CO_2 Laser-assisted Deep Sclerectomy in Glaucoma Patients

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Purpose: To evaluate the safety and efficacy of CO_2 laser-assisted deep sclerectomy surgery (CLASS) in patients with open angle glaucoma.

Design: A prospective single-arm, nonrandomized clinical investigation for the evaluation of technology.

Methods: Fifteen eyes of 15 consecutive patients diagnosed with either primary open angle glaucoma or pseudoexfoliation glaucoma who were the candidates for glaucoma filtration surgery were included. Laser-assisted deep sclerectomy using a CO_2 laser system was performed in all patients. A half-thickness scleral flap was created, the use of 0.04% mitomycin C for 60 seconds was left at the surgeon's discretion, and a CO_2 laser with a beam-manipulating system was used to achieve deep scleral ablation and unroofing of Schlemm's canal zone. Visual acuity, complete ophthalmologic examination, and intraocular pressure (IOP) were measured and documented at baseline, 1, 2, 4, and 6 weeks and at 3, 6, and 12 months, respectively. Complete success was defined as $5 \leq$ IOP ≤ 21 mm Hg and 20% IOP reduction with no medication at the 12-month endpoint visit. Qualified success was defined as a similar IOP reduction with medication.

Results: The preoperative IOP of 27.3 ± 4.2 mm Hg (mean ± SD) dropped to 15.0 ± 3.7 mm Hg at 6 months and 16.6 ± 3.4 mm Hg at 12 months postoperatively, yielding an average IOP reductions at 6 and 12 months of 13.1 ± 4.3 mm Hg (45.1%; 95% CI, 11, 15.3) and 11.5 ± 5.5 mm Hg (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%. Mitomycin C was used in 76.9% of the CLASS subjects.

Key Words: nonpenetrating deep sclerectomy, CO_2 laser, primary open angle glaucoma, exfoliative glaucoma

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Lowering the intraocular pressure (IOP) is one of the main treatment goals in the management of glaucoma patients, aiming to arrest the characteristic progressive optic neuropathy and prevent the expected irreversible visual field loss.[1,2] This goal may be achieved either by medical, laser, or surgical modalities.

Surgical treatment is usually indicated when glaucomatous optic neuropathy worsens or visual field damage progresses despite laser trabeculoplasty or maximally tolerated medical therapy.

Trabeculectomy is the most common surgical approach to reduce IOP in glaucoma patients. Trabeculectomy is considered effective in many cases, but is associated with a variety of complications, such as shallow anterior chamber (AC) due to overfiltration, hypotony maculopathy, choroidal detachment or hemorrhage, hyphema, aqueous misdirection, cataract, or endophthalmitis.[3–5] Most of these complications are due to the fact that the surgery is invasive and involves penetration of the AC. Other procedures, such as glaucoma drainage devices, which shunt aqueous from AC to the posterior subconjunctival space, may be also associated with similar complications such as hypotony, diplopia tube extrusion, and infection.[6,7] Other novel surgical techniques have been investigated in an attempt to develop a "bleb-less" procedure, such as trabectome,[8] canaloplasty,[9] Gold Micro Shunt to the supraciliary space,[7] Istent,[10] etc.[11]

We report in this issue our preliminary experience with the CO_2 laser-assisted sclerectomy (CLASS), which is a modification of nonpenetrating deep sclerectomy (NPDS).

The NPDS procedure, first described by Krasnov[12] and Walker and Kanagasundaram[13] in 1964, includes unroofing of Schlemm's canal and exposure of the juxtacanalicular trabeculum in order to allow effective fluid percolation,[14] while the AC is not penetrated. This procedure is known to have a higher safety profile as compared with trabeculectomy[15,16] with almost similar success in controlling IOP.[17]

In the manual NPDS procedure, a deep scleral flap is first dissected and then a second scleral layer is cut out, leaving an exposed thin layer of trabecular meshwork and Descemet's membrane. Fluid percolation through the remaining tissue is the desired outcome of the procedure. However, as the scleral tissue needs to be dissected manually to >95% of its depth (leaving a residual intact layer of only several tens of microns), this procedure requires high surgical skills and experience with long learning curve. For that reason NPDS was adopted only by a minority of surgeons and did not gain a wide popularity despite its obvious advantages,[18] which include less frequent flattening of the AC, less choroidal detachments, and reduced inflammation due to the avoidance of penetrating the AC.

