Ologen implant versus mitomycin C in combined trabeculectomy and phacoemulsification

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Purpose: To comparatively evaluate in Indian eyes with coexisting cataract and primary open-angle glaucoma the outcome of mitomycin C (MMC) and Ologen implant as adjunctives in combined phacoemulsification with trabeculectomy. Methods: Eyes with primary open-angle glaucoma that underwent trabeculectomy and phacoemulsification with IOL implantation with either MMC application or Ologen implant between June 2019 and February 2020 were followed up for 12 months. Thirty-four eyes of 34 participants were studied. The primary outcome was intraocular pressure (IOP), and the secondary outcomes were the number of ocular hypotensive, best distance visual acuity (BDVA), and bleb morphology. Results: In 16 eyes treated with MMC and 18 eyes treated with Ologen implant, it was observed that the mean postoperative IOP (14.62 ± 2.89 mm Hg with MMC and 14.56 ± 4.14 mm Hg with Ologen implant) was not significantly different in both groups (P = 0.47). Number of ocular hypotensives and BDVA were also comparable between the two groups. However, bleb morphology was better with Ologen implantation. One eye in the MMC group developed hypotony which was conservatively managed. Conclusion: MMC and Ologen are both effective adjunctives in combined phaco-trabeculectomy. However, the Ologen implant provides better bleb health and safety.

Key words: Bleb morphology, bleb safety, Mitomycin C, Ologen, phaco-trabeculectomy

Trabeculectomy is the most commonly performed filtering surgery for the treatment of glaucoma.[1‑3] Bleb failure is a major factor challenging the long-term success of this procedure, caused by subconjunctival fibrosis and bleb.[4‑5] To enhance the success of the procedure, we have an array of adjunctives. Selecting the most appropriate one for an individual patient ensures better outcomes.

The most commonly used agents are antimetabolites, such as Mitomycin C (MMC) and 5-fluorouracil (5-FU). MMC is a cell cycle nonspecific antitumor antibiotic obtained from Streptomyces caesipes, which inhibits the synthesis of DNA, cellular RNA, and protein. Thus, it inhibits fibroblast proliferation and migration and hence the synthesis of collagen by fibroblasts.[6‑8] However, MMC is a relatively toxic substance that impairs healing and leads to irregular epithelialization and fibroblast destruction, consequently increasing corneal toxicity and bleb-related complications such as thin avascular blebs, wound leak, overfiltration, hypotony, blebitis, and endophthalmitis.[9‑10] Anti-vascular endothelial growth factor agents, anniotic membrane, and other biodegradable implants are devised to prevent fibroblast activation and thus modify wound healing in a safer manner.[11‑12]

Ologen®Collagen matrix (Aeon Astron Europe B. V., Leiden, the Netherlands) is a biodegradable, porous, porcine collagen implant aimed at decreasing subconjunctival fibrosis with fewer bleb-related complications. It contains >90% type I atelocollagen (pepsin-treated type I porcine collagen) and <10% lyophilized porcine glycosaminoglycan and has a pore size of 10–300 µm, permitting controlled fibroblast regeneration in a loose, random, nonlinear fashion, thus preventing compression of collagen lamellae and resistance to aqueous outflow. It acts by providing a scaffold for the growth of fibroblasts, thus aiding in tissue remodeling and reducing scar formation and simultaneously preventing adhesions between the episcleral surface and conjunctiva by separating them. The implant can be placed subconjunctival or subconjunctivally. After implantation, it degrades within 90–180 days.[13‑16]

Studies have shown Ologen blebs to be vascular, thicker-walled, and diffuse, with good bleb height and microcysts in comparison to MMC-treated ones.[17‑19] Ologen has also been used with low doses of MMC for treating hypotony after trabeculectomy.[20‑22]

Glucoma is a public health concern as it is one of the leading causes of irreversible blindness.[23] Pigmented eyes have a greater genetic predisposition for subconjunctival fibrosis.[24‑29] Thus, the use of adjunctives in trabeculectomy is frequently needed in these eyes. Filtering procedures are a requirement...
owing to late diagnosis as a result of lack of access to quality eye care, noncompliance to medication, and financial constraints. Moreover, there is a rising need for successful trabeculectomy to preserve visual function. Greater proportions of these patients are middle-aged or elderly and are noted to have coexisting cataracts. A combined procedure gives these patients the advantage of one-step management with decreased number of total hospital visits, thus increasing compliance.

