

Intraoperative injection versus sponge-applied mitomycin C during trabeculectomy: One-year study

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Purpose: To determine the safety and efficacy of mitomycin C (MMC) injection versus sponge during trabeculectomy. **Methods:** It is a prospective analysis of patients who underwent trabeculectomy with MMC and followed up for 1 year, divided into two groups, namely, group 1- injection ($n = 21$), group 2- sponge ($n = 21$). The same concentration of MMC was used for both groups. Inclusion criteria were trabeculectomies with MMC for intraocular pressure (IOP) control in eyes with glaucoma (primary + secondary) with a follow-up of 1 year. **Results:** Mean preoperative IOP in group 1 was 29.00 ± 11.92 mmHg and group 2 was 25.87 ± 11.09 mmHg, which reduced to 12.19 ± 4.03 and 15.56 ± 10.72 mmHg at final visit with P value of 0.0002 and 0.001, respectively. Mean preoperative number of antiglaucoma medications was 2.4 ± 0.87 in group 1 and 2.3 ± 0.96 in group 2, which reduced to 0.38 ± 0.5 and 0.91 ± 0.85 with P value of 0.001 and 0.0003, respectively. The complete success rate was 52.4% in the injection group and 26.1% in the sponge group at end of 1 year. Overall, success rate (complete + qualified) was 90.5% and 87% in group 1 and group 2 at final visit. All major complications were encountered in sponge group. 1 (11.1%) patient developed choroidal detachment and one had malignant glaucoma which got resolved by medical management. 33.3% cases had encapsulated bleb which received bleb needling. 44.4% cases underwent Argon laser suture lysis postoperatively. **Conclusion:** The MMC injection may be as safe and as effective as conventional sponge application with comparable estimated complete treatment success.

Key words: Injectable mitomycin C, sponge soaked mitomycin C, trabeculectomy

The introduction of mitomycin C (MMC) as an adjunct to trabeculectomy was a major advance in the ability to improve the intraocular pressure (IOP) lowering efficacy of the procedure.^[1] MMC is an antineoplastic antibiotic agent isolated from the fermentation filtrate of *Streptomyces caespitosus*, has been shown to suppress fibroblastic activity. It acts as a deoxyribonucleic acid cross-linker, which inhibits fibroblast proliferation. It is used widely in medicine as a chemotherapeutic agent to treat a variety of cancers. Its use and application in ophthalmology is common practice because of its modulatory effects on wound healing.^[2]

Current applications of MMC include glaucoma surgery, pterygium surgery, corneal refractive surgery, cicatricial eye disease, conjunctival neoplasia, and allergic eye disease.^[3] For more than two decades, MMC has been routinely used during trabeculectomy to reduce postoperative (postop) episcleral fibrosis and bleb failure due to scarring by the wound healing process.^[4] The use of MMC in trabeculectomy is indicated in patients who are young, African American, or have had previous surgery, and has been shown to increase fibroblast density and compact connective tissue over time.^[5] Studies have shown that the use of MMC improves outcomes in glaucoma filtration surgery with good long-term IOP control.^[6-8]

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The time-tested route of administration of MMC is via a sponge soaked in it.^[9] This sponge is applied to the subconjunctival space. Both the concentration of the drug used and the duration of exposure can be altered, depending on the risk of failure. A subconjunctival injection of MMC instead of these sponges is recently being studied as an alternative.^[10] The initial result suggests that this new method of application of MMC is associated with superior surgical outcomes and no increase in complications.

Our current study is a randomized, prospective, open-label, interventional one aimed at comparing these two modalities of MMC administration in trabeculectomy surgery in Indian population. The purpose of this study was to determine the safety and efficacy of intraoperative injection of MMC against conventional sponge-applied MMC during trabeculectomy. It is with this background that this study was undertaken.

Methods

Study design

This study was a randomized, prospective, comparative case series designed from a consecutive series of

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trabeculectomies with MMC performed in Aravind eye hospital, Tirunelveli, Tamil Nadu. A computer-generated table was used to randomize the cases. Inclusion criteria were trabeculectomies with MMC for IOP control in eyes with glaucoma (primary + secondary) with a follow-up of 1 year. The study and control groups (injection and sponge) included all trabeculectomies that met the above inclusion criteria and were performed consecutively between January 2016 and January 2017 ($n = 43$). Exclusion criteria were patients undergoing any other glaucoma procedure such as tube-shunt procedures, nonpenetrating glaucoma surgery, combination surgery (i.e., phacoemulsification + trabeculectomy), use of an antimetabolite, such as 5-FU and any patients with glaucoma (i.e., uveitic, neovascular, traumatic glaucoma). This study was approved by the Institutional Review Board/Ethics Committee of the Aravind eye hospital.