The OT-135 system, used in our study, is a beam manipulator system, conjugated with an "off the shelf" CO_2 laser (IOPtiMate"; IOPtima Ltd., Ramat-Gan, Israel). Recognizing the specific requirements of NPDS, this system, which was first described by Assia et al,[19,20] enables deep tissue ablation with minimal risk of perforation. As such, it offers a potential alternative to the manual NPDS, making the procedure simpler and less surgeon dependent.[21] The unique characteristic of the CO_2 laser is its effectiveness in ablating only dry tissues. This inherent

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characteristic is due to the fact that the far infrared radiation of this laser (wavelength of 10,600) is absorbed in water and thus is ineffective when applied over wet tissues. Applying CO_2 laser energy on the dried scleral tissue over the trabecular meshwork then results in a localized ablation of the sclera up until the point at which fluid begins to percolate through the thinned wall of the AC. Once percolation begins, further laser application is ineffective and thus further tissue ablation does not occur. In this manner, tissue ablation is "automatically" halted when the desired endpoint of the procedure is achieved.[19]

The purpose of this study is to evaluate prospectively the safety and efficacy of the CO_2 laser-assisted deep sclerectomy surgery (CLASS).

METHODS

The study received approval from the Sheba Medical Center Institutional Review Board committee and was registered in the US National Institutes of Health registry (NCT01059162).

Patients

Fifteen eyes of 15 consecutive patients diagnosed with either primary open angle glaucoma or exfoliative glaucoma who were the candidates for primary glaucoma filtration surgery were included. A subject was eligible to participate in the study if he/she meets all of the following inclusion criteria and none of the exclusion criteria shown in Table 1.

The study was conducted according to the tenets of the Declaration of Helsinki, received approval from the Sheba Medical Center Institutional Review Board committee, and was registered in the US National Institutes of Health registry (NCT01059162). Informed consent was obtained from all patients before the procedure.

Comprehensive ophthalmologic examination was performed before and at intervals of 1, 2, 4, and 6 weeks, and 3, 6, and 12 months after the surgical procedure. The examination included assessment of best corrected visual acuity, measured under photopic lighting conditions (85 cd/m^2) using the ETDRS chart, IOP measurement using Goldman applanation tonometry (average of 3 repeated measurements taken at the same time of the day $\pm$ 1 h), slit-lamp examination, optic disc evaluation, and posterior pole examination. Patients also underwent gonioscopy and assessment of central corneal thickness (average of 3 repeated measurements). Information regarding age, sex, type of glaucoma, cup-disc ratio, and visual field pattern was collected. Three consecutive threshold 24-2 Humphrey perimetry tests were performed, the last of which was performed within 2 weeks before surgery.

Intraoperative and postoperative complications were documented according to severity and their relationship to the studied device. The incidence of intraoperative macroperforations, defined as perforations accompanied by iris prolapse or AC shallowing or both was also recorded.

Surgical Procedure

The procedure was performed under subconjunctival anesthesia with 2% lidocaine without epinephrine. The perilimbal conjunctiva and tenon capsule were dissected. A half-thickness 5×4 mm superior scleral flap was fashioned with a crescent knife. A red laser (HeNe) aiming beam was used to mark the scanning area boundaries, with 4 clear red dots at the corners. Scan dimensions (width and length) could be changed within the range of 1 to 4 mm. Initially a wide scan area was used to repeatedly remove layers of sclera until a percolation zone could be readily identified. The CO_2 laser was repeatedly applied with time intervals of 2 to 3 seconds between applications to allow percolation to take place and be detected, until sufficient percolation zone of at least 3 mm in region length was clearly evident. The scleral flap was then repositioned and sutured with 10-0 nylon sutures. Short video demonstrating the procedure is attached (Movie 1) (Supplemental Material, http://links.lww.com/IJG/A13).

