EXPERT REVIEWS

Performing accurate CO_2 laser-assisted sclerectomy surgery

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Most glaucoma surgeries achieve intraocular pressure (IOP) reduction by penetrating the sclerotrabecular wall. Deep sclerectomy surgery aims to enhance aqueous drainage without penetrating the globe and also aims to avoid some of the severe complications associated with violating ocular integrity; however, this procedure is difficult to perform manually in a safe and effective way. CO_2 laser has been suggested as a tool to facilitate deep, effective ablation over the ocular drainage system to reduce IOP without penetrating the eyeball in a procedure called CO_2 laser-assisted sclerectomy surgery. In this study, the authors report the rationale of choosing this type of laser, the development of the laser delivery and control systems (IOPtiMate; IOPtima, Tel Aviv, Israel) and the experimental and clinical experience to date.

Keywords: carbon dioxide laser • CLASS procedure • filtration procedure • glaucoma surgery • laser surgery

Open-angle glaucoma (OAG) is a progressive optic neuropathy, resulting in loss of retinal ganglion cells leading to progressive damage of the visual field and blindness [1]. Elevated intraocular pressure (IOP) is a major risk factor for glaucoma. Long-term clinical trials have confirmed the need for effective pressure reduction [2–4]. Glaucoma treatments are directed at reducing IOP, the only modifiable factor [5].

The IOP may be reduced either pharmacologically or surgically. The fundamental feature of penetrating incisional surgery, such as trabeculectomy and glaucoma drainage devices, is creating a permanent fistula enabling aqueous filtration outside the eye [6]. Trabeculectomy, the gold standard filtration procedure, is associated with numerous possible complications, including infection, inflammation, bleb leak, bleb encapsulation, hypotony, cataract and even vision loss [7–11]. Thus most ophthalmologists are reluctant to use it as an early intervention [8], and surgery is usually performed when IOP control is not achieved by medications or laser treatment [12].

To avoid sight threatening complications emerging from violating the ocular wall integrity, a nonpenetrating deep sclerectomy (NPDS) procedure had been developed. Deep sclerectomy is achieved by performing a partial thickness scleral flap, followed by a second flap dissection deep in the sclera above the anterior trabeculum and peripheral cornea. The residual extremely thin, yet intact, tissue allows fluid transfer from inside the eye out to the subconjunctival space [13,14]. In cases of tissue perforation, conversion to trabeculectomy is the preferable option [15]. The highly demanding dissection in NPDS is difficult to perform manually, resulting in a slow learning curve [16].

CO_2 lasers are widely used as a treatment modality mainly for lesions of the skin and membranes. CO_2 irradiation is used to facilitate scleral dissection in a procedure called CO_2 laser-assisted sclerectomy surgery (CLASS) [17–20].

The rational of CLASS procedure

Important CO_2 laser characteristics are precise ablation of dry tissues, photocoagulability and efficient absorption by fluid. When applied on a dry bare scleral bed, under the dissected scleral flap, the laser action is directed toward tissue removal. Repeated ablations would result in a progressive controlled thinning of tissue. Once the tissue is thin enough to allow percolation of aqueous from the anterior chamber

