REVIEW ARTICLE

Ciliary Body Procedures in Glaucoma: A Narrative Review from the Past to the Future

Cicloprocedimentos no Glaucoma: Uma Revisão Narrativa do Passado ao Futuro

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ABSTRACT

Ciliary body treatments have been used in glaucoma for many decades. They reduce the intraocular pressure by decreasing the aqueous humour production. Initially, the developed techniques, like cyclocryotherapy, had high rates of complications and were reserved only for advanced and refractory glaucoma. In recent years, other procedures such as laser cyclophotocoagulation (endoscopic and transscleral) or ultrasound cycloprocedures have replaced the older techniques due to their safer characteristics. We recognize that there has been a great evolution throughout the years, moving from more aggressive techniques with serious postoperative complications to procedures with an excellent safety profile and effectiveness. Their indications are still evolving, and further studies are needed to elucidate the ideal timing of treatment and the best parameters. This review aims to understand the current role of cycloprocedures in glaucoma, describe the available modalities and compare the most used techniques.

KEYWORDS: Ciliary Body; Glaucoma; High-Intensity Focused Ultrasound Ablation; Laser Coagulation.

RESUMO

Os procedimentos do corpo ciliar têm sido usados no glaucoma por muitas décadas. Reduzem a pressão intraocular ao reduzir a produção de humor aquoso. Inicialmente, as técnicas desenvolvidas, como a ciclocrioterapia, tinham altas taxas de complicações e eram reservadas apenas para os casos de glaucoma avançado e refratário. Nos últimos anos, outros procedimentos como a ciclofotocoagulação laser (endoscópica e transcleral) e os cicloprocedimentos por ultrassons têm substituído técnicas mais antigas devido à sua maior segurança. Reconhecemos que tem havido um grande progresso ao longo dos anos, passando de técnicas agressivas com complicações pós-operatórias graves a procedimentos com excelente perfil de segurança e eficácia. As suas indicações estão em constante evolução e mais estudos são necessários para elucidar qual o *timing* ideal de tratamento e quais os parâmetros mais adequados. Esta revisão tem como objetivo avaliar o papel atual dos cicloprocedimentos no tratamento do glaucoma, descrever as modalidades existentes e comparar as técnicas mais usadas.

PALAVRAS-CHAVE: Ablação por Ultrassom Focalizado de Alta Intensidade; Corpo Ciliar; Coagulação Laser; Glaucoma.

INTRODUCTION

Glaucoma is a chronic, progressive optic neuropathy and it is the first cause of irreversible blindness worldwide.[1] From all the identified risk factors, intraocular pressure (IOP) is the only known risk factor that can be modified and its reduction is associated with a slowing down of disease progression.[2] IOP results from the balance between aqueous humour production and its drainage. The ciliary body epithelium is the main responsible for producing aqueous humour.[3]

Cycloprocedures lower the IOP by acting on the ciliary body epithelium and stroma leading to a decrease in aqueous humour production. Historically, these were last resort procedures used in refractory glaucomas with low visual potential due to their possible serious postoperative complications (hypotony, chronic inflammation, macular edema, and phthisis) and unpredictability.[4] New surgical techniques have been developed to obtain the same hypotensive efficacy with an improved safety profile.

Cycloprocedures were introduced in the 1930s to decrease IOP and consequently slow down glaucoma progression, by remodelling the ciliary body epithelium.[5] The first method, developed by Verhoeff, was called 'cyclectomy' where the ciliary body was surgically excised.[6] Then Vogt, inspired by those discoveries refined a technique called 'cyclodiathermy' using an electrode to cauterize the ciliary body.[7] Finally, in 1950, Bietti demonstrated that freezing the ciliary body would reduce the IOP, and many other authors diffused 'cyclocryotherapy' in the following years, which is still used today.[8]

Those initial surgical modalities had a poor safety profile but most importantly a questionable hypotensive clinical response. Being more effective and less destructive than cyclodiathermy, cyclocryotherapy replaced the latter as the procedure of choice.[2,9] Both were reserved for refractory glaucoma patients due to the higher risk of severe complications like postoperative pain, uveitis, hyphema, hypotony, and even phthisis bulbi.[10] These limitations led to the advent of newer techniques like transscleral cyclophotocoagulation (TSCPC) and high-intensity focused ultrasound (HIFU) as a more polished approach to the ciliary body epithelium.[4]

This narrative review aims to emphasize the growing role of cycloprocedures in glaucoma over the years, describe the available modalities, and highlight the difference between the outcomes and safety profiles of the most used techniques.

