Trabeculectomy With Combined Use of Subconjunctival Collagen Implant and Low-dose Mitomycin C

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Purpose: To evaluate outcomes of trabeculectomy with use of a subconjunctival biodegradable collagen implant (Ologen) combined with mitomycin C (MMC).

Methods: This retrospective study included 33 eyes of 24 patients with primary open-angle glaucoma who underwent fornix-based trabeculectomy with subconjunctival Ologen implant and MMC (0.1 mg/mL x 1 min) between October 2008 and April 2010. Data pertaining to the preoperative parameters and postoperative outcomes were recorded. Each patient was followed up for at least 12 months.

Results: The mean age of the study participants was 53.03 ± 7.08 years. Mean preoperative intraocular pressure (IOP) was 34.06 ± 6.56 mm Hg, and decreased to 11.87 ± 2.23 mm Hg, 12.27 ± 2.05 mm Hg, and 12.54 ± 1.67 mm Hg at 3, 6, and 12 months, respectively. Mean postoperative IOP readings at all follow-up visits were significantly lower than those at preoperative levels (P < 0.001). Two eyes required ocular hypotensive medications to lower the IOP in the postoperative period. All eyes had a diffuse elevated well-formed bleb, with the implant being visible for 6 to 9 months. Two eyes had a shallow anterior chamber with hypotony during the early postoperative period due to wound leak, whereas 1 case developed implant exposure at 1-week follow-up; all these cases were managed by conjunctival resuturing. Two cases developed a Tenon cyst at 8 to 12 weeks and required needling for restoration of bleb function.

Conclusions: Trabeculectomy with implantation of an Ologen implant and use of low-dose MMC appears to offer encouraging short-term results for IOP control in eyes with primary open-angle glaucoma.

Key Words: trabeculectomy, collagen implant, mitomycin C, intraocular pressure, Ologen (J Glaucoma 2012;00:000–000)

Intraocular pressure (IOP) is consistently identified as a risk factor for the presence or progression of glaucoma. Trabeculectomy, introduced in 1968, has been used for the surgical management of glaucoma for >40 years and remains the most commonly used incisional surgery for glaucoma. However, long-term IOP control after trabeculectomy may be limited by scarring at the level of the conjunctiva-Tenon-episcleral interface, the scleral flap, its overlying episclera, or the internal ostium. The introduction of antiproliferative agents has significantly improved the long-term outcome of this procedure.4–6 Recently, there has been a new approach to use a bioengineered, biodegradable, porous collagen-glycosaminoglycan matrix implant in the subconjunctival space to allow remodeling of the wound-healing process after filtration surgery. The application of 3-dimensional, collagen-glycosaminoglycan copolymers can lead to random and relatively loose reorganization of regenerating myofibroblasts, fibroblasts, and the secreted extracellular matrix (ie, collagen), resulting in reduced scar formation.7–9 Although recent studies have shown successful outcome of the use of these implants in deep sclerectomy, the results with their application as adjuvants in trabeculectomy have not been very favorable.10–12

This study was conducted to evaluate the outcomes of trabeculectomy with subconjunctival biodegradable collagen implant (Ologen, Aeon Astron Europe, the Netherlands) combined with use of low-dose mitomycin C (MMC). To our knowledge, this is the first study in which these implants have been used in conjunction with antiproliferative agents in trabeculectomy.

MATERIALS AND METHODS

This study was conducted at Dr Rajendra Prasad Centre for Ophthalmic Sciences, a tertiary ophthalmic care university center in New Delhi, India. Patients who underwent fornix-based trabeculectomy with Ologen implant and low-dose MMC (0.1 mg/mL x 1 min) between October 2008 and April 2010 were evaluated. The inclusion criteria included: patients with primary open-angle glaucoma (POAG) aged above 40 years identified by IOP > 21 mm Hg; glaucomatous visual field defects confirmed by 30-2 SITA Standard Humphrey visual field analysis (cluster of 3 points with a probability of 5% on the pattern deviation map in at least 1 hemifield, including at least 1 point with a probability of 1%; and a glaucoma hemifield test outside 99% of age-specific normal limits, and a pattern SD outside 95% of normal limits); the presence of a glaucomatous optic disc that showed cupping, diffuse, or focal neural rim thinning, hemorrhage, and nerve fiber layer defects; and the presence of open angles on gonioscopy. Subjects with angle-closure glaucoma, posttraumatic, uveitic, neovascular, or any other form of secondary glaucoma, aphakia/pseudophakia, and previous operated glaucoma/vitro-retinal surgery were excluded from the study.

For each patient, the following parameters were recorded: age at the time of surgery, preoperative corrected distance visual acuity (CDVA), gonioscopy, IOP (Goldmann applanation tonometry), standard automated perimetry (Humphrey 30-2 test), and number of medications used during the 3 months before surgery. Further,
intraoperative and postoperative complications, postoperative IOP readings, number of medications, postoperative CDVA, and any secondary procedures performed after trabeculectomy were recorded. Each patient had to have a follow-up of at least 12 months after trabeculectomy. Criteria for complete success was defined as IOP < 18 mm Hg without medications.