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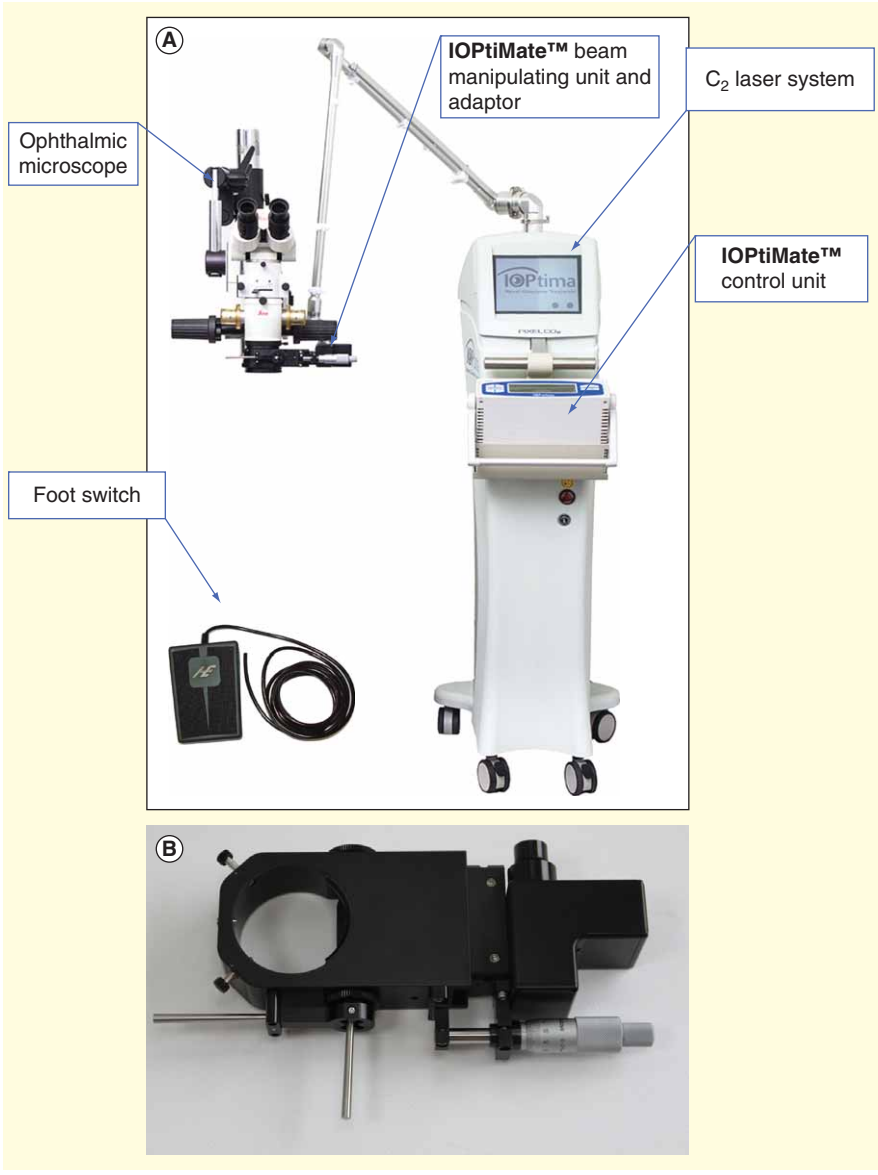

Figure 1. The IOPtiMate CO_2 laser system. (A) An illustration of the IOPtiMate CO_2 laser system consisting of a control unit and a scanner, which delivers laser energy from CO_2 laser platform to the operating microscope. Laser is applied using a foot pedal, allowing the surgeon to operate with both hands. **(B)** The IOPtiMate OT-135P2 laser scanner (beam manipulating unit) and an adaptor designed for assembly to most ophthalmic microscopes.

to the ocular surface, additional laser energy would be absorbed by the fluid, preventing deeper ablation and perforation.

This unique combination of effective tissue ablation and blockage of the laser energy by fluid leads to cessation of the laser action at the clinical endpoint of the surgical procedure, namely sufficient fluid filtration out the eye via a thin continuous trabeculoscleral wall.

The system components

The system for CLASS procedure named IOPtiMate, manufactured by IOPtima Ltd., Tel Aviv, Israel, consists of the following (Figure 1):

- A CO_2 laser system.
- A scanner (beam manipulating unit) that is integrated to the ophthalmic microscope and delivers laser energy from a CO_2 laser platform to the area being treated under guidance from the operating microscope.
- A control unit, controlling the shape and size of the laser beam scans.

The area being treated is clearly marked with red laser aiming beam on the chosen pattern perimeter.

The first generation of the system was the OT-133. On the basis of experimental and clinical experience gained with the OT-133, the next generation, the OT-134, was developed, followed by the OT-135P. The IOPtiMate™ scanning parameters were optimized to ensure safety and improve the efficacy. The dimensions of the ablation area were modified to accomplish a perfect fit to the anatomy of the eye. The laser control parameters such as dwell time and density were also adjusted, and the user interface was improved. The current model, the OT-135P2, is more compact, safe, effective and user friendly. The current system includes advanced software that allows various scanning options, and a highly adjustable adaptor that may be assembled on most ophthalmic microscopes.