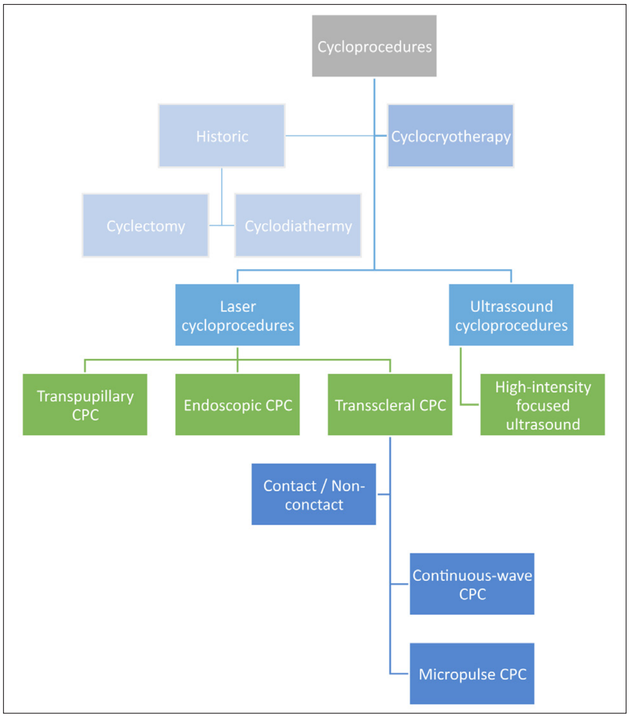

Diagram 1. General diagram of all available cycloprocedures.

CYCLOCRYOTHERAPY

Cyclocryotherapy stands for the trans-scleral application of a cryo-probe to ablate ciliary tissue and reduce the aqueous humour production.[4] Bietti introduced this technique in 1950 but because of the unavailability of cryogenic systems, it took 10 years for this procedure to be applied more widely after the works of de Roeth *et al*.[8]

The cryotherapy unit regulates a gas flow reservoir (of nitric oxide or carbon dioxide) so that the probe tip reaches freezing temperatures around -70ºC to -80ºC. Applying the tip at 1 – 1.5 mm from the limbus for 60 seconds can produce the desired -10ºC at the target tissue over an arc of 180º. The 3 and 9 o'clock positions should be avoided to prevent damage to the long posterior ciliary nerves.[4,8]

With those parameters, cyclocryotherapy obtains moderate necrosis of the ciliary body by two main mechanisms of cell damage: toxic action of a concentrated solution of electrolytes and the formation of intracellular crystals. Early studies had a wide range of results depending on the type of glaucoma, having better IOP control rates in patients with open-angle glaucoma compared to other types like neovascular glaucoma. On the other hand, some of the series had up to 32% of patients with major complications like phthisis bulbi.[8]

LASER CYCLOPROCEDURES

For the last sixty years, laser cycloprocedures have been developed and improved. The first one was performed with a 693 nm Ruby Laser by Beckman.[11] Until today, three main types of lasers were used: neodymium-doped: yttrium-aluminium-garnet (Nd: YAG), argon, and diode. The latter is mostly preferred due to its cost, efficiency, and portability. Several approaches have been implemented, namely: transpupillary (TPCPC), endoscopic (ECP), and transscleral cyclophotocoagulation (TSCPC).[2,9] Almost simultaneously, in the 1980s, ultrasound cycloplasty (UCP) was introduced and then refined in what we call today high-intensity focused ultrasound (HIFU).[12,13]

