success rates dropped to 66% and were stable until the last follow-up for patients with at least 6 months of follow-up.

Emanuel et al. conducted a retrospective review of 84 eyes with a mean follow up of 4.3 months. There was a 41% and 53% reduction in IOP at 1 month and 3 months postoperatively, respectively [13].

Another retrospective review compared 320 s of MP-TSCPC results in nine pediatric (age 1–17 years) and 37 adult glaucoma patients [14]. At the 12-month follow-up period, success was achieved in 72% (26/36) of adult patients but only in 22%

(2/9) of pediatric patients ($p = 0.02$). Success was defined as IOP between 5 and 21 mmHg and ≥20% reduction from baseline at 12 months of follow-up without the use of oral carbonic anhydrase inhibitors, loss of light perception vision, or reoperation for glaucoma within the 12-month follow-up period. The mean IOP at postoperative months 1 and 6 was significantly decreased from baseline in the pediatric group, but the effect lost significance at 12 months. A majority (7/9) of pediatric eyes required reoperation to control IOP during the follow-up period.

9.3.5 Complications

The complications of MP-TSCPC in the retrospective review of 79 eyes by Williams et al. [12] included 7 patients with hypotony (9%), 21 (26%) patients with prolonged A/C inflammation, 13 (16%) patients with loss of two or more lines of best-corrected VA for ≥3 months, 4 (5%) patients with macular edema, 2 (2.5%) patients with corneal edema, and 2 (2.5%) patients with phthisis bulbi. There were no reported cases of mydriasis or loss of accommodation; however, given the retrospective nature of the study, this information was not directly elicited from the patients. The ten patients who underwent re-treatment did not seem to be more inclined to complications.

Tan et al. [11] did not observe any cases of hypotony or loss of vision after MP-TSCPC. All eyes had mild postoperative inflammation that resolved by 2 weeks in 90% of eyes and by 4 weeks in the remainder of eyes. Seven (17.5%) eyes with NVG developed hyphema. This study employed shorter treatment duration (100 s) compared to Williams et al. (120–360 s). Further studies would be required to ascertain whether there is a treatment duration related effect on outcomes and complications.

Emanuel et al. [13] observed 5 (6%) cases of persistent hypotony, 3 (4%) cases of IOP spikes, as well as hyphema (4%) and choroidals (1%). Persistent inflammation at postoperative month 3 was found in 74% of eyes. At postoperative month 1, 35% of eyes lost two more lines of vision. Three patients lost light-perception vision but were light perception at baseline. Tan et al. also found that MP-TSCPC caused significantly greater conjunctival inflammation and scarring compared to controls in Dutch Belted Rabbits, similar to continuous wave TSCPC [25]. Hence, further studies are required to investigate the effect of post-TSCPC conjunctival changes on future bleb morphology and survival.

9.4 High-Intensity Focused Ultrasound (HIFU)

High-Intensity Focused Ultrasound (HIFU) (Therapeutic Ultrasound System; Sonocare Inc., Ridgewood, NJ, USA) was evaluated as an alternative to ciliary body destruction in the 1980s [15]. Interest in HIFU initially faded due to the duration and complexity of treatment as well as significant complications (scleral staphyloma, phthisis, persistent hypotony, corneal thinning, and vision loss). However, modifications of the HIFU technology have resulted in recent renewed interest in this treatment modality. A miniaturized HIFU technique, ultrasonic circular cyclophotocoagulation (UC3, EyeOP1

HIFU, EyeTechCare, Rillieux-la-Pape, France), employs a circular operator-independent probe that focuses the ultrasound energy circumferentially on the ciliary body without operator movement. Unlike diode laser, focused ultrasound technology can treat a defined tissue volume at any depth or location within the eye, without being affected by pigmentation. The complex transducers and higher operating frequency allow for more selective treatment areas.

9.4.1 Procedure

- UC3 can be performed under topical, regional (peribulbar/subtenon's/retrobulbar), or general anesthesia.
- The coupling cone is placed in direct contact with the ocular surface and centered around the limbus. The coupling cone is then connected to a suction ring that establishes a low-level vacuum (70 mmHg) to maintain the cone in contact with the ocular surface to achieve alignment and control distance during the procedure. The probe is inserted into a coupling cone; probes are available in 11, 12, and 13 mm ring diameters (ring diameter size is determined preoperatively based on biometric data). The space between the ocular surface, the coupling cone, and the probe is filled with about 4 mL of room-temperature balanced salted solution. The probe (30 mm diameter, 15 mm height) is divided into six cylindrical piezoceramic transducers that generate ultrasound beams that allow treatment of up to 45% of the ciliary body. The ultrasound beam is focused at the depth of the ciliary body (2 mm below the sclera) [1] (Fig. 9.2).
- Each of the six transducers is activated for 4, 6, or 8 s (depending on treatment protocol), with a 20 s gap between each transducer, allowing cool down between each partial treatment. The entire treatment, which automatically proceeds with the activated foot pedal, is about 2.5 min.
- The settings specifically aim to avoid treatment of the retina, cornea, lens, as well as nasal and temporal zones.