CLASS surgical procedure

Conjunctival fornix-based peritomy is followed by a wide 5 mm half-thickness rectangular scleral flap, extending centrally up to the clear cornea (Figure 2A). The laser scanning area is aimed at the gray zone (Figure 2B), to reveal the underlying Schlemm's canal and trabecular meshwork, not seen prior to laser application (Figure 2C). Laser energy is repeatedly applied to ablate the trabeculoscleral tissue (Figure 2D) and the charred coagulated tissue is gently wiped with a wet sponge. The surgeon should ensure that sufficient amount of fluid is percolating from a wide zone along the treatment area before suturing the scleral flap and conjunctiva back in place (Figure 2E). Mitomycin C (MMC) may be used during the procedure.

Experimental models & clinical trials

CLASS was first tested using the earlier prototype (model OT-133) micromanipulating system. The feasibility and safety of the procedure were examined in experimental models [17]

and in a clinical trial [21] The preliminary studies were performed in three experimental models: enucleated sheep and cow eyes (n = 18) to determine optimal irradiation parameters, live rabbit eyes (n = 20) to test feasibility and cadaver eyes (40 procedures in 20 eyes) to study effects in a human eye tissue [17]. Fluid percolation was repeatedly achieved without penetration in sheep and cow eyes. Deep sclerectomy was achieved without perforation in 19/20 eyes of living rabbits. Intraocular pressure was significantly decreased on the first postoperative day (10.3 ± 5.1 mmHg lower, on average, than in the nonoperated fellow eye; $p < 0.001$). Histologically, a thin sclerocorneal intact wall was demonstrated at the sclerectomy bed. Collateral tissue damage did not extend beyond 100 m and adjacent structures remained unharmed. The CLASS procedure with the OT-133 micromanipulating system was also tested in a pilot clinical study [21] in a series of 23 eyes. The mean preoperative IOP dropped from 27.2 to 11.3 mmHg after 1 week and to 16.9 mmHg 6 months after the procedure. However, six patients required medications and three patients failed and required conventional trabeculectomy.