1. TRANSPUPILLARY CYCLOPHOTOCOAGULATION

TPCPC is a treatment option used when on complete mydriasis and serves specific patients like those with aniridia, large iridectomies, and anterior iris displacement because it needs a clear view of the ciliary processes through gonioscopy. An argon laser with 488 nm is used to coagulate the ciliary processes and the usual settings are 125 μm spot size, 700-740 mW of energy, and 0.3 – 0.5 seconds of pulse duration. It is limited as a last-line treatment for the selected cases referred to above.[4,9]

2. ENDOSCOPIC CYCLOPHOTOCOAGULATION

This cyclodestructive procedure was developed by Martin Uram in 1992.[14] One of the differences between ECP and TSCPC is the extent of the affected tissue. The first procedure, by going endoscopically, only damages the ciliary processes and its capillaries, but the second one, by crossing several anatomical structures before reaching the ciliary body, can even damage the ciliary muscle and stroma.[2]

The ECP probe (Endo Optiks from BVI Inc.®) consists of a semiconductor diode laser, an aiming beam, a light source, and a 20-gauge optical fiber endoscope. Unlike other procedures, ECP is performed through the anterior segment of the eye using a limbal or pars plana approach. Therefore, the surgeon carries out the surgery while watching a monitor rather than looking directly at the probe, which implies a greater learning curve. Although it can be performed alone, it's usually combined with cataract surgery.[2,4] Thereby, most published studies report the combined treatment rather than the ECP alone.

Even though there is some loss in efficacy over time, long-term results (12-18 months) were still relatively good, with IOP reductions between 23.9% - 66% and a statistically significant reduction in the mean number of medications in almost all studies. It is a relatively safe surgery and the most common postoperative complications are IOP spikes and hyphema, with 14.5% and 3.8%, respectively. The major complication is cystoid macular edema in 0.7% to 6% of cases. To date, there are no standardized parameters for the treatment, reaching between 180º and 360º of treatment.[2,4]

3. TRANSSCLERAL CYCLOPHOTOCOAGULATION

In this modality, the laser is transmitted through the overlying sclera, absorbed by the melanin in the ciliary processes, resulting in selective thermal coagulation of the ciliary body. It can be performed with a 1064 nm Nd:YAG laser or an 810 nm semiconductor diode continuous laser. They were first introduced in the 1970s, but only the latter is mainly used today, due to its equivalent efficacy and lower incidence of adverse effects.[2,9] These are commonly used when all the current medical and surgical options are exhausted or when patients are not fit for surgery.[9] There are various anaesthetic options for these procedures, including general, sedation, retrobulbar, peribulbar, and sub-tenon / conjunctival anaesthesia. The chosen method depends on the surgeon and patient's preference and the availability at the location of practice.[2]

3.1. Contact and Non-Contact Laser

There are two existing methods, and both use Nd:YAG laser. The non-contact method is performed using a slit-lamp delivery system (Microruptor II and III from Meridian AG™) with a non-Q switched thermal pulse mode. Most often, a contact lens is used to immobilize the globe, keep the eyelids open and blanch the conjunctiva so the energy is more precisely delivered. Normally, the treating laser beam is applied to the sclera at 1.5 mm posterior to the surgical limbus superiorly and inferiorly and 1 mm posterior to the surgical limbus nasally and temporally. It is focused 3.6 mm into the eye and each application lasts 0.02 seconds with the power ranging between 4-9 J. In each session, approximately 30-40 spots are evenly applied over 360º, avoiding the 3 and 9 o'clock positions.[9,10]

On the other side, the contact method (Microruptor III from Meridian AG™) requires the patient to be in the supine position. An optical fibre handpiece connected to a sapphire-tipped probe is placed perpendicularly on the conjunctiva around 0.5-1 mm posterior to the limbus. Approximately 16-40 spots are applied over 360º, always sparing the 3 and 9 o'clock positions. Each spot lasts 0.5-0.7 seconds and has a power setting between 4-7 W.[15]

Due to their lack of practicality and safety profile, these two methods were replaced with the following techniques.