Application of 0.04% mitomycin C (MMC) was left at the surgeon's discretion. Surgeons were also permitted to convert to conventional trabeculectomy at any stage of the operation.

Postoperative Analysis

"Complete success" was defined as IOP values measure at the 12-month endpoint, ranging between 5 and 21 mm Hg and IOP reduction $\geq 20\%$ as compared with baseline IOP without additional hypotensive medications or repeat filtration surgery. The same outcome, but also including subjects who required hypotensive medications postoperatively, was defined as "qualified success." Failure was defined as an IOP value < 5 and > 21 mm Hg, IOP reduction of $< 20\%$ as compared with baseline IOP, severe loss of vision, or the need to undergo additional glaucoma surgery. Goniopuncture or needling was not defined as failure as both are commonly used as normal postoperative interventions that are required to maintain or augment the operative results of glaucoma surgeries.[21] The number of hypotensive medications being used by each patient was documented in all visits.

Statistical Methods

Statistical analysis was performed using a paired samples t test to compare preoperative and postoperative data. A P value of ≤ 0.05 was considered significant. The 95% confidence intervals (CI) were calculated for the mean IOP measurements and for the success rates at 6-month follow-up and the 12-month endpoint. Data was analyzed using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA) and SPSS software version 13.0 (SPSS Inc., Chicago, IL).

RESULTS

Fifteen patients were enrolled in the study between May 2010 and July 2011. Ten men (66%) and 5 women (33%) with a mean (SD) age of 69.9 (14.9) years were included. Nine patients (60%) had primary open angle glaucoma and 6 had exfoliative glaucoma (40%). None of the patients had previous glaucoma surgery or a glaucoma drainage device.

In 2 patients (#14 and #15) the surgeons opted to convert to conventional trabeculectomy due to iris prolapse into the surgical site, demonstrating a perforation into the AC. This patient therefore was excluded from the performance analysis but was included in the safety analysis.

Baseline and follow-up visits data (including IOP measurement and number of lowering pressure medications) of all patients are summarized in Table 2.

All subjects were followed up for 12 months except 2 subjects (patient #2 and #5) who were lost to follow-up 3 months after the procedure.

TABLE 1. Patient Inclusion and Exclusion Criteria

Inclusion criteria
Patient age 18 y or older.
Patient must have primary open angle glaucoma or pseudoexfoliative glaucoma in the study eye; diagnosis is based on glaucomatous optic neuropathy, Shaffer angle of + 2 and visual field defect attributed to glaucoma [at least 2 consecutive abnormal visual field test results, defined as a pattern SD (PSD) outside the 95% normal confidence limits and/or glaucoma Hemifield Test (Carl Zeiss Meditec Inc.].
Treated eye must be phakic or pseudophakic eye with no ocular disorder or ocular diseases but cataract, and no prior surgical intervention in study eye but cataract surgery with clear corneal incision and trabeculoplasty performed > 3 mo ago.
Patient is indicated for filtration surgery.
Presence of ocular hypertension, defined as an intraocular corrected pressure (IOP) ≥ 21 mm Hg in the study eye, while on maximal tolerated medications (Patients on maximal tolerated medications refer to those patients who cannot or will not use medications due to cost issues, memory problems, difficulty of instillation, or inability to tolerate medications.). This IOP level of above or equal 21 mm Hg must be verified and recorded in the most recent 2 consecutive measurements (but not taken on the same day) before operation.
Best corrected visual acuity (BCVA) better than 20/200 in the fellow eye.
Optic neuropathy is attributed exclusively to glaucoma
Exclusion criteria
Diagnosis of glaucoma other than primary open angle glaucoma or pseudoexfoliative glaucoma.
History of previous intraocular surgery in the study eye; referring to but not limited to glaucoma filtering surgery (penetrating and nonpenetrating), laser gonioplasty, corneal transplant, and history of any other laser ocular procedures except for laser trabeculoplasty surgery.
Laser trabeculoplasty surgery within the last 3 mo in the study eye.
Study eye is aphakic.
Patients with previous cataract extraction with scleral tunnel and or conjunctival incision in the study eye.
Proliferative or severe nonproliferative retinopathy in either eye.
Eyes with (dilated) pupil diameter of < 2 mm in the study eye.
Discernable congenital anomaly of the anterior chamber angle in the study eye.
Patients with neuropathy other than glaucoma in the study eye.
Patient with RVO (retinal vein occlusion) or RAO (retinal artery occlusion) in the study eye.
History of prior vitrectomy or vitreous hemorrhage (VH) in the study eye.
Patient with media opacification that may interfere with optic nerve evaluation in the study eye.
Patient with ocular malformations such as microphthalmia in the study eye.
Patient with concurrent inflammatory/infective eye disorder (eg, episcleritis, scleritis) in the study eye
Patient with any sign of past or present uveitis (anterior/posterior)
Patient with known allergy to the study medications.
Patient with severe systemic disease or disabling conditions such as chronic renal failure requiring dialysis, severe and disenabling neurological disease, and postorgan transplants.
Patient participating in another clinical trial or participation in another clinical trial is < 3 mo.
Patient is pregnant or breast feeding.