Data were collected preoperatively on the first day, the day prior to the surgery and postoperatively at 2 weeks, 1 month, 3 months, 6 months and 1 year after surgery. Demographic data and posop visits (number of visits within 3 months) were recorded. Baseline IOP was calculated using the average of measurements from the two most recent visits prior to surgery using Goldmann applanation tonometer. Best-corrected VA (BCVA), number of glaucoma medications, the need for posop interventions, and posop complications were recorded at 2 weeks, 1 month, 3 months, 6 months, and 1 year. Specifically, posop data on complications including bleb leak, hypotony (defined as IOP < 6 mm Hg), shallow AC (defined as iris/cornea touch beyond the mid-iris centrally), infection, corneal edema/haze, and cataract formation were collected.

Surgical procedure

All trabeculectomies were performed at a single institution by a single surgeon (Dr. DM). Our preparation of MMC includes mixing 4 mg of MMC powder with 10 ml sterile water diluent to achieve concentration of 0.4 mg/ml. To prepare the MMC injection, the surgeon used a 20- μ g preparation starting with MMC 0.4 mg/mL, diluting 0.1 mL of MMC (40 μ g) in 0.1 mL of lidocaine (1:1, total volume of 0.2 mL). Half of that solution (0.1 mL of MMC: lidocaine [20 μ g]) was used for injection. Topical anesthesia was instilled. A 30-gauge needle was introduced 7 to 8 mm from the limbus. The MMC preparation was injected posterior to the anticipated flap location subconjunctivally. To avoid egress to the surface, a cotton swab was used to move the conjunctiva toward the intended quadrant to place the needle entry point as far away from the bleb site as possible. The conjunctival peritomy was then completed. Wet-field bipolar cautery was performed for hemostasis with copious irrigation using saline solution. The trabeculectomy was completed in the standard fashion by delineating a 6 \times 4 mm scleral flap. A 15 no blade was then used to dissect the partial thickness scleral flap. A paracentesis was performed using a 1-mm side port blade in the temporal cornea. A sclerotomy was created with Kelly's punch. A peripheral iridectomy was created with DeWecker scissors. The scleral flap was repositioned in place using three 10-0 nylon sutures. Out of those, one apical suture was put using releasable suture technique and rest two were interrupted sutures. Once flow was determined to be adequate, with the anterior chamber remaining well-maintained, conjunctival closure proceeded using a running 8-0 vicryl suture. At the end of the case, the conjunctival incision was checked for lack of leakage.

The conventional sponge-applied technique was used in the control group. On two separate semicircular surgical sponges (7-mm corneal light shield cut in half), MMC solution of 0.4 mg/mL was used and then inserted subconjunctivally at the surgical site. The sponges were applied for 2 min and removed, and then the area was copiously irrigated with saline solution before the case proceeded in the usual fashion as described earlier.

Statistical analysis

Descriptive variables were presented with frequency (percentage) or mean (standard deviation [SD]). A Chi-square test was used to find out the association between categorical variables. Student's *t*-test or Mann-Whitney U test was used to find out the significant difference of continuous variables between the study procedure (MMC and Sponge). Pre and post comparisons were done using Wilcoxon sign rank test. To find out the cumulative probability of success, Kaplan-Meier survival analysis was performed. A *P* value less than 0.05 was considered as statistically significant and the statistical analysis was performed using statistical software STATA 14.1 (Texas, USA).

Surgical outcome definition

1. Complete success- Posop IOP ≤ 18 mmHg but more than 6 mmHg without the addition of antiglaucoma medication or other interventions
2. Qualified success-IOP ≤ 18 mm Hg but more than 6 mmHg with additional antiglaucoma medication
3. Failure-IOP > 18 mmHg with additional antiglaucoma medication.

Results

In total 43 eyes were included, including 21 intraoperative injections and 21 sponge-applied MMC. One eye was excluded because of the poor follow-up.

Intraocular pressure (IOP)

There is a significant difference between baseline and final IOP in sponge ($P = 0.001$) and injection ($P = 0.0002$) [Table 1].

Number of antiglaucoma medications (AGM)

The number of AGM was significantly reduced in the injection group ($P = 0.0001$) and in the sponge group ($P = 0.0003$) from the baseline. The *P* value ($0.021 < 0.05$) shows there is a significant difference between injection and sponge at the end of 1 year [Table 2].