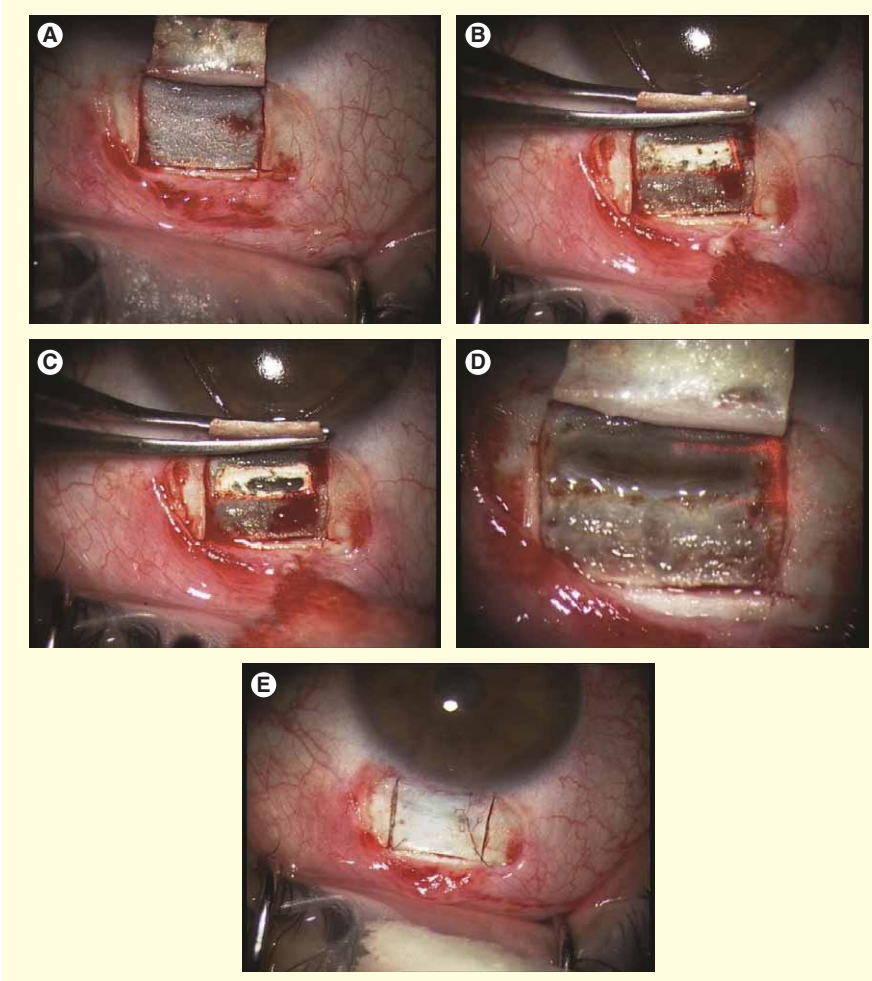

Figure 2. Surgical steps in CLASS procedure. (A) A wide partial thickness scleral flap is performed up to clear cornea. **(B)** CO_2 laser is applied over the gray zone. The pattern and size of the scanned area are demarcated by a red laser line. **(C)** Initial aqueous percolation can be detected **(D)** Schlemm's canal roof and trabeculum are wide open **(E)** the sclera flap is sutured over the treated area.

Overall, the short-term success was convincing and the CLASS procedure using the OT-133 micromanipulating system was found to be a safe and a promising procedure; however, there were also several drawbacks such as excessive charring and tissue coagulation around the treated area, leading to peripheral anterior synechiae with consequent failure of the filtration.

On the basis of lessons learned from the first model, the next generation of micromanipulating system, the OT-134 (IOPtiMate; IOPtima Ltd., Tel Aviv, Israel), was developed. The improved version provided faster scanning, higher power focused laser beam, evenly distributed over the scanned area with some beam overlap to ensure uniform, effective ablation with minimal coagulative thermal damage to adjacent tissues [20]. The procedure was tested in three experimental models to evaluate its safety and performance [21]. The procedure was tested using enucleated porcine eyes, human cadaver eyes and live rabbits eyes. Deep scleral ablation and aqueous percolation were successfully achieved in all models. The postoperative follow-up duration in live rabbits was up to 21 days. A significant IOP reduction was recorded (by 6.3 ± 3.6 mmHg) on the first postoperative day ($p < 0.0001$) although IOP gradually returned to preoperative levels. Deep scleral craters with a thin intact sclerocorneal tissue layer were demonstrated as evident in the histological slides (Figure 3). Mild and temporary thermal damage limited to the ablated scleral walls was detected and resolved 10 days after the procedure. The study group concluded that the procedure is safe and effective in achieving fluid percolation and decided to move on to the clinical trial.

In a prospective, nonrandomized, noncomparative, multinational, multicenter clinical research study, CLASS was conducted in primary OAG and pseudoexfoliative glaucoma patients presenting with uncontrolled disease under maximally tolerated hypotensive medical treatment. The clinical trials were carried out in 9 medical centers located in four different continents: Mexico City, Mexico (Drs Gil Carrasco and Turati), in Madanapalle, India (Drs Thomas and Naveen), in Moscow, Russia (Dr Anisimova), in Ancona, Italy (Dr. Mariotti), in Valencia, Spain (Dr. Muñoz), in Genève, Switzerland (Dr. Shaarawy), in Lausanne, Switzerland (Dr. Mermoud), in Tel Aviv, Israel (Dr. Melamed) and in Kfar Saba, Israel (Dr. Geffen).