MMC is the most commonly used adjunctive in trabeculectomy. However, bleb safety remains a concern with its use as the long-term rate of visually debilitating complications is reported to be around 23% (over 5 years). Thus, safer but effective alternatives to MMC are much required.[10]

Some studies have found MMC and Ologen to provide comparable IOP reduction,[13,16,27,30] whereas some others suggest that Ologen is either inferior[10,26,29] or superior. Moreover, in eyes with coexisting cataract and glaucoma, cataract has been seen to progress after trabeculectomy. Combined phacoemulsification and trabeculectomy has been performed in our study as vision is one of the variables, and coexisting cataract progressing after surgery may be a confounding factor. In this study, we aim to compare the efficacy and safety of Ologen implant with MMC in combined phacoemulsification and trabeculectomy in Indian eyes.

Methods

This study was conducted in accordance with the tenets of the Declaration of Helsinki. Approval of the ethics committee of the institution was obtained. Informed consent was obtained from all the participants. It was a prospective, open, randomized controlled trial. A total of 34 eyes of 34 patients, all over 45 years of age, were enrolled, with 18 eyes randomly assigned to Ologen implantation and 16 eyes to MMC, recruited from June 2019 to February 2020 in a tertiary referral center. Following trabeculectomy with the respective adjunctive combined with phacoemulsification and IOL implantation, the eyes were followed up for a period of 12 months. Eyes with coexisting cataract and primary open-angle glaucoma with IOP not reaching the threshold value despite maximal compliance and medication were included in the study. Eyes with other comorbidities compromising the outcome, that is, secondary glaucoma or corneal or retinal pathology were excluded from the study. Parameters evaluated included IOP, number of ocular hypotensive medications required, best distance visual acuity (BDVA), and bleb morphology by using the Moorfields bleb grading system.[18]

Surgical technique

This was a single-surgeon study. All participants were operated under peribulbar anesthesia. Trabeculectomy was performed with fornix-based conjunctival flap superficially, 8 mm in dimension. A 4.5 mm × 4 mm rectangular scleral flap was dissected, and two 10-0 monofilament nylon releasable sutures were preplaced. In MMC eyes, pledgets soaked with 0.2 mg/cm³ were placed subserosally and subconjunctivally, sparing the cut ends of the conjunctiva, and care was taken to avoid the cornea. After 1 min, the pledgets were removed and a thorough wash was given with 30 ml of balanced salt solution. After completion of standard phacoemulsification with IOL implantation, Descemet’s membrane was punched and the anterior chamber was entered. Releasable sutures were completed and anterior chamber integrity was ensured. Ologen implant of 6 mm × 2 mm dimensions (Model 830601, Aeon Astron Europe B.V.) was placed subconjunctivally. The conjunctival flap was sutured back with continuous 9-0 monofilament nylon sutures to form the bleb, and bleb integrity was ensured through the side port. In the postoperative period, all eyes were treated with topical antibiotic-steroid combination (moxifloxacin 0.5% and prednisolone acetate 1%) eye drops six times daily, tapered over 6 weeks, and cyclopentolate 0.5% eye drops for 1 week. Ocular hypotensives were added as per the requirement, titrated against the IOP. Releasable sutures were released when bleb height was inadequate or IOP rose to over 15 mm Hg. Patients were assessed at day 1, 6 weeks, 3 months, 6 months, and 12 months post-operatively.

Mean postoperative IOP was the primary outcome variable. Success was defined as IOP between 5 and 21 mm Hg with (qualified success) or without (complete success) use of ocular hypotensives. The number of ocular hypotensives used post-operatively, BDVA, and bleb morphology were the secondary outcome variables. IOP was measured by Goldmann Applanation tonometry, BDVA was assessed by Snellen chart for distance and converted to logMAR, and bleb morphology was assessed by slit-lamp examination and anterior segment optical coherence tomography. Blebs with IOP moderate wall thickness and vascularity and with microcystic spaces were considered successful, whereas those with extremely thin walls, avascularity, scarring, or absence of microcystic spaces, or other complications were considered to have failed. Statistical analysis was done using paired t test (P < 0.05) and Kaplan–Meier analysis. A random number table was used for randomization. The sample size was calculated to be 18 in each group with a confidence interval of 95%, significance level of 0.05, and power of 80% in accordance with a study by Senthil et al.,[10] which gave comparable results at 12 months with both Ologen and MMC. One patient had to be excluded owing to inadequate follow-up.