3.2. Continuous-Wave Diode Cyclophotocoagulation (CW-TSCPC)

A semiconductor solid-state diode laser system is coupled with a special probe (G-probe) and a built-in optic fibre handpiece that has transillumination. It delivers energy from a continuous-wave 810 nm diode laser, being absorbed by the melanin in the ciliary body epithelium. When placed 1.2 mm posterior to the limbus, the laser beam focuses on the ciliary processes and since the ciliary body does not have a perfectly circular root, it is recommended to transilluminate the eyeball to identify its location through the sclera.[16] Like contact Nd:YAG laser, it is applied with the patient in the supine position and with a lid speculum. A total of 16-20 spots are applied with a typical duration of 2000 milliseconds over 360º, sparing 3 and 9 o'clock positions to spare the long posterior ciliary nerves. The power settings normally start at 1750 mW and should be titrated individually (100 – 250 mW) such that the minimum power required to produce an audible "pop".[9,10] Other protocols, such as the slow coagulation CW-TSCPC, use lower power settings and longer application times (between 1250 – 1500 mW for 4 seconds) with similar outcomes and fewer complications in different types of glaucoma.[17,18]

Two long-term studies using CW-TSCPC found that success rates oscillated between 63% and 89% after treatment, achieving a target IOP of less than 22 mmHg after a mean follow-up time of 17 months.[19,20] Moreover, a recent review noted that an important contributing factor to the percentage of IOP reduction is the preoperative IOP. Patients with higher preoperative IOP were more likely to achieve a higher IOP reduction (over 30%). This review even stated that the average reduction in glaucoma medications was around 1.2 (particularly oral acetazolamide suspension, between 55%-80% reduction).[2]

Two types of glaucoma must be highlighted, neovascular and pediatric glaucoma.[2] In neovascular glaucoma, a comparison study with the Ahmed filtration valve reached similar overall success rates (61.18% *vs* 59.26% in the Ahmed valve group), achieving a target IOP of less than 21 mmHg after a mean follow-up time of two years.[21] In pediatric glaucomas, a satisfying IOP reduction was reached at a one-year follow-up in only 37% of cases (achieving more than 30% reduction), and generally requires retreatment to maintain IOP control (66% of cases, compared to 49% in the adult series).[22]

On the other side, various complications were reported, including hypotony (0%-18%), chronic macular edema (0%-6%), a decrease in visual acuity (around 20%) and phthisis bulbi (0%-9.9%).[2] A special provision for patients with neovascular glaucoma that had up to 76% of hypotony in one of the reported series. In pediatric glaucoma, the complication rates, especially the ones associated with inflammation, are more common (up to 25%) compared to adults.[2,16]

3.3. Micropulse Trasnsscleral Cyclophotocoagulation (MP-TSCPC)

The newer transscleral diode system was developed to overcome the problems of the anterior modality, trying to reduce the complications and maintain the same effects on IOP reduction. It uses the same diode 810 nm laser with a different probe (MP3 – Micropulse P3™ probe, by Iridex®) and with a different mechanism of action. In contrast to CW-TSCPC, it emits energy in a series of short pulses separated by rest periods (which is the concept of a micropulsed laser). With this "on'' and "off" cycle mode, it induces a thermal reaction on the pigmented ciliary epithelium when "on'' and gives the adjacent structures time to recover during the "off" cycle. Therefore, the exposure time is shorter than the thermic relaxation time of the affected tissues which prevents the formation of a heatwave, avoiding reaching the coagulation threshold of surrounding non-pigmentary tissues. Consequently, the laser activity time is reduced to 31.3%, which is called the duty cycle.[23]

The exact mechanism of action is not yet clear, and it is thought to lower the IOP through a combination of more than one mechanism: the first one by reducing the aqueous humour production after remodelling the ciliary body epithelium; a second by increasing the uveoscleral outflow through the remodelling of the extracellular matrix; and a third, a pilocarpine-like effect that increases the conventional outflow of the aqueous humor.[24]