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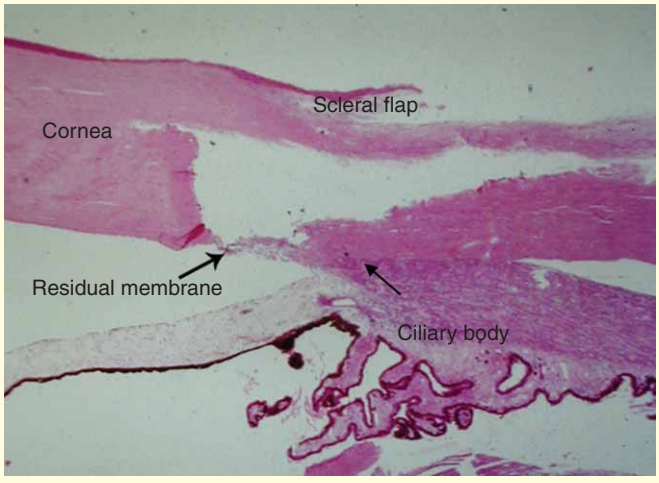

Figure 3. Histological slide of a human cadaver eye following CO_2 laser-assisted sclerectomy surgery procedure, showing a thin membrane at the peripheral cornea and over the drainage system.

The studies were conducted in accordance with the Declaration of Helsinki with the approval of the Human Research Committee of the participating medical centers with applicable regulations pertaining to Good Clinical Practice. Inclusion criteria were uncontrolled glaucoma under maximally tolerated hypotensive medical treatment, baseline IOP higher than 18 mmHg and no other ocular surgery or laser treatment, except prior clear corneal incision cataract surgery. Exclusion criteria were previous ocular surgery (other than cataract), ocular media opacity preventing proper evaluation of the optic nerve, extremely small pupil size and poor vision in the fellow eye. Complete success was defined as 20% IOP reduction and IOP between 5 and 18 mmHg. Similar IOP requirements achieved with hypotensive medications were defined as qualified success.

Between December 2007 and February 2011, 111 consecutive eyes of 111 subjects that met the inclusion/exclusion criteria were enrolled in the study. The results of the first 37 patients, who were followed up for 1 year, were previously published by our group [20]. The reported 37 subjects were operated on in following countries: 13 patients in Mexico, 14 in India and 10 in Russia. Depending on the depth of the initial manually created scleral flap, four to eight laser ablations were usually required to reach sufficient aqueous percolation, lasting approximately 2–5 min with a total of 30–60 min duration for the entire surgical procedure. Postoperative treatment included prednisolone acetate 1% drops (Pred Forte; Allergan, Irvine, CA, USA) six-times daily for 4 weeks and with moxifloxacin 0.5% drops (Vigamox; Alcon Laboratories, Fort Worth, TX, USA) four times daily for 2 weeks.

Neither serious complications nor device malfunctions were reported in the clinical results. The reported complications were mostly graded as mild and transitory [20]. No cases of blebitis or endophthalmitis were reported, and one case of conjunctivitis that was probably unrelated to the studied procedure was documented. MMC was used in 73.5% of the patients and no implants were used. Complete success rates at 12-month visit with and without MMC were 68.2 and 42.9%, respectively, ($p = 0.375$), whereas the rates of qualified success were 95.5 and 71.4%, respectively, ($p = 0.136$). The average number of hypotensive medications was significantly reduced from an average of 2.5 ± 1.3 medications per patient to 0.1 ± 0.4 at 6 months and 0.6 ± 0.9 at 12 months ($p < 0.001$). Eight needling procedures were performed in seven subjects; 3.8 weeks (mean) post CLASS procedure. YAG laser goniopuncture was performed 2 and 4 weeks post procedure.

The results of other 15 patients operated in one of the study centers were analyzed and published by Skaat *et al.* [22]. Preoperative IOP of 27.3 ± 4.2 mmHg (mean ± SD) dropped to 15.0 ± 3.7 mmHg at 6 months and to 16.6 ± 3.4 mmHg at 12 months postoperatively, yielding an average IOP reductions at 6 and 12 months of 13.1 ± 4.3 (45.1%; 95% CI: 11, 15.3) and 11.5 ± 5.5 mmHg (39.2%; 95% CI: 8.8, 14.3), respectively ($p < 0.001$). The complete success rate after 12 months was 45.5%, whereas qualified success was 90.9%. MMC was used in76.9% of the subjects.

The results of the total 111 participants in the multicenter clinical trial are currently analyzed and will be published in the near future.

Discussion

CO_2 laser is inherently absorbed by fluid, blocking further tissue removal once percolation of aqueous is achieved. This combination of efficient ablation of dry tissue and high absorption by fluid prevents undesired penetration through the sclera and trabeculum. The concept of CLASS procedure offers laser-controlled ablation deep within the sclera, limited to the point where fluid can exit the eye via extremely thin continuous residual membrane.