Results

Thirty-four eyes of 34 patients were studied. All the patients underwent trabeculectomy and phacoemulsification with IOL implantation in one eye and were followed up for a period of 12 months.

There was no significant difference between the preoperative parameters and demographics between the two groups as shown in Table 1.

There was a significant decrease in IOP (P < 0.00001) and number of ocular hypotensive medications (P < 0.00001) used and improvement in BDVA (P < 0.00001) from the first follow-up visit, and this was maintained until the 12-month follow-up in both groups. However, there was no significant difference between the two groups regarding the abovementioned parameters. The postoperative outcomes of both groups are summarized in Tables 2 and 3.

In the MMC group, mean IOP dropped from 30.12 ± 3.78 mm Hg preoperatively to 11.94 ± 2.35 mm Hg (P < 0.00001) on day 1, 12 ± 1.97 mm Hg (P < 0.00001) at 6 weeks, 13.56 ± 2.39 mm Hg (P < 0.00001) at 3 months, 13.62 ± 2.66 mm Hg (P < 0.00001) at 6 months, and 14.62 ± 2.89 mm Hg (P < 0.00001) at 12 months postoperatively. In the Ologen group, it dropped
Table 1: Preoperative parameters and demographic data of participants in the MMC group and Ologen group

|                  | MMC group (n=16) | Ologen group (n=18) | P   |
|------------------|------------------|---------------------|-----|
| Mean age         | 54.96±2.02 years | 56.32±2.31 years    | 0.36|
| Male: Female     | 9:7              | 11:7                |     |
| Mean IOP         | 30.12±3.78 mm Hg | 29.44±3.48 mm Hg    | 0.27|
| Mean BDVA        | 0.91±0.13 logMAR | 0.91±0.12 logMAR    | 0.1 |
| Number of antiglaucoma medications used | 2.94±0.77 | 2.89±0.67 | 0.42 |

Table 2: Primary and secondary outcomes of trabeculectomy in eyes treated with MMC and Ologen at 12 months

|                  | MMC group | Ologen group | P   |
|------------------|-----------|--------------|-----|
| Mean IOP         | 14.62±2.89 mm Hg | 14.56±4.14 mm Hg | 0.47|
| Mean BDVA        | 0.17±0.09 logMAR | 0.78±0.94 logMAR | 0.47|
| Reduction in IOP | 51.06%    | 50.58        |     |

Table 3: Bleb morphology of eyes post-trabeculectomy in the MMC group and Ologen group

|                 | MMC group | Ologen group |
|------------------|-----------|--------------|
| Microcystic      | 5         | 7            |
| Diffuse          | 5         | 10           |
| Flat             | 4         | Nil          |
| Encapsulated     | 1         | 1            |
| Overhanging      | 1         | Nil          |

from 29.44 3.48 mm Hg preoperatively to 12.89 ± 1.96 mm Hg (P<0.00001) on day 1, 15.22±2.48 mm Hg (P<0.00001) at 6 weeks, 14.33±4.82 mm Hg (P<0.00001) at 3 months, 14.33±4.82 mm Hg (P<0.00001) at 6 months, and 14.56±4.14 mm Hg (P<0.00001) at 12 months postoperatively.

Number of ocular hypotensives used reduced from median 2 (IQR 1–3) preoperatively to IQR 0–0 on day 1 (P<0.00001), IQR 0–1 (P<0.00001) at 6 weeks, IQR 0–1 (P<0.00001) at 3 months, IQR 0–1 (P<0.00001) at 6 months, and median 1 (IQR 0–1) (P<0.00001) at 12 months postoperatively in the MMC group. In the Ologen group, it reduced from median 2 (IQR 1–3) preoperatively to IQR 0–0 (P<0.00001), IQR 0–1 (P<0.00001), IQR 0–1 (P<0.00001), median 0.5 (IQR 0–1) (P<0.00001), and median 0.5 (IQR 0–1) (P<0.00001) on day 1, at 6 weeks, 3 months, 6 months, and 12 months, respectively.