MMC was used in 10 CLASS subjects (76.9%) and in the 2 converted to trabeculectomy cases at a concentration of 0.04% for 60 seconds. Shallow diffuse blebs were observed in all cases.

Performance Analysis

The preoperative IOP of 27.3 ± 4.2 mm Hg (mean ± SD) dropped to 15 ± 3.7 mm Hg at 6 months and 16.6 ± 3.4 mm Hg at 12 months postoperatively (Fig. 1), yielding an average IOP reductions at 6 and 12 months of 13.1 ± 4.3 mm Hg (45.1%; 95% CI, 11, 15.3) and 11.5 ± 5.5 mm Hg (39.2%; 95% CI, 8.8, 14.3), respectively ($P < 0.001$). Defining success as $5 \leq IOP \leq 21$ mm Hg and 20% IOP reduction, the complete success rate after 12 months was 45.5%, whereas qualified success was 90.9%.

Preoperative use of hypotensive medications per patient dropped from an average of 2.1 ± 0.9 to 1 ± 1 at 12 months visit ($P < 0.001$) (Table 2).

No needling procedures, YAG laser goniopuncture, suture lysis, or 5FU injections were needed. No cataract extraction was needed during the study period.

The preoperative VA acuity of 70 ± 12.5 (mean ± SD) letters at EDTRS was stable during the follow-up year with VA of 67.8 ± 9.1 at the 12 months visit, without a significant difference ($P = 0.7$).

Safety Analysis

Data on all 15 enrolled participants was used in the analysis of safety outcomes. No device malfunctions occurred. Two cases of iris prolapse without loss of depth of the AC was recorded and therefore converted to trabeculectomy. The AC remained deep and stable in all cases.

No microhyphema, wound dehiscence, or leaks were reported. No major complications (such as hypotony maculopathy, choroidal detachment or hemorrhage, hyphema, aqueous misdirection, or endophthalmitis) were reported.

There was 1 case (patient #4) that developed iris incarceration into sclerectomy with pear-shaped pupil 1-month postoperatively. Surgical correction was performed, with IOP back to normal throughout the follow-up period.

DISCUSSION

NPDS is an accepted surgical mode for glaucoma for more than 40 years.[12,13] Clinical trials have shown NPDS to be an effective method of lowering IOP, although a bit less effective when compared with trabeculectomy.[22–24] All studies have reported significantly lower risk of complications[5,17,22–24] attributed to NPDS being less invasive than trabeculectomy.[25]

The main disadvantage of NPDS and the main reason for its poor adoption by glaucoma surgeons is high surgical

TABLE 2. Demographic, Pre-operative, and Postoperative IOP and Number of Medications Data