The simplicity of performance is an appealing advantage because it obviates the prolonged learning curve and surgery duration characteristic of manual NPDS, and thus can be confidently performed by surgeons with a wide range of experience in filtration surgery.

The advantages of performing a noninvasive procedure are potentially reduced risk of adverse events, especially bleb or ocular infections and lower risk of hypotony, choroidal effusion, hyphema, cataract and shallow anterior chamber [16,23–25]. CLASS procedure attempts to overcome some of the safety issues related to penetrating procedures while achieving adequate IOP control, better than the one achieved using manual NPDS and currently available minimally invasive glaucoma procedures.

The Cochrane database systematic review performed by Eldaly MA *et al.* [16] compared the effectiveness and the safety of non-penetrating trabecular surgery with conventional trabeculectomy in glaucoma patients. The review included five studies with a total of 311 eyes (247 participants). One hundred sixty eyes that had trabeculectomy were compared with 151 eyes that had non-penetrating glaucoma surgery (of which 101 eyes had deep sclerectomy and 50 eyes had

viscocanalostomy). Relatively fewer complications with non-filtering surgery were recorded compared with trabeculectomy (17 and 65% respectively), and cataract was more commonly reported in the trabeculectomy studies.

No severe device-related complications were recorded in the clinical studies. The recorded complications were mostly mild, treated conservatively and resolved within the early postoperative period [20,22]. Although microperforations were occasionally detected with no sequelae, macroperforations associated with anterior chamber shallowing or iris prolapse throughout the incision were not reported. The safety of the procedure and the clinical outcome were not compromised by the occurrence of microperforations, which might have facilitated aqueous filtration.

The efficacy of the CLASS procedure was noninferior to that reported in a series of studies investigating manual NPDS [16,26]. The results of the clinical trials using the OT-135 suggest that the reduction in average IOP, at 12 and 24 months following CLASS procedure, are comparable with those of two large studies reporting the efficacy of trabeculectomy [7,27].

According to Dahan *et al.* [28], NPDS has a favorable outcome in patients not having topical medications prior to surgery. The favorable safety profile and efficacy reported in the clinical trial suggests that the CLASS procedure might be considered as a primary intervention to prevent long years of medical treatment.

No implants were used in the present study, and MMC was used in most but not all of the cases. Scarring is the most important cause of failure of filtration procedures. The use of antimetabolites, such as MMC and 5-fluorouracil, is known to improve the long-term results [29,30]. Although the difference of qualified and complete success rates of the procedure with and without MMC did not reach significance, longer follow-up and a higher number of participants are required to appreciate the value of MMC use in these cases.

The results of this study may be further improved by the use of scleral implants, such as hydrogel, reticulated hyaluronic acid or autologous scleral implants [31–34].

The main limitation of the clinical data interpretation is the absence of a control group. Therefore, prospective, randomized controlled clinical trials comparing the CLASS procedure to alternatives are required to further evaluate and substantiate the safety and long-term efficacy of the CLASS procedure and compare it with other techniques.

In conclusion, CLASS offers a simple to perform, low-risk alternative, minimal interventional surgery for OAG patients whose target pressure is within the expected outcome of this procedure.

Expert commentary

Glaucoma is a leading cause of global irreversible blindness. Tham *et al.* had recently reported that in 2013, the number of people (aged 40–80 years) with glaucoma worldwide was estimated to be 64.3 million, increasing to 76.0 million in 2020 and 111.8 million in 2040 [35]. These estimates are important in guiding the designs of glaucoma screening, treatment and related public health strategies.