Success criteria

The complete success rate was 52.4% in the injection group and 26.1% in the sponge group at the final visit. Overall, the success rate (complete + qualified) was 90.5% in the MMC injection group and 87.0% in the MMC sponge group at posop year 1.

Kaplan-Meier survival analysis

This plot shows the cumulative probability of success against time. From the graph, the predicted probability of success at month 1, month 3, month 6 and month 12 in Injection group is 100.0%, 100.0%, 85.7% and 42.9% and in sponge group is 100.0%, 88.9%, 81.5% and 61.1% [Table 3]. The logrank test for equality of survivor function *P* value (0.917) shows that there

Table 1: IOP

Visits	Sponge soaked			Injection			P
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	
Preop	25.87 (11.09)	24	12-46	29.00 (11.92)	27	12-56	0.417
2 week	16.74 (8.81)	14	4-37	12.00 (6.12)	10	4-30	0.047
1 month	14.61 (7.85)	14	4-36	11.95 (5.93)	12	4-26	0.283
3 month	12.52 (5.52)	12	4-24	11.00 (3.61)	10	6-23	0.319
6 month	12.87 (7.54)	10	2-40	12.30 (3.70)	12	6-20	0.599
12 month	15.56 (10.72)	12	8-62	12.19 (4.03)	12	6-25	0.134
P		0.001			0.0002		-

IOP: Intraocular pressure, Preop: Preoperative, SD: Standard deviation

is no significant difference between the curve of injection and sponge group [Fig. 1].

Posop complications and procedures

All major complications were encountered in the sponge group. 1 (11.1%) patient developed choroidal detachment and 1 developed malignant glaucoma which got resolved by medical management. 33.3% of cases had encapsulated bleb which received bleb needling. Postoperatively, 44.4% cases underwent Argon laser suture lysis [Table 4].

Best corrected visual acuity

There is a significant difference between baseline and final visual acuity in the sponge group ($P = 0.024$) and there is no significant difference in the injection group ($P = 0.470 > 0.05$).

Discussion

Treatment of patients having glaucoma requires both clinical skills and keen judgment. Consultants treating these patients have to decide on the timing of surgery, the type of surgical procedure and the details of the procedure. To increase the success rate of the surgical procedure, augmentation with an antimetabolite is usually done. The most commonly used antimetabolite for an augmented glaucoma filtration surgery is MMC. Out of the many modes of administration of MMC, sponge soaked method is the most common. Administration of MMC as a subconjunctival injection is a newly developed method for augmentation of a glaucoma filtration surgery. This study was done to compare these two methods of augmentation of Trabeculectomy with MMC.

Our study shows that the efficacy of injection of MMC is comparable to sponge application, with less need for visits and 5-FU intervention. Overall, treatment success in the MMC injection group at 1 year was 90.5% compared to sponge (87%) which is consistent with a prior comparative study reporting 1-year outcomes of MMC injection in trabeculectomy versus sponge.^[11]

Intraoperative injection of MMC in trabeculectomy has several advantages over conventional sponge application. A large MMC treatment area produces more diffuse and elevated blebs.^[12] Large- area MMC application also seems to increase long-term success without increasing the complication rates in trabeculectomies.^[13,14] Direct and diffuse application of MMC by injection may promote less scarring and vascularization of the bleb.^[15] To achieve the same surface area of exposure with sponges, i.e., achieved with injection,

Table 2: Number of AGM

AGM	n	Injection		Sponge		P
		n	Mean (SD)	n	Mean (SD)	
Baseline	21	21	2.4 (0.87)	21	2.3 (0.96)	0.620*
At 12 months	21	21	0.38 (0.5)	21	0.91 (0.85)	0.021*
P			0.0001**		0.0003**	-

AGM: Antiglaucoma medications, SD: Standard deviation, *Mann–Whitney U test, **Wilcoxon signed-rank test

Table 3: Cumulative probability of success

Visits	Survival probability	
	Injection	Sponge
Month 1	100.0%	100.0%
Month 3	100.0%	88.9%
Month 6	85.7%	81.5%
Month 12	42.9%	61.1%

Table 4: Postop Complications and Procedures

Postop complication	n
Malignant glaucoma	1 (11.1)
Bleb needling	3 (33.3)
ALS	4 (44.4)
CD	1 (11.1)
Total	9

Postop: Postoperative ALS: Argon laser Suture lysis, CD: Choroidal detachment, n: Number

the surgeon must use multiple sponges, all of which must be carefully collected thereafter. The injection method, therefore, eliminates the risk of retained sponges.