**Surgical Technique**

All trabeculectomy surgeries were performed by a single glaucoma surgeon (T.D.) under peribulbar anesthesia. Under surgical asepsis, a cornel traction suture was placed using 8-0 vicryl and a fornix-based conjunctival flap was designed. Sub-Tenon dissection and hemostasis were performed. A half-thickness 5.0 x 5.0 mm rectangular scleral flap was made in the superior area. Multiple sponges (n = 4) in a 0.1 mg/mL solution of MMC were applied for 1 minute in a diffuse area under the superior bulbar conjunctiva over an area of 4 clock hours. The area was irrigated thoroughly with balanced salt solution after 1 minute. A 3.0 x 1.0 mm sclerectomy was then performed followed by a peripheral iridectomy. The scleral flap was repositioned and closed with 1 interrupted suture of 10-0 monofilament nylon. Ologen implant (cylindrical implant with a diameter of 7 mm and a height of 4 mm) was positioned on top of the scleral flap without the use of any suture. Finally, the conjunctiva was closed with an 8-0 polyglactin vicryl suture. The postoperative regimen consisted of topical moxifloxacin 3 times a day and prednisolone eye drops 4 times a day in a preservative-free preparation. The steroid drops were tapered over the following 6 weeks. Ultrasound biomicroscopy of the filtering bleb was performed at 3, 6, 9, and 12 months after surgery using the Paradigm P40 UBM machine.

The data were managed on the excel spreadsheet and statistical analysis was performed using SPSS (v 19.0 IBM SPSS). Paired t test was used for comparisons, and the level of significance was set at P < 0.001.

### RESULTS

A total of 33 eyes of 24 patients (male:female, 19:5) with POAG underwent trabeculectomy with Ologen and low-dose MMC application. Nine patients underwent bilateral surgery. The mean age of study participants was 53.03 ± 7.08 years (range, 48 to 62 y). Preoperative CDVA was ≤ 20/120 in 17 eyes, 20/40 to 20/60 in 9 eyes, and ≥ 20/40 in 7 eyes. The mean follow-up duration was 13.03 ± 1.13 months (range, 12 to 18 mo).

The mean preoperative IOP was 34.06 ± 6.56 mm Hg. The mean postoperative IOP at 12 months follow-up was 12.54 ± 1.67 mm Hg (range, 8 to 14 mm Hg). Postoperative IOP levels were significantly lower than preoperative levels at all postoperative visits (P < 0.001; Table 1). All eyes had the implant and well-maintained subconjunctival space during follow-up visits (Fig. 3). The implant was visible at 6 months in all cases and up to 9 months in 6 cases. At a follow-up period of 12 months, there was a decrease in CDVA by 2 lines in 1 patient and 1 line in 2 patients due to progression of lenticular cataractous changes.

### Complications

During the first week, 2 eyes were noted to have a shallow anterior chamber with hypotony. Both the cases demonstrated a positive Seidel test suggestive of conjunctival wound leak. In another eye, implant exposure was noted at 1-week follow-up. All these cases were managed with conjunctival resuturing. Two eyes were noted to develop Tenon cysts at the 8-week and 12-week postoperative visits with elevation of IOP. Both the cases responded well to needling with 5-mg 5-flourouracil injection. In these cases, the 26G needle was passed through the collagen implant in addition to puncturing the cyst wall.

### DISCUSSION

Results of the Advanced Glaucoma Intervention Study, the Early Manifest Glaucoma Trial, and the Ocular Hypertension Treatment Study demonstrated that lower IOP is associated with a reduced risk for progression of visual field damage.13–15 Surgical management for glaucoma is usually reserved for cases unresponsive or noncompliant to medical therapy or in which target pressure cannot be achieved despite medical therapy. The success rates of penetrating glaucoma surgeries have improved with the introduction of antiproliferative agents, 5-flourouracil, and MMC used during the surgical procedures.16–18 However, the use of these agents has been reported to be associated with significant postoperative complications like hypotony, cataract, avascular filtering blebs, and endophthalmitis.19,20 These adverse events seen with MMC application have been related to the dose and exposure times.21–24 Many studies have shown that MMC-related complications, especially hypotony and cataract, are more common with increased concentration and longer exposure times.21,22,25

The process of wound healing is composed of 2 processes: the initial steps in wound healing are inflammation and coagulation, leading to a cascade of biological events including cellular, hormonal, and growth factor release. The second phase involves replacement and regeneration by collagen laid down from fibroblasts. These phases are subject to modification with the use of antiproliferative

