

# Surgical Outcome of Trabeculectomy Using Mitomycin C Versus Combined Use of Low Dose Mitomycin C and Collagen Implant: A Quasi-Experimental Study

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## ABSTRACT

**Background:** To compare alternate methods of glaucoma surgery.

**Method:** Sixty eyes of 60 patients were selected and divided in 2 groups, 30 patient each, pre-operative evaluation was done. Data including Age, Sex, type of Glaucoma, IOP, HVFA were collected. Group A underwent Trabeculectomy with Mitomycin C and Group B underwent trabeculectomy with low dose Mitomycin C and Ologen implant. Postoperative IOP, antiglaucoma drugs requirement, Bleb condition, Complications were evaluated. Follow up was done upto 3 months.

**Result:** Post-operative IOP reduction was significant in both the groups, which persisted throughout the follow up period. No statistical significant difference between two groups were noticed according to complications, success of surgery and IOP reduction.

**Conclusion:** Study results indicate that MMC alone and low dose MMC plus Collagen implant appear to be safe and effective adjunctive for trabeculectomy for both POAG and PACG.

**Keywords:** Glaucoma, Trabeculectomy, IOP, MMC, Collagen.

## Introduction

The glaucoma is a group of progressive optic neuropathies characterized by progressive degeneration of retinal ganglion cells. These are central nervous system neurons that have their cell bodies in the inner retina and axons in the optic nerve.

Glaucoma affects more than 70 million people worldwide with approximately 10% being bilaterally blind, making it the leading cause of irreversible blindness in the world<sup>1</sup>. In a preliminary report of glaucoma prevalence survey carried out by Bangladesh Eye Care Society (BECS), the incidence of glaucoma was 2.8 percent in the population above 35 years of age in the country<sup>2</sup>. Results from several multicenter

clinical trials have demonstrated the benefit of lowering IOP in preventing the development and slowing the disease's progression<sup>3</sup>.

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<sup>4</sup>. 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<sup>5</sup>. Thus, inhibition of scar formation during the process of wound healing should promote greater success.

In 1990, anti-fibrotic agents such as mitomycin C (MMC) significantly improved the long-term outcome of this procedure and produced lower IOP when applied intraoperatively during trabeculectomy<sup>6,7</sup>. Further advanced the concept of using a porous collagen matrix (CM) implant as an adjunct to trabeculectomy. Their approach was to use the implant to resist over-filtration in the early post-operative period by acting as a physical

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barrier and to maintain long-term pressure control by promoting the development of a loosely organized scar as the implant degrades. In a rabbit model, eyes undergoing trabeculectomy with CM implantation maintained IOP reduction to 55% below baseline at day 28, whereas control eyes undergoing trabeculectomy without CM reverted to baseline IOP levels by day 21. The Ologen CM (Aeon Astron Europe B.V., Leiden, Netherlands) is a porous, disc-shaped implant that is commercially available in two sizes, a 6-mm diameter disc with a thickness of 2 mm and a 12-mm diameter disc with a thickness of 1 mm. It is composed of a collagen-glycosaminoglycan copolymer and was developed for use as an adjunctive device for trabeculectomy surgery. The CM serves as a spacer and a scaffolding to modulate the fibrotic response as fibroblasts and myofibroblasts proliferate in response to surgically induced tissue injury. The success of the use of trabeculectomy with CM compared to adjunctive therapy with MMC has varied with respect to the reported outcomes. In a recently published meta-analysis, the authors found that outcomes were similar, but pointed out that additional experimental studies are needed<sup>8</sup>.

In 2010, Dada et al., (2012)<sup>9</sup> conducted a study to evaluate the outcomes of trabeculectomy with subconjunctival collagen implant combined with use of low-dose MMC. This was the first study in which these implants have been used in conjunction with antiproliferative agents in trabeculectomy and showed an encouraging short term results for IOP control.

Considering these context, we designed this quasi-experimental study to compare the efficacy and safety of trabeculectomy with low dose MMC and trabeculectomy with combined collagen implant and low dose MMC in our hospital.