				Preoperative			1 D		1 wk		2 wk		4 wk		6 wk		3 mo		6 mo		12 mo	
Patient No.	Sex	Glaucoma Type		IOP	MED	Use of MMC	IOP	MED	IOP	MED	IOP	MED	IOP	MED	IOP	MED	IOP	MED	IOP	MED	IOP	MED
1	F	PXFG		25	2	No	3	0	8	0	14	0	14	0	15	0	13	0	16	0	17	0
2	M	POAG		25	3	Yes	6	0	12	0	22	0	22	0	22	1	22	1	—	—	—	—
3	M	POAG		27	2	Yes	4	0	5	0	3	0	21	1	22	2	13	2	10	2	19	2
4	M	POAG		26	3	Yes	5	0	5	0	10	0	20	2	22	2	21	2	14	2	18	2
5	M	PXFG		24	1	Yes	11	0	12	0	3	0	5	0	5	0	7	0	—	—	—	—
6	F	POAG		24	3	Yes	6	0	6	0	6	0	6	0	10	0	10	0	12	0	12	0
7	M	POAG		26	1	Yes	6	0	15	0	17	0	16	0	12	0	6	0	8	0	10	0
8	M	PXFG		40	3	No	10	0	10	0	13	0	13	0	17	0	17	0	18	0	15	0
9	M	POAG		30	2	Yes	6	0	18	0	18	2	20	2	25	3	16	3	19	2	18	2
10	M	POAG		26	2	Yes	2	0	6	0	8	0	26	2	18	2	17	2	15	2	15	2
11	F	POAG		28	3	Yes	11	0	11	0	18	0	24	1	19	1	16	2	16	2	18	2
12	F	PXFG		25	1	Yes	12	0	15	0	18	0	16	0	14	0	16	0	18	0	22	1
13	M	PXFG		29	1	No	4	0	12	0	17	0	18	0	12	0	13	0	19	0	19	0
14	F	POAG		24	3	Yes	3	0	2	0	8	0	8	0	7	0	7	0	8	0	10	0
15	M	PXFG		24	2	Yes	11	0	13	0	13	0	15	0	12	0	14	0	14	0	17	0
Average				**27.3**	**2.1**		**6.6**	**0**	**10.4**	**0**	**12.8**	**0.2**	**17.0**	**0.6**	**16.4**	**0.8**	**14.4**	**0.9**	**15.0**	**0.9**	**16.6**	**1.0**
SD				**4.2**	**0.9**		**3.3**	**0**	**4.2**	**0**	**6.3**	**0.6**	**6.3**	**0.9**	**5.7**	**1.1**	**4.8**	**1.1**	**3.7**	**1.0**	**3.4**	**1.0**

skill required and the long learning curve needed for performing the manual technique. Perforation of the thin trabeculo-Descemet's membrane in manual NPDS occurs in about 30% to 50% of the cases in the early stages of the learning curve of this procedure.[26] In the case of perforation, the procedure may be converted to a conventional trabeculectomy; however, the high rates of perforation limit the use of deep sclerectomy as a treatment procedure. In contrast, although the risk of perforation is relatively high, if the tissue is not cut deep enough, the filtration may not be effective and the IOP will not be reduced to the desired level. CLASS procedure resolves this issue and enables the surgeon and patient to enjoy the advantages of NPDS without its major complications.

We reported that in 2 patients (#14 and #15) the surgeons opted to convert to conventional trabeculectomy due to iris prolapse into the surgical site. We believe that excessive percolation of aqueous in certain cases, associated with inadvertent opening of the inner wall of Schlemm's canal may trigger iris prolapse into the surgical zone. We recommend that in cases where excessive percolation is detected during surgery, either intraoperative injection of Miochol or postoperative administration of Pilocarpine drops should be administered. Such treatment may prevent incarceration of the iris periphery into the "trabeculotomy" site in such cases.

Attempts to use lasers in NPDS surgery were reported previously in the literature (such as the use of a femtosecond laser in laboratory model[25,27] and erbium:YAG laser[28]) although none of these attempts have been demonstrated in continuing clinical trials.