<table>
<thead>
<tr>
<th>IOP Follow-up Period</th>
<th>(Mean ± SD) (mm Hg)</th>
<th>Range (mm Hg)</th>
<th>P (vs. Preoperative IOP Readings)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>34.06 ± 6.56</td>
<td>26-38</td>
<td>—</td>
</tr>
<tr>
<td>1 d</td>
<td>9.58 ± 1.56</td>
<td>5-12</td>
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<tr>
<td>1 wk</td>
<td>9.84 ± 1.8</td>
<td>8-12</td>
<td>0.001</td>
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<tr>
<td>1 mo</td>
<td>10.24 ± 1.92</td>
<td>8-14</td>
<td>0.001</td>
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<tr>
<td>3 mo</td>
<td>11.87 ± 2.23</td>
<td>8-18</td>
<td>0.001</td>
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<tr>
<td>6 mo</td>
<td>12.27 ± 2.05</td>
<td>8-16</td>
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<td>9 mo</td>
<td>12.36 ± 1.45</td>
<td>8-14</td>
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<tr>
<td>12 mo</td>
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IOP indicates intraocular pressure.
or wound modulatory agents, used either singly or in combination. Sherwood, in an experimental study, has published successful results following a combined approach to wound modulation after glaucoma filtering surgery. This study used targeted, sequential inhibition of transforming growth factor \( \beta \), connective tissue growth factor, and matrix metalloproteinases to enhance bleb survival.

Ologen is a porous collagen matrix scaffold. The pores, having a size of 20 to 200 μm, are believed to guide the fibroblasts to grow through the body of the implant randomly and reduce scar formation. In early stages, the matrix scaffold absorbs aqueous humor and may press the sclera flap providing physical resistance against overfiltration. Hence, multiple/tight sutures may not be necessary in these cases. This resistance is expected to reduce progressively as the implant degrades and is replaced by a random connective tissue matrix to create a loosely organized bleb structure.

Recent studies have embarked upon the use of Ologen to replace antifibrotic agents in filtering surgery for glaucoma. Aptel et al reported that deep sclerectomy with Ologen implantation is effective and well tolerated. Ologen implant has also been used to manage some complications related with glaucoma drainage devices. However, the outcome of cases in which trabeculectomy was performed with Ologen alone has not been encouraging. In a prospective randomized study, Rosentreter et al noted that the success rate in the trabeculectomy with Ologen group was half of that of the trabeculectomy with MMC group. However, the filtering blebs were significantly less avascular than those with MMC. Cillino and colleagues performed a prospective study up to 24 months comparing Ologen and MMC (concentration: 0.2 mg/mL) as adjuvants to trabeculectomy. They did not find any difference in lowering IOP between the 2 groups. In another randomized study, Papaconstantinou et al did not find any significant difference between patients undergoing trabeculectomy alone and those who underwent trabeculectomy with Ologen. In our study, we evaluated the results of trabeculectomy with subconjunctival Ologen implantation combined with low-dose MMC. Nearly all patients achieved surgical success (IOP between 6 and 18 mm Hg), and 94% of our cases did not require antiglaucoma medication for IOP control during the follow-up period.

There were no sight-threatening complications in the present study; however, 2 eyes developed hypotony and a shallow anterior chamber during the early postoperative course. Both the cases were found to have a leaky conjunctival wound by the Seidel test. Another case was noted to have implant exposure at 1 week. Early conjunctival leakage was also reported by Rosentreter et al in 30% of their cases undergoing trabeculectomy with Ologen implantation. This emphasizes that during surgery the conjunctiva should be carefully draped over the implant and closed meticulously to avoid postoperative wound leaks, and the implant should be placed at a slightly posterior position such that it does not impinge on the suture line at the limbus. We also noted Tenon cyst formation in 2 eyes during the late postoperative course, which was resolved successfully with needling. It is important to emphasize that needling in such cases differs from routine trabeculectomy cases as the needle should be passed through the implant itself to create multiple porous channels and enhance the flow of the aqueous. Rosentreter et al also reported the development of endophthalmitis in 1 case in which trabeculectomy with Ologen implant was performed. However, no such complication was noted among our subjects.

Our study is limited by the lack of a control group, and this makes it difficult to ascertain the efficacy of the procedure to the use of the MMC alone or in a combination of Ologen and MMC. However, as most of the literature reports are with use of MMC at a concentration of 0.2 to 0.5 mg/mL and an exposure time of 2 to 5 minutes, we believe that use of Ologen during trabeculectomy may allow the surgeon to reduce the dosage of the MMC required and hence decrease potential complications associated with the use of MMC, and at the same time maintain the advantage of Ologen leading to a better anatomic and functional outcome.

In conclusion, the early results of trabeculectomy with implantation of an Ologen implant combined with low-dose MMC. Nearly all patients achieved surgical success (IOP between 6 and 18 mm Hg), and 94% of our cases did not require antiglaucoma medication for IOP control during the follow-up period.

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MMC for the management of POAG are encouraging. Future randomized controlled trials may be needed to confirm the safety and efficacy of this combined modality therapy.

REFERENCES