## **Materials and Method**

The study design was a Quasi-experimental study which was conducted at the department of Ophthalmology, Chittagong Medical College Hospital, Chattogram from July 2017 to September 2019. Patients attending the Ophthalmology department of CMCH with primary open angle glaucoma and primary angle closure glaucoma during study period were the study population. Patient of primary open angle glaucoma and primary angle closure glaucoma

selected for trabeculectomy with MMC and with combined MMC and collagen implant.

All patients attending the Department of Ophthalmology with a diagnosis of primary open-angle and closed angle glaucoma were assessed for eligibility. Informed written consent was obtained from the patients or attendants after full explanation of the ultimate outcome, complications and purpose of the study. They were informed of their right to withdraw from the study at any stage. After consenting, the consecutive eligible patients were assigned to undergo a trabeculectomy either with MMC (Group A) or a trabeculectomy with combined MMC and collagen implant (Group B) in Department of Ophthalmology, Chittagong Medical College Hospital.

The preoperative data regarding age, gender, medical history, including the presence of any ocular pathology, number of antiglaucoma drugs used, applanation tonometry under maximum-tolerated topical therapy, biomicroscopy, gonioscopy and computerized Humphrey visual field Analysis done.

## **Surgical techniques**

All operations were carried out under local peribulbar anesthesia. The technique included creating a superior fornix-based conjunctival/Tenon's flap with a 9-mm limbal conjunctival incision keeping half mm conjunctiva at the limbus.

A triangular 4×4 mm scleral incision, partial thickness scleral flap were dissected at the 12-o'clock position using a bevel-up crescent knife.

When MMC were the adjunctive therapy, a Weck-cell sponge soaked with MMC at a concentration of 0.4mg/ml and placed under the dissected conjunctiva surrounding the scleral flap and on the scleral bed. The sponges were left in position for 2 min in order to maintain contact with the Tenon's capsule side of conjunctiva. Thereafter, the eye was irrigated with 15ml of balanced salt solution.

An ophthalmic viscoelastic were injected to increase the iris-cornea depth and anterior chamber were entered at the base of scleral flap

with a 3.2 precalibrated knife. 2×2mm scleral block created with a straight vannus scissor or punch, in order to obtain an excision of corneoscleral tissue including the trabecular meshwork.

A peripheral iridectomy then performed. The scleral flap was closed with two 10-0 nylon sutures.

In combined Group, a Weck-cell sponge, soaked with MMC at a concentration of 0.2mg/ml and placed under the dissected conjunctiva surrounding the scleral flap and on the scleral bed for 2 min and then irrigated by balanced salt solution, a 2×2mm sclerectomy were performed followed by a peripheral iridectomy.

The scleral flap was repositioned and closed with 1 suture of 10-0 monofilament nylon. Collagen implant (cylindrical implant with a diameter of 7mm and a height of 4mm) were positioned on top of the scleral flap under the Tenon's capsule without the use of any suture. Finally, the conjunctiva were closed with an 10-0 monofilament nylon suture. Irrigation through the

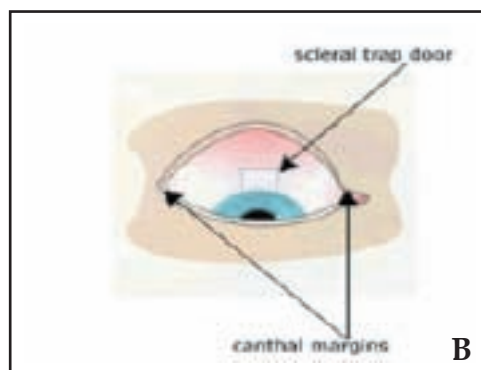
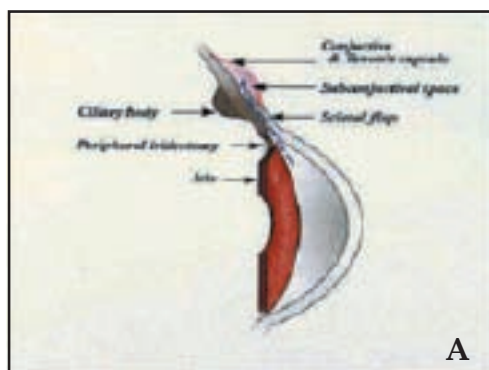
paracentesis is repeated to produce a bleb which is checked for leakage.