Our study is one of the pioneering studies using CLASS in glaucoma patients.[21]

We defined "complete success" and "qualified success" based on core literature.[16–27,29] According to these definitions and further validation of processes based on the additional data presented in the Cochrane Database of Systematic Reviews[30] (published on the use of MMC in glaucoma surgery by Wilkins and colleagues), the expected qualified success rate at 6 months for patients undergoing manual nonpenetrating glaucoma surgery without the use of antimetabolites and/or collagen implants is approximately 80%. In our study we demonstrated that CLASS qualified success after longer period (12 mo compared with 6 mo) is higher (90.9% compared with the estimated 80% manual NPDS) and is correlated to 95.5% qualified success achieved in recent publications.[21] This improvement (compared with the old nonpenetrating techniques) might be attributed to the priority of the laser and its accuracy in achieving the expected surgical result.

This enhanced accuracy evolves from the physical properties of the CO_2 laser with almost total absorption of energy by percolating aqueous humor after unroofing of Schlemm's canal, protecting deeper tissues such as trabecular meshwork from the laser energy.[19–21] Another improvement of the beam manipulator system version (OT-135) is its ability to diminish localized heating and tissue photocoagulation, which can cause early fibrosis, adhesions, and surgery failure, as reported previously in sporadic cases.[19,20] It is also associated with reduced coagulative thermal damage to adjacent tissues, as demonstrated in the experimental models by Assia et al.[19]

The IOP reduction pattern in our study is similar to recent publications,[21] which also demonstrate initial postoperative descent that stabilized after a 4-week

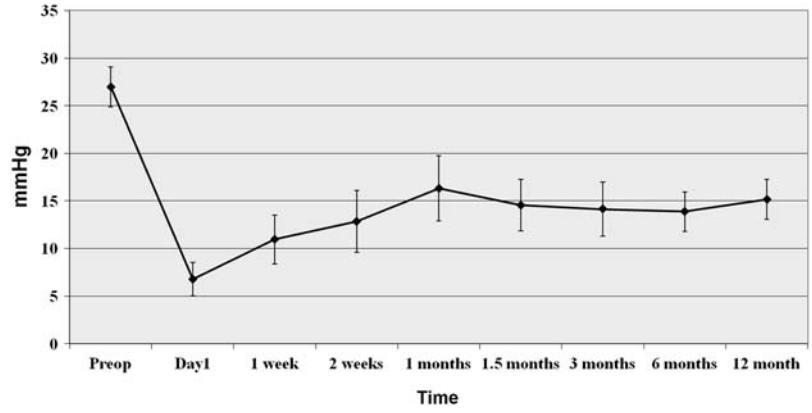

FIGURE 1. Cumulative IOP ± SD measurements from the preoperative stage up to 12 months postoperatively. Average IOP reduction at 12 months was 46.7%.

postoperative period until the 12 months at last follow-up visit.

IOP stabilization in manual NPDS has been demonstrated[23] after a mean follow-up of 31.3 months, therefore one of the limitations of our study is the relatively short follow-up.

The use of MMC, a well-known drug used during the initial stages of glaucoma surgery to prevent the scarring and fibrosis of the filtering bleb, was left in our patients at the surgeon's discretion and was applied in 12 of the 15 cases (Table 2). A recently published meta-analysis[31] on the use of MMC in nonpenetrating glaucoma surgeries, found that intraoperative MMC application was associated with greater IOP lowering efficacy, with statistically significant differences in IOP reduction after 1-year postoperatively. The use of MMC was also associated with significantly greater proportions of patients achieving the IOP target without medication at all measurement times. In this meta-analysis, as in our patients, the intraoperative use of MMC was not associated with any drug-induced complications, such as wound leaks, hypotony, expulsive hemorrhage, shallow AC, or cataract.

As the 3 patients who did not receive MMC (Patients #1, #8 and #13) were "complete successes" compared with some of those who received MMC, a study comparing CLASS with and without MMC will be of interest and is planned to take place in the near future.

Other limitations of our study are the lack of a control group, a small number of patients, and the lack of prospective comparison between application and non-application of MMC. Despite these limitations, we are encouraged by the ease of surgery and excellent safety and efficacy of this novel methodology. More studies evaluating CLASS in more patients and for longer follow-up periods are required.

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