BDVA improved from 0.91 ± 0.13 logMAR preoperatively to 0.16 ± 0.09 logMAR (P<0.00001), 0.16 ± 0.09 logMAR (P<0.00001), 0.16 ± 0.09 logMAR (P<0.00001), 0.17±0.09 logMAR (P<0.00001), and 0.17±0.09 logMAR (P<0.00001) on day 1 and at 6 weeks, 3 months, 6 months, and 12 months, respectively, in the postoperative period in the MMC group. In the Ologen group, BDVA improved from 0.91 ± 0.12 logMAR preoperatively to 0.17 ± 0.09 logMAR on day 1 (P<0.00001), at 6 weeks (P<0.00001), 3 months (P<0.00001), 6 months (P<0.00001), and 12 months (P<0.00001).

Visual deterioration was seen in only one eye in the MMC group which developed hypotony in the immediate postoperative period. It was managed with bandage contact lens and atropine 1% eye drops and improved by 6 weeks. None of the other eyes in either group had any complications.

The mean change in IOP did not vary significantly (P = 0.35) between the two groups. No significant correlation was seen between the study parameters and the age or gender of the participants.

At the end of 12 months, the overall success rates were 93.75% and 94.44% in the Ologen and MMC groups, respectively. Complete success was achieved in 48.63% of eyes in the Ologen group, and the remaining 45.12% of eyes achieved qualified success. In the MMC group, 47.85% of eyes achieved complete success and 46.59% of eyes achieved qualified success.

Blebs in the Ologen group showed better morphology as compared to those in the MMC group, as shown in Table 3. Fig. 1 demonstrates the difference in bleb morphology between a MMC bleb and an Ologen bleb.

None of the eyes underwent any further surgical procedures for IOP reduction.

Discussion

Combined phacoemulsification with IOL implantation and trabeculectomy was performed with either MMC or Ologen as the adjunctive. A significant drop in IOP was recorded after the procedure in both groups, and the decrease in IOP was comparable between the groups. The number of ocular hypotensives used postoperatively, BDVA, and success rates were also comparable between the two groups. However, there was only one isolated event of hypotony in the MMC group which was managed medically. However, bleb morphology was noted to be better in the Ologen group.

The concern with the use of Ologen is that Ologen blebs fail to achieve the same IOP-lowering effect as MMC blebs as these blebs are more vascular and have lesser height.[32] As reported by some previous studies,[27,30] our study also found Ologen to be non-inferior to MMC in its IOP-lowering effect, with a mean IOP reduction of ~51% in the MMC group and ~50.5% in the Ologen group. This is comparable with the IOP reduction obtained with trabeculectomy in other studies comparing the two adjunctives.[33]

Though the criterion for success of the procedure in our study was an IOP of <21 mm Hg, studies suggest a value of <17 mm Hg to be more appropriate.[34] This might have been a confounding factor.
One eye in the MMC group developed hypotony in the first week with an IOP of 6 mm Hg. A shallow anterior chamber and minimal bleb leak were observed, and this was managed conservatively with a bandage contact lens and 1% atropine eye drops daily. The IOP eventually improved to 8 mm Hg and remained the same 6 weeks postoperatively.

Although there was only a single eye with hypotony, the bleb morphology was observably better in the Ologen group in comparison with the MMC group. El-Sayyad et al.\(^3\) also reported better scoring (Moorfields bleb grading system) with Ologen blebs. Though less frequent, bleb leakage, implant exposure, encapsulated blebs, and blebitis have also been reported in Ologen blebs.\(^3\),\(^2\),\(^3\)

None of the eyes studied had any toxicity or allergy in the postoperative period. Though there is a theoretical risk of increased inflammation with Ologen,\(^3\) none have been reported. MMC has been shown to cause have toxic intraocular effects.\(^6\) The risk is higher in combined phacoemulsification with trabeculectomy. As phacoemulsification itself brings down IOP by ~2 mm Hg, Ologen as an adjunctive would suffice to further decrease the IOP to the desired levels, as would be possible with MMC which is significantly more toxic.\(^3\)

The main limitations of this study are the small sample size and short follow-up duration. The data is from a single center. Thus, institutional practices may have affected the outcome. In addition, healing responses vary between individuals. A multi-center randomized control trial of patients with bilateral primary open-angle glaucoma with one eye receiving MMC and the other receiving an Ologen implant followed up for a longer duration is recommended.