Post-operatively, all eyes were treated with topical tobramycin 0.3% six times daily until day 14, and with topical dexamethasone drops 0.1% five times daily for 7 days, three times daily for 6 weeks and twice a day for a final 1 week. If corkscrew bleb vessels are present, more frequent topical steroid administration were allowed, according to the 'intensified postoperative care' (IPC) protocol. Instillation of 1% atropine drops added during the first few days, and continued up to 1 week in cases with hypotony.

### Evaluation of the patient

Postoperative visits were scheduled at 24 hour, 7 days, and 1st and 3rd month. IOP (average of two separate readings), biomicroscopy findings, number of antiglaucoma medications, and post-operative complications were assessed at each visit as well as any bleb complications.

Reference photographs are provided.



Ref. Comprehensive Ophthalmology by A K Khurana; 7<sup>th</sup> Edition

Figure-01 [A, B]: Trabeculectomy site and anatomy

Study was conducted after getting approval by ethical committee and review committee of Chittagong Medical College.

Informed written consent from all patients or from their real guardians of this study was taken prior to including in this study. All issues regarding the patient's welfare was approved by the local ethical committee. Confidentiality right

was maintained properly.

The interview of the patients, clinical examination and procedure were performed after explaining the nature and purpose of study to them and assuring that the information given by them were used for the interest of the community and particulars of the patients were not be disclosed any way.

**RESULTS AND OBSERVATIONS****Table-01: Age and sex distribution of the glaucoma patients underwent trabeculectomy**

Variables (unit) (n=60)	Intervention group		P value
	MMC group (n=30)	MMC & collagen implant group (n=30)	
Age (years)			
Mean $\pm$ SD	55.57 $\pm$ 10.78	54.67 $\pm$ 8.99	0.73
Range	38-81	40-70	
Sex			
Male	17 (56.7%)	19 (63.3%)	0.60
Female	13 (43.3%)	11 (36.7%)	

A total of 60 patients were included in the study and 30 patients were undergone trabeculectomy by Mitomycin-C only (MMC group) and other 30 were undergone trabeculectomy by low dose Mitomycin-C and collagen implant (MMC & collagen implant group). The age and sex distribution of the study population by the intervention groups is shown in Table I. In both groups male patients outnumbered female patients and the age of the patients ranged from 38 to 81 years. However, both the groups were comparable at baseline in terms of age and sex distribution.

**Table-02: Glaucoma type and visual field characteristics and Number of preoperative medications of the glaucoma patients underwent trabeculectomy**

Variables (unit) (n=60)	Intervention group		P value
	MMC group (n=30)	MMC & collagen implant group (n=30)	
Type			
POAG	23 (76.7%)	20 (66.7%)	0.39
PACG	7 (23.3%)	10 (33.3%)	
Visual field			
Superior arcuate	17 (56.7%)	15 (50.0%)	
			0.56
Ring scotoma	7 (23.3%)	5 (16.7%)	
Both superior	6 (20.0%)	9 (30.0%)	
Nasal step	0 (0%)	1 (3.3%)	1.00
Number of preoperative medications			
Mean $\pm$ SD	3.76 $\pm$ 0.43	3.73 $\pm$ 0.45	0.77

In both groups majority of the patients were cases of POAG and visual fields were superior arcuate type. There were no significant differences between two groups with respect to glaucoma type and visual field defect (Table II). Moreover, patients in the two treatment groups did not significantly differ in mean number of preoperative topical antiglaucomatous medication ( $p=0.770$ ).