As with CW-TSCPC, the patient needs to be in the supine position with a lid speculum and under similar types of anaesthesia. The procedure itself is different from CW-TSCPC, as this technique is mostly applied with the probe having several sweeps around the limbus in a slow-motion manner although there are reports of a stop-and-continue technique like CW-TSCPC.[2] However, the ideal parameters are still not standardized. The pulses are delivered 3 mm posterior to the limbus. The duration of treatment is usually at least 80 seconds for each hemisphere but it is highly variable (between 40-160 seconds) according to the desired effect and the power normally starts around 2000 mW but can go up to 2500 mW.[2,4,16,23,24]

A recent Portuguese retrospective study conducted by Basto R *et al*,[25] evaluated 61 eyes and their two-year results of MP-TSCPC (using the Cyclo G6TM Glaucoma Laser System from Iridex®; Figs. 1 and 2). Most patients had primary open-angle glaucoma (POAG) (64%), followed by pseudoexfoliative glaucoma (20%). Another important note was that close to 38% of the eyes had previous filtration surgery. The mean IOP reduction was 40.4% at 1 week, 27.1% at 12 months and 17.7% at 24 months. The mean starting IOP was 24.9 mmHg (± 8.6 mmHg) being reduced to 16.1 mmHg and 17.6 mmHg at 12 and 24 months, respectively. Average topical glaucoma drugs decreased from 4 to 3.4 and 17 out of 19 patients discontinued acetazolamide. According to the success definition of the World Glaucoma Association,[26] it had a total success (IOP between 6 and 21 mmHg or IOP reduction of at least 20% from baseline or discontinuation of oral carbonic anhydrase inhibitors or topical antiglaucomatous drugs) of 86.4% and 81.9% at 12 and 24 months respectively. Only 8 patients (17.4%) reported mild pain during the immediate postoperative period. No inflammation, chronic hypotony, decreased vision, or phthisis bulbi were observed.

Special note for the research of Varikuti *et al* which evaluated the outcomes of MP-TSCPC on 61 eyes with good central vision (at least 20/60 of best-corrected visual acuity, BVCA). They found an IOP reduction of 40.2% from baseline (25.69 ± 5.63 mmHg) at 12 months follow-up, without a statistically significant reduction in BVCA. Their overall qualified success (IOP between 6 and 21 mmHg or ≥ 20% IOP reduction, no need for retreatment or BVCA loss more than 2 lines) was 93.75% at 12 months. They state that MP-TSCPC might be an option in the earlier stages of glaucoma due to their results.[27]

Nonetheless, all the published studies have reported similar efficacy results and fewer complications compared to CW-TSCPC.

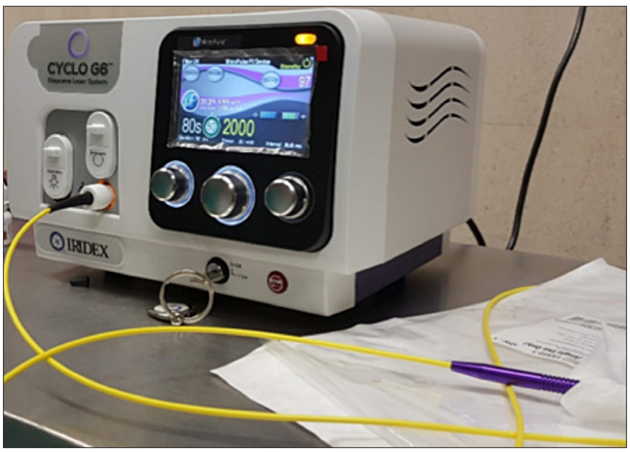

Figure 1. Cyclo G6TM Glaucoma Laser System from Iridex®.

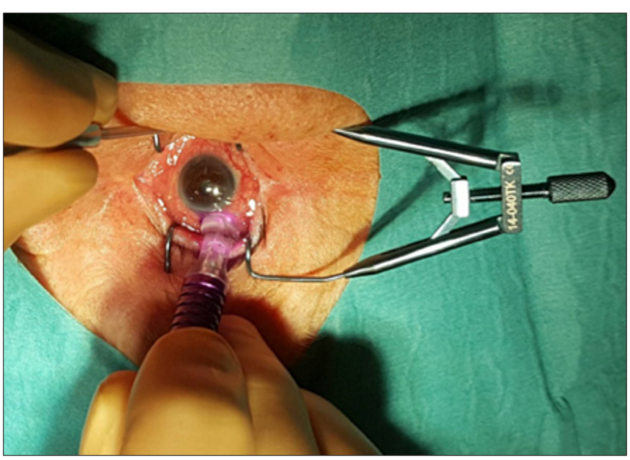

Figure 2. Probe placement during MP-TSCPC.