Glaucoma is a progressive optic neuropathy characterized by degeneration of retinal ganglion cells. The disease is considered multifactorial. Loss of ganglion cells is related to the level of IOP, as well as to other factor [36]. Treatment is usually initiated with topical antiglaucoma agents. Chronic use of topical agents induces side effects, such as ocular inflammation, allergy and dry eye syndrome and may be associated with failure of subsequent filtration surgery. Many patients with glaucoma require more than one ocular hypotensive medication to achieve and maintain their target IOP; however, the use of multiple topical medications is associated with factors that may decrease treatment efficacy and increase adverse effects [37]. Effective medical control of IOP is predicated upon patient compliance with pharmacotherapy. The use of multiple topical glaucoma agents is also associated with noncompliance issues [38]. Thus, some would advocate for early surgical intervention to avoid prolonged treatment with IOP-lowering agents damaging the ocular surface and conjunctiva [28,39]. However, the current surgical procedures are associated with a wide range of possible complications, and most surgeons would postpone operating until progression is detected despite maximally tolerated medical treatment and laser trabeculoplasty.

The quest for an effective and yet safe procedure still continues. Because the eye is optimized for the transmission of light and its transduction into neural signals, lasers are particularly well suited for ophthalmic therapy. New scanning laser systems, including image-guided systems with eye tracking, real-time feedback, and ultra-short pulse durations, have enabled increased selectivity, precision and safety in ocular therapy [40]. CLASS procedure has been developed for the treatment of OAG patients. Keeping the ocular surface intact, this procedure has a relatively high safety profile, and clinical results suggest promising long-term efficacy.

Considering the demanding success criteria defined in the study, the results suggest relatively high efficacy. However, the study population included only Primary open angle glaucoma and Pseudoexfoliating glaucoma patients, without previous filtration procedures. High-risk patients and patients with relative contraindications to nonpenetrating filtration procedures were not included in this study. The authors were reluctant to recommend the performance of CLASS in such patients and additional studies are required for such recommendations.

One of the main limitations of the described procedure is the financial burden on the healthcare system as it requires additional equipment. On the contrary, CLASS procedure may reduce the complications rate, some of which are sight threatening and involve further costly treatment, both medical and surgical.

Five-year view

- For chronic and typically asymptomatic conditions, such as ocular hypertension and glaucoma, treatment adherence (consistent daily use of medication in accordance with dosage

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recommendations) and persistence (continued use of medication over time) pose a particular challenge [41]. Glaucoma surgeries overcome this difficulty and have the potential to replace the pharmacological option as a primary treatment. However, the current surgical options are far from being perfect. Trabeculectomy is still the reference procedure in glaucoma treatment, although it carries a risk of complications and a high rate of surgical failure. We believe that new surgical procedures with improved efficacy and safety profile will replace the traditional trabeculectomy.

- Lasers represent a new frontier in ophthalmic surgeries, such as in cataract and refractive surgeries. With a growing patient demand for perfection and high expectations of outstanding visual outcomes [42], lasers will replace many manual procedures. The most important advantage of laser technology at present is that surgical steps can be planned and customized, delivering unparalleled accuracy, repeatability and consistency in surgical results [43]. Considering the issues of quality of life and poor adherence to topical therapy, as well as the relatively low-risk profile of laser treatments, we anticipate a trend toward an earlier use of lasers in glaucoma treatment. We believe that the use of lasers as a leading surgical tool will become a reality in the near future. The development of technology will allow the production of more compact, portable, accurate and reliable lasers in low cost.
- CLASS procedure uses CO_2 laser to control the IOP in a safe manner. Novel imaging techniques for structural and dynamic assessment may improve the performance of CLASS. Intraoperative use of anterior segment optical coherence tomography may be used in the future to determine ablation location and depth to facilitate performance.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Key issues

- CO_2 laser-assisted sclerectomy surgery procedure in patients with open-angle glaucoma and pseudoexfoliative glaucoma uses CO_2 laser for deep scleral dissection.
- CO_2 laser characteristics include photoablation of dry tissue, as well as the effective absorption of laser energy by fluids. The progressive ablation of scleral tissue ceases when aqueous percolation is achieved as fluid absorbs the laser energy and prevents penetration through the remaining thinned scleral wall.
- The IOPtiMate system consists of a scanner and a control unit, which enable applying CO_2 laser over the trabecular meshwork and Schlemm's canal.
- Experimental models showed repetitive fluid percolation with a low rate of perforations.
- Clinical studies proved efficacy and safety. A significant IOP reduction was recorded with convincing success rates and a high safety profile.

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