**Conclusion**

Our study demonstrated similar outcomes for combined trabeculectomy and phacoemulsification with MMC and Ologen. However, bleb morphology and bleb health were better in Ologen blebs.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Razeghinejad MR, Fudemberg SJ, Spaeth GL. The changing conceptual basis of trabeculectomy: A review of past and current surgical techniques. Surv Ophthalmol 2012;57:1-25.
2. Rao K, Ahmed I, Blake DA, Ayyala RS. New devices in glaucoma surgery. Exp Rev Ophthalmol 2009;4:491-504.
3. Lockwood A, Brochini S, Khaw PT. New developments in the pharmacological modulation of wound healing after glaucoma filtration surgery. Curr Opin Pharmacol 2013;13:65-71.
4. Wang W, Zhou M, Huang W, Zhang X. Ex-PRESS Implantation versus trabeculectomy in uncontrolled glaucoma: A meta-analysis. PLoS One 2013;8:e63591.
5. Husain R, Clarke JC, Seah SK, Khaw PT. A review of trabeculectomy in East Asian people: The influence of race. Eye (Lond) 2005;19:243-52.
6. Lin ZJ, Li Y, Cheng JW, Lu XH. Intraoperative mitomycin C versus
intraoperative 5-fluorouracil for trabeculectomy: A systematic review and meta-analysis. J Ocul Pharmacol 2012;28:166-73.

7. Hollo G. Wound healing and glaucoma surgery: Modulating the scarring process with conventional antimetabolites and new molecules. Dev Ophthalmol 2012;50:79-89.

8. Mearza AA, Aslanides IM. Uses and complications of mitomycin C in ophthalmology: Expert Opin Drug Saf 2007;6:27-32.

9. Mietz H, Brunner R, Addicks K, Kriegstein GK. Histopathology of an avascular filtering bleb after trabeculectomy with mitomycin-C. J Glaucoma 1993;2:266-70.

10. DeBry PW, Perkins TW, Heatley G, Kaufman P, Brumback LC. Incidence of late-onset bleb-related complications following trabeculectomy with mitomycin. Arch Ophthalmol 2002;120:297-300.

11. Stavrakas P, Georgopoulos G, Milia M, Papaconstantinou D, Bafa M, Stavrakas E, et al. The use of amniotic membrane in trabeculectomy for the treatment of primary open-angle glaucoma: A prospective study. Clin Ophthalmol 2012;6:209-12.

12. Hu F, Zeng XY, Xie ZL, Liu LL, Huang L. Clinical outcomes of amniotic membrane loaded with 5-FU PLGA nanoparticles in experimental trabeculectomy. Int J Ophthalmol 2015;8:29-34.

13. Chen HS, Ritch R, Krupin T, Hsu WC. Control of filtering bleb structure through tissue bioengineering: An animal model. Invest Ophthalmol Vis Sci 2006;47:5310-4.

14. Hsu WC, Spilker MH, Yannas IV, Rubin PA. Inhibition of conjunctival scarring and contraction by a porous collagen-glycosaminoglycan implant. Invest Ophthalmol Vis Sci 2000;41:2404-11.

15. Rosentreter A, Schild AM, Jordan JF, Kriegstein GK, Dietlein TS. A prospective randomized trial of trabeculectomy using mitomycin C vs. an ologen implant in open angle glaucoma. Eye (Lond) 2010;24:1449-57.

16. Senthil S, Rao HL, Babu JG, Mandal AK, Garudadri CS. Comparison of outcomes of trabeculectomy with mitomycin C vs. ologen implant in primary glaucoma. Indian J Ophthalmol 2013;61:338-42.

17. Angmo D, Wadhwani M, Upadhyay AD, Temkar S, Dada T. Outcomes of trabeculectomy augmented with subconjunctival and sub sclerallogen implantation in primary advanced glaucoma. J Glaucoma 2017;26:8-14.