COMPARISON BETWEEN CW-TSCPC AND MP-TSCPC

CW-TSCPC and MP-TSCPC are the most used cycloprocedures to date and it is why it is important to compare them.

Aquino *et al* compared the two techniques in eyes with various types of refractory glaucoma (23 eyes for each group), with or without previous filtering surgery, and demonstrated that MP-TSCPC had higher short to mid-term success rates compared to CW-TSCPC (52% *vs* 30% at 18 months). Also, the MP-TSCPC group had a lower incidence of complications (1 case of prolonged inflammation compared to 7 cases and 1 of hypotony).[28]

Another study using patients with non-refractory POAG (without previous incisional surgery) compared both modalities (10 eyes each) and added a third group treated with HIFU. With just 6 months of follow-up, the success rates (60% for MP-TSCPC, 50% for CW-TSCPC and 50% for HIFU) had no statistically significant difference. Regarding complications, although the CW-TSCPC group was the only one with major complications (1 case hypotony, 1 choroidal detachment, 1 phthisis bulbi) it was not statistically significant.[29]

A larger and more recent study used patients with various types of glaucoma to compare both modalities (47 eyes for MP-TSCPC and 150 eyes for CW-TSCPC) with a 12-month follow-up. The success rates were similar between both groups (88.6% for MP-TSCPC and 87.5% for CW-TSCPC). Unfortunately, the complications were not explored due to the design of the study (except for the visual acuity which was not significantly different).[30]

Moreover, a pediatric study with almost all patients previously treated with surgery, found that the difference in the success rate between both techniques of TSCPC was also not statistically significant (MP-TSCPC with 71% compared to 46% in CW-TSCPC). Similarly, none of the MP-TSCPC had serious complications but the CW-TSCPC group, reported 2 cases of prolonged inflammation and 3 of hypotony (1 leading to phthisis bulbi).[31]

Most of the studies that focused on the efficacy and safety of MP-TSCPC alone only showed short-term results but all of them had success rates higher than 50% after 12 months and the majority had success rates around 80% (most success definitions fell within the following: >20% reduction of baseline's IOP and IOP between 5-21 mmHg and absence of serious complications).[28,29,31–33] One of the studies with the biggest cohort of patients evaluated the intermediate-term results (12 months follow-up) of MP-TSCPC with similar success rates (71% in a total of 161 eyes).[34]

Unfortunately, since they use different parameters, it's difficult to compare them directly.

ULTRASOUND PROCEDURES

High-intensity focused ultrasound (HIFU) is a recent technique employing 6 piezoelectric transducers arranged circularly to deliver transconjunctival focused ultrasound to the ciliary body resulting in partial cyclocoagulation, therefore reducing IOP. This treatment modality is fast, computer-assisted, non-operator-dependent, non-invasive, and relatively painless. Different circular probes (Figs. 3 and 4) exist with varying sizes and treatment time delivery (4 to 8 seconds).

A prospective study of 49 eyes with refractory glaucoma showed that HIFU reduced IOP by 34% in 1 year with a significant reduction of both topical and oral medication. Additional filtration surgery was needed in eight eyes (16%) with HIFU allowing for a 6-month delay to a second procedure. Most adverse effects were mild, mainly anisocoria and local discomfort. However, seven patients lost more than two visual acuity lines at the last follow-up, five of which lost light perception, with most having a very low pre-operative visual acuity (counting fingers or worse), highlighting the need for careful patient selection.[35]

Hugo *et al* published a report focusing on IOP outcomes, flare measurement, endothelial cell count, and quality of life after the procedure in 15 eyes with severe or refractory glaucoma. Their results showed a 42% decrease in IOP at 6 months, an inverse relationship between flare and IOP in the first 3 months, and significant endothelial cell loss (11%). However, there was no significant modification in quality-of-life assessments during follow-up and there were no major postoperative complications.[36]