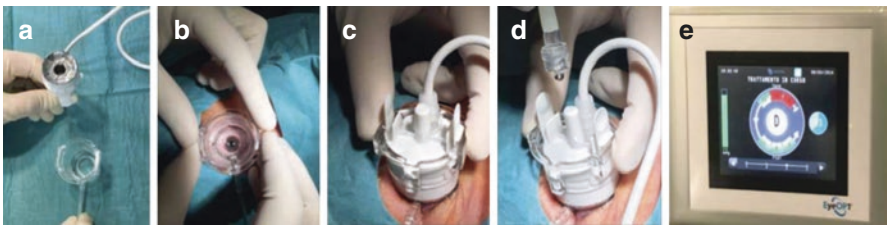

Fig. 9.2 Ultrasonic circular cyclophotocoagulation (UC3) procedure comprises two elements: the probe with the six piezoelectric transducers generating the ultrasound beam and the coupling cone (**a**). The correctly positioned cone must show a homogeneous ring of visible sclera; when this ring is regular, the cone is then maintained by a mild vacuum system (**b**). After verification of the effective suction, the probe is inserted and stabilized into the cone (**c**). During the procedure, the cone is continuously filled with saline solution (**d**), in order to allow the ultrasound transmission. The treatment starts in the superior sectors with a progressive activation of each transducer (**e**). (This figure and description have been reproduced from an open-access article by Mastropasqua et al. [1])

9.4.2 Mechanism

Ultrasound can cause thermal increase of up to 80 °C. The primary mechanism of action is reduction of aqueous production due to thermal necrosis of the ciliary epithelium. Histopathology studies in rabbits by Aptel et al. demonstrated focal necrotic changes in distal and intermediate ciliary processes, while sparing the basal and remaining parts of the ciliary body [15]. Untreated adjacent areas lacked signs of inflammation and had preserved architecture and vasculature. Additionally, there appears to be a correlation of treatment dosage and extent of ciliary process destruction [1]. Additional mechanisms of action could include modification of the scleral and conjunctival anatomy [16] and an increase in suprachoroidal and transscleral outflow [17–19].

9.4.3 Results

Giannacare et al. conducted a prospective multicenter interventional study of 30 eyes on maximum medical therapy with a 6-month follow-up [20]. Qualified and complete success (IOP reduction ≥20% and IOP ≥ 5 mmHg) was achieved in 70% and 46.7% of patients, respectively, while treatment failure was recorded in 6.6%. Eyes that were randomized to receive greater ultrasound exposure time (8 s per transducer) had greater IOP reduction compared to eyes with shorter ultrasound exposure time (4 or 6 s). There was significant IOP reduction on postoperative day 1 (39%) despite study protocol requiring discontinuation of ocular hypotensive medications in the immediate postoperative period unless IOP was above 21 mmHg.

The EyeMUST1 study was a prospective multicenter interventional study of 52 patients with refractory glaucoma [18]. Patients received either 4 s (group 1) or 6 s (group 2) exposure time per transducer (non-randomized). Success was defined as at least a 20% IOP reduction and IOP > 5 mmHg without additional hypotensive medications but with possible HIFU retreatment. Success was achieved at 6 months in 61.9% of group 1 patients and 65.4% of group 2 patients, while at 12 months the proportion was 57.1% and 48.0%, respectively (no significance at either time point). This difference was not statistically significant. Eight (15%) patients received HIFU retreatment. Twelve (22%) patients required a secondary glaucoma surgical intervention between 6 and 12 months post-HIFU.

Melamed et al. performed a prospective interventional study of 20 patients who received HIFU treatment (using 6 s exposure time per transducer), with 4 (20%) requiring retreatment [21]. Complete (IOP reduction ≥20% and IOP >5 mmHg) and qualified (allowance of additional medication and/or retreatment) surgical success was achieved in 45% and 65%, respectively.

Aptel et al. conducted a multicenter prospective clinical trial of 30 glaucoma patients without prior history of filtering surgery with a 6 s exposure time per transducer and 12-month follow up [22]. Complete success (IOP reduction ≥20%, IOP >5 mmHg and IOP < 21 mmHg with possible re-intervention and without additional hypotensive medication) was achieved in 47% of eyes and qualified success (allowance of retreatment without additional medications) was found in 63% of eyes.

De Gregorio et al. completed a prospective interventional study of 40 patients with an 8 s exposure time per transducer [23]. At 4 months, if the IOP was >21 mmHg with no adverse major complications related to HIFU procedure, the decision was made to retreat. Success was defined as IOP >5 mmHg and IOP < 21 mmHg without hypotensive medication and vision-threatening complications. Eighteen (45%) eyes achieved complete success with a mean IOP reduction of 44.3% at 4 months and 45.7% at 12 months. At 12 months, success was achieved in 85% of treated eyes with a maximum of three HIFU procedures.

9.4.4 Complications

Transient complications such as a fixed and dilated pupil (0–3%), anterior chamber inflammation (20–24%), superficial punctate keratitis (13–45%), subconjunctival hemorrhage (4–30%), corneal edema (7–20%), IOP spikes (0–7%), induced corneal astigmatism (0–3%), macular edema (0–3%), and hypotony (0–2%) have been identified [18, 20–23]. Loss of three or more lines of best-corrected VA was reported in 5–20% of patients [18, 22]. Notably, DeGregorio et al. noted scleral thinning in the treated sectors in 25% of eyes [23]. This evidence along with AS-OCT data suggesting scleral remodeling after UC_3 treatment highlights the importance of further analysis of the degree of scleral remodeling and how this may affect future filtration surgery. To our knowledge, there are no reports of persistent hypotony or phthisis after UC_3 treatment.

It is important to note that the UC_3 device requires suction to couple the device to the ocular surface, which increases the IOP for a period of 2.5 min. Although there are no reported cases of associated optic neuropathy, vein/artery occlusion, or visual field loss related to this specific device, this should be considered given the reports of LASIK-related complications [24].

9.5 Conclusion

Cycloablative treatment options for glaucoma continue to evolve. Recent developments such as MP-TSCPC and HIFU have improved safety profiles with variable results. We encourage the readers to balance the importance of safety and efficacy when choosing any surgical procedure, but especially a cycloablative procedure.

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