**Table-03: Comparison of IOP between two groups of glaucoma patients at different time intervals**

Assessment time (n=60)	Mean $\pm$ SD of IOP (mmHg)		P value
	MMC group (n=30)	MMC & collagen implant group (n=30)	
Before surgery	30.37 $\pm$ 9.59	34.93 $\pm$ 12.52	0.12
1st day after surgery	13.30 $\pm$ 1.92	9.73 $\pm$ 1.72	<0.001
At 1st week	14.20 $\pm$ 1.75	10.13 $\pm$ 1.48	<0.001
At 1 month	13.73 $\pm$ 0.87	10.87 $\pm$ 1.36	<0.001
At 3 month	13.73 $\pm$ 0.69	11.07 $\pm$ 1.14	<0.001

IOP was measured in all patients before surgery, 1st day after surgery, at 1st week, at 1 month and at 3 month. Table III indicated that, before surgery mean IOP was similar in both groups ( $p=0.118$ ). After surgery regardless of assessment time mean IOP was significantly lower in patients of low dose MMC & collagen implant group than the patients underwent trabeculectomy only with MMC ( $p<0.001$ ).

**Table-04: Postoperative complications in patients with glaucoma after trabeculectomy**

Complications (n=60)	Study group		P value
	MMC group (n=30)	MMC & collagen implant group (n=30)	
Hyphema	2 (6.7%)	0 (0%)	0.49
Bleb leakage	0 (0%)	1 (3.3%)	1.0
Hypotonia	1 (3.3%)	1 (3.3%)	NA
Choroidal detachment	0 (0%)	0 (0%)	NA
Shallow anterior chamber	1 (3.3%)	1 (3.3%)	NA
Blebitis	0 (0%)	0 (0%)	NA
Implant exposure	0 (0%)	0 (0%)	NA
Encapsulated bleb	0 (0%)	1 (3.3%)	1.0

Only Two cases in MMC group developed hyphema which were managed conservatively. One case of hypotonia was observed in both groups, which were managed by conservatively by cycloplegic and steroid. No case needed revision surgery. There was no significant difference in complications rate between two groups (Table IV).

**Table-05: Bleb characteristics of the patients with glaucoma after trabeculectomy by their intervention groups (n=60)**

Bleb (n=60)	Mean $\pm$ SD of IOP (mmHg)		P value
	MMC group (n=30)	MMC & collagen implant group (n=30)	
Diffuse	27 (90.0%)	27 (90.0%)	0.35
Cystic	2 (6.7%)	3 (10.0%)	1.00
Flat	1 (3.3%)	0 (0%)	

Bleb was cystic in MMC only group and three cases in combined group. One case in MMC only group developed flat bleb. There was no significant difference in bleb characteristics between two groups (Table V).

## Discussion

The present study was designed as a trial to compare the combined use of low dose MMC (0.2mg/ml) and collagen implant with standard dose of MMC alone as augmentation method with trabeculectomy operation in both primary open-angle and angle closure glaucoma. Findings of the present study revealed that both the methods were effective in significant reduction of IOP from 1st post-operative day to the 3 month after surgery, but the mean IOP reduction was significantly more in patients who had combined low dose MMC and collagen implant in comparison to the patients who had trabeculectomy with MMC alone.

Recent studies have embarked upon the use of Ologen to replace antifibrotic agents in filtering surgery for glaucoma<sup>10</sup>. Reported that deep sclerectomy with Ologen implantation is effective, However<sup>11</sup>. Performed a prospective study up to 24 months comparing Ologen and MMC (concentration: 0.2mg/mL) as adjuvants to trabeculectomy. They did not find any difference in lowering IOP between the 2 groups. In the present study, we evaluated the results of trabeculectomy with subconjunctival Ologen implantation combined with low dose MMC. Irrespective of the study groups all patients achieved surgical success (IOP between 6 and 18mm Hg), and only 2 cases in MMC only group required anti-glaucoma medication for IOP control during the follow-up period.

In the present study, mean ( $\pm$  SD) pre-operative IOP were  $30.37 \pm 9.59$  mm Hg and  $34.93 \pm 12.52$  respectively in MMC only group and in combined MMC and collagen implant group. After 3 months of trabeculectomy the corresponding values were  $13.73 \pm 0.69$  mmHg and  $11.07 \pm 1.14$  mmHg respectively in two groups. IOP were significantly reduced in both groups. It was in agreement with the findings of Salem et al., (2015) where after 3 months of trabeculectomy, mean ( $\pm$  SD) pre-operative IOP were  $12.65 \pm 1.63$  mm Hg and  $13.30 \pm 0.80$  respectively in MMC only group and in combined MMC and collagen implant group. However, in contrast to the findings of Salem et al., (2015) in the present study we have observed a significantly better reduction of IOP in combination group ( $p < 0.001$ ) whereas Salem et al., (2015) noticed no significant difference in the mean IOP after 3 months of trabeculectomy ( $P = 0.14$ ). The reason for the disagreement was probably due to the duration of MMC used in the study. Moreover, the baseline IOP was higher than the patients of Salem et al., (2015) in the present study<sup>12</sup>.