18. Boey PY, Narayanaswamy A, Zheng C, Perera SA, Htoo HM, Tun A, et al. Imaging of blebs after phacotrabeculectomy with ologen collagen matrix implants. Br J Ophthalmol 2011;95:340-4.

19. Khamar MB, Soni SR, Mehta SV, Srivastava S, Vasavada VA. Morphology of functioning trabeculectomy blebs using anterior segment optical coherence tomography. Indian J Ophthalmol 2014;62:711-4.

20. Dietlein TS, Lappas A, Rosentreter A. Secondary subconjunctival implantation of a biodegradable collagen-glycosaminoglycan matrix to treat ocular hypotony following trabeculectomy with mitomycin C. Br J Ophthalmol 2013;97:985-8.

21. Data T, Kushmure R, Bali SJ, Sharma S, Sobti A, Arora V, et al. Trabeculectomy with combined use of subconjunctival collagen implant and low-dose mitomycin C. J Glaucoma 2013;22:659-62.

22. Tanito M, Okada A, Mori Y, Sano I, Ikeda Y, Fujihara E, et al. Subconjunctival implantation of ologen collagen matrix to treat ocular hypotony after filtration glaucoma surgery. Eye (Lond) 2017;31:1475-9.

23. Varma R, Lee PP, Goldberg I, Kotak S. An assessment of the health and economic burdens of glaucoma. Am J Ophthalmol 2011;152:515-22.

24. Khaw PT, Migdal CS. Current techniques in wound healing modulation in glaucoma surgery. Curr Opin Ophthalmol 1996;7:24-33.

25. Spaeth GL, Mutlukan E. The use of antimetabolites with trabeculectomy: A critical appraisal. J Glaucoma 2001;10:145-51.

26. Ro, Fechtner RD. Antifibrotics and wound healing in glaucoma surgery. Surv Ophthalmol 2003;48:314-46.

27. Thomas R, Paul P, Muniyil J. Glaucoma in India. J Glaucoma 2003;12:81-7.

28. Narayanaswamy A, Perera SA, Htoo HM, Hoh ST, Seah SK, Wong TT, et al. Efficacy and safety of collagen matrix implants in phacotrabeculectomy and comparison with mitomycin C augmented phacotrabeculectomy at one year. Clin Exp Ophthalmol 2013;41:552-60.

29. Papaconstantinou D, Georgalas I, Karmiris E, Diagourtas A, Koutsandrea C, Ladas I, et al. Trabeculectomy with ologen versus trabeculectomy for the treatment of glaucoma: A pilot study. Acta Ophthalmol 2010;88:80-5.

30. Ji Q, Qi B, Liu L, Guo X, Zhong J. Efficacy and safety of ologen implant versus mitomycin C in primary trabeculectomy: A meta-analysis of randomized clinical trials. J Glaucoma 2015;24:e88-94.

31. Wells AP, Crowston JG, Kirwan JF, Clarke JC, et al. A pilot study of a system for grading of drainage blebs after glaucoma surgery. J Glaucoma 2004;13:454-60.

32. E-Saied HMA, Abdelbakim MASE. Ologen with secondary glaucoma. Eye 2016;30:1126-34.

33. Singh K, Bhattacharyya M, Mutreja A, Dangda S. Trabeculectomy with subconjunctival collagen implant in Indian eyes: Long-term results. Indian J Ophthalmol 2018;66:1429-34.

34. Sibota R, Angmo D, Ramasswamy D, Dada T. Simplifying “target” intraocular pressure for different stages of primary open-angle glaucoma and primary angle-closure glaucoma. Indian J Ophthalmol 2018;66:495-505.

35. El-Sayyad F, El-Saied HMA, Abdelbakim MASE. Trabeculectomy with ologen versus Mitomycin C in Juvenile open-angle glaucoma: A 1-year study. Ophthalmic Res 2017;57:230-8.

36. Derick RJ, Pasquale L, Quigley HA, Jampel H. Potential toxicity of Mitomycin C. Arch Ophthalmol 1991;109:1635.

37. Slabaugh MA, Bojjikian KD, Moore DB, Chen PP. The effect of phacoemulsification on intraocular pressure in medically controlled open-angle glaucoma patients. Am J Ophthalmol 2014;157:26-31.