Leshno *et al* conducted a 2-year prospective trial using 15 patients with moderate open-angle glaucoma and showed a fairly good and sustained IOP lowering effect (34% reduction), with 91% of the patients completing the 2-year follow-up period maintaining the 20% reduction from baseline. There were also no major or sight-threatening adverse effects recorded.[37]

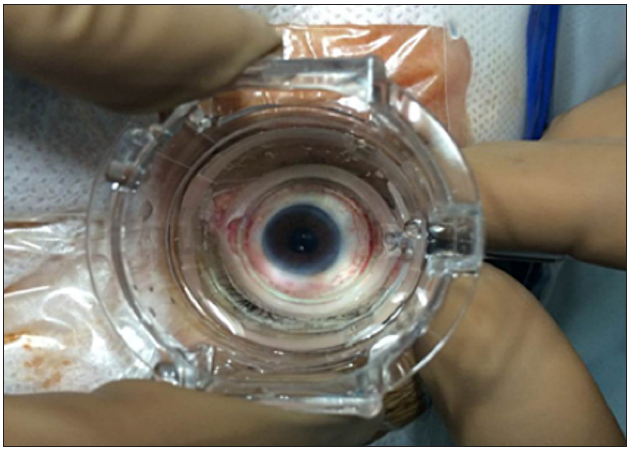

Figure 3. Eye exposure before ultrasound cycloplasty.

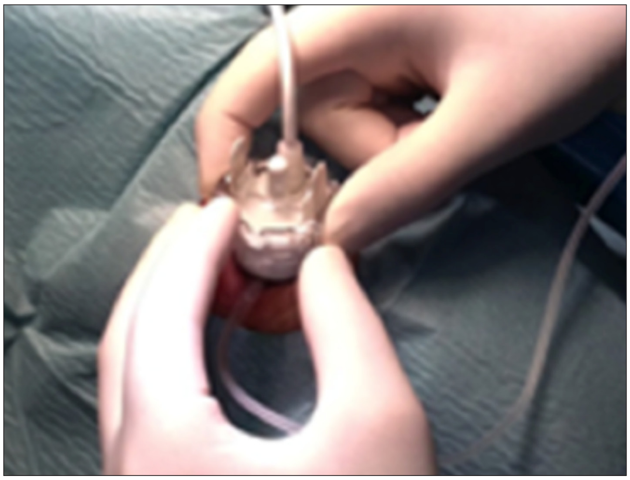

Figure 4. Ultrasound cycloplasty probe duringprocedure.

CONCLUSION

Cycloprocedures have been an alternative treatment for glaucoma since the 1950s and their indications are changing with time and with newly developed techniques. It started as a last-resort treatment for refractory glaucoma patients and it had a high risk of severe postoperative complications but, nowadays, there are more effective modalities with better safety profiles and hypotensive results that could lead to earlier use.

Laser cyclophotocoagulation is now the most used cycloprocedure, but various other techniques are being developed alongside ultrasound-based procedures such as HIFU. Regarding TSCPC, according to some authors, MP-TSCPC can be an alternative to CW-TSCPC due to its similar results in efficacy and significantly better safety profile. It is also important to emphasize that most studies show a slight loss of efficacy in the long term. Nevertheless, more studies are needed to elucidate their differences.

Unfortunately, there are still many uncertainties about which parameters are the best regarding the type and stage of glaucoma, and if they are suitable for every patient. From another perspective, these interventions are not entirely predictable, creating some instability in the exact post-procedure outcomes.

Also, there are hardly any studies on the real long-term impact of repeating these techniques and their consequences on eyes that need additional interventions for glaucoma.

Finally, the definitive role of cycloprocedures in glaucoma is still under discussion and more studies are needed to validate the correct indications.

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JA, MV, CM and RB: Drafting the manuscript.
ASL, LAP, FTV and IP: Drafting and revising the manuscript.
All authors approved the final version to be published.

JA, MV, CM e RB: Elaboração do manuscrito.
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