In the study of Dada et al., (2012) where trabeculectomy was done with subconjunctival Ologen implant and MMC (0.1mg/ml 1 min); baseline IOP was  $34.06 \pm 6.56$  mmHg and is quite similar to our study. After 3 months IOP reduced to  $11.87 \pm 2.23$  mmHg with a range of 8-18 mmHg. In the present study the IOP range was 8-12 mmHg in patients of combined augmentation<sup>9</sup>.

The overall success rates (combined complete and qualified success, with medication) were reported in literatures after trabeculectomy surgery with different criteria. In the present study, 100% patients who had trabeculectomy with MMC and collagen implant had complete success (IOP  $>5$  and  $\leq 21$  mmHg with at least a 20% reduction below the baseline study visit IOP and without subsequent ocular hypotensive medication or additional glaucoma surgery). On the other hand, 28 (93.3%) of patients with trabeculectomy with MMC only had complete success and the remaining two (6.7%) had qualified success (IOP  $>5$  and  $\leq 21$  mmHg with at least a 20% reduction below the baseline study visit IOP with subsequent ocular hypotensive medication or additional glaucoma surgery). However, the differences in success rate was not statistically significant ( $p=0.492$ ). The overall success rate was higher than the findings of Salem et al., (2015) and Dada et al., (2012)<sup>9,12</sup>.

In the present study stable visual acuity was stable in both groups of patients during the study period. This is in agreement with the study of Tanna et al., (2016) where visual acuity, visual field mean deviation, and rates of visual field change were statistically similar between groups at all time points<sup>13</sup>.

There were no sight-threatening complications in the present study. There were only two cases of hypotonia (1 in each group) which did not need revision surgery and managed conservatively. In the MMC only group 2 cases developed hyphema which were also managed successfully by conservative treatment with pad bandage, cycloplagic and steroid. Other infrequent complications were bleb leakage, shallow anterior chamber, encapsulated bleb. In the literature different complications like encapsulated filtering bleb (Tenon's cyst), shallow anterior chamber, hyphema, choroidal effusion, persistent leakage, hypotony (IOP  $<6$  mmHg), macular edema, corneal complications, allergy, suprachoroidal hemorrhage, and blebitis/ endophthalmitis were reported in varying degree after trabeculectomy

and augmentation. Among these shallow anterior chamber, hyphema and hypotony were reported in  $<10\%$  of case in the study of Salem et al., (2015) and Dada et al., (2012). In the present study skill of the surgeons which might effect the overall low rate of complications<sup>9,12</sup>.

Rationale to combine both MMC and collagen implant as augmentation during trabeculectomy is to avoid dose related complication of MMC. Dada et al., (2012) in one group pre and post test design found encouraging results of the efficacy and safety of this combined modality. Later on Salem et al., (2015) confirmed these results with a randomized controlled trial. Our study added to these growing bodies of evidence and supports the use of both MMC with Ologen implants as an augmented procedure in trabeculectomy for primary glaucoma<sup>9,12</sup>.

## Conclusion

The study results indicate that, both MMC alone and low dose MMC plus collagen implant appear to be safe, effective, and promising as augmentation procedures with trabeculectomy in patients with both primary open-angle and angle closure glaucoma. However, the IOP reduction effect was more prominent in combination group.

## Limitations

The results were interpreted with short term follow up, so for further evaluation long term follow up is necessary.

Small sample size is another limitation.

Lack of randomization.

## Recommendations

Collagen implant with low dose MMC is a successful adjunct to glaucoma surgeries. Intra-operative and post-operative precautions should be taken to maintain proper aqueous drainage, functioning blebs, and better degree of success, reaching the target IOP and a stable visual field. However, our results are needed to be confirmed with further study with large sample size and longer follow up.

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