Another advantage of using injection vs sponge application of MMC is the predictable dose of delivery. In sponge application, the surface area of cut pieces of surgical sponges is very variable. A study found that the quantities of MMC contained in sponges prepared for glaucoma surgery differed for a given surgeon and between surgeons. The estimated actual dose delivered in a sponge soaked with MMC 0.2 mg/mL varied between 1.9 and 17.3 µg.^[16] With this unpredictable sponge dosing, surgeons run the risk of overdosing MMC. Irrigation is often used after delivery of MMC; however, it appears to

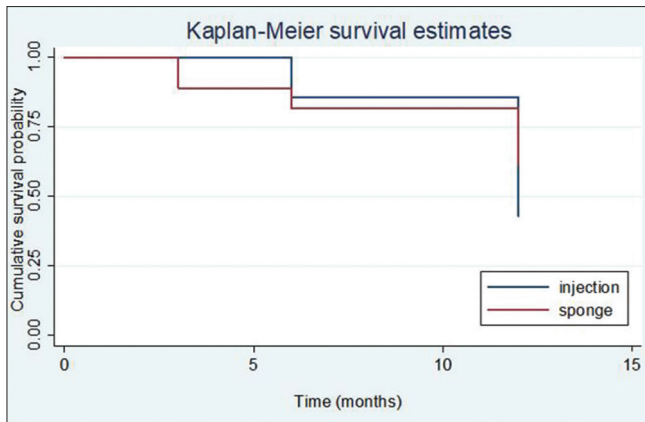


Figure 1: Kaplan–Meier survival analysis

only have an effect at reducing MMC concentrations in the superficial scleral layers, with no effect on MMC concentrations in the deep scleral and subsceral layers.^[17] Another advantage of the subtenon injection technique is that the tumescent tenon is more easily dissected and provides an accessible handle for manipulation and thereby reduces conjunctival damage.

Although IOP is frequently considered as the primary outcome measure of success in glaucoma surgery, the success of trabeculectomy actually relies on a functioning bleb. In contrast to posop measurement of IOP that may sometimes be misleading, bleb morphology could be a surrogate of bleb functionality and IOP.^[18]

The bleb characteristics were studied for each visit in each group. In general, a diffuse bleb with normal vascularization is associated with greater survival. A thickened vascularized bleb is associated with failure while a thin cystic avascular bleb is associated with increase in risk of bleb infections and the Moorfields Bleb Grading System graded bleb leaks.^[19] In our study, the blebs. Thus more diffuse blebs are seen with injectable MMC as well as with sponge soaked MMC in contrast to the findings of Hung *et al.*, who found more diffuse blebs by using subconjunctival injections of MMC for trabeculectomy over a 12 month follow-up period.^[20]

MMC bleb-related complications, namely thin-walled and cystic blebs, hypotony, bleb leakage, blebitis, and endophthalmitis, others include hypotony maculopathy, corneal epithelial toxicity, etc., compromise the outcome of surgery.^[21,22] Hypotony and its sequelae may be related to intraocular toxicity of MMC.^[23]

Routinely, glaucoma surgeons apply titrated doses of MMC-soaked sponges under the scleral flap for 1–3 min to modulate wound healing and prevent fibrosis.^[24] There are concerns regarding the sponge method of MMC delivery including a physical barrier to treat a larger area, conjunctival damage during sponge manipulation, risk of sponge fragmentation and retention and the need for some extra minutes. The pharmacological action of MMC is limited to its area of exposure and larger treatment areas are believed to produce more diffuse blebs and reduce the risk of cystic bleb formation.^[11,25] Occasionally, sponge application can also create a whitish MMC “burn” often due to overdosing of MMC. The avascular, thin bleb produced is at increased risk

of early and late bleb leaks as well as of infection. Premature scar formation around an insufficiently treated area could lead to an encapsulated bleb, the ‘ring of steel’ phenomenon and bleb failure.^[26]

Our study shows that the injection of MMC is safe, with nil posop complications compared to conventional sponge in contrast to a prior noncomparative study of MMC injection where the most frequent early posop complications encountered were hypotony, hyphema, and serous choroidal detachments.^[11]

Lee *et al.* first reported the outcome of 108 consecutive trabeculectomies and phacotrabeculectomies who received a variable concentration of intratenon MMC, 0.2–0.5 mg/mL at the time of surgery. Although they considered their outcomes “favorable” in comparison with the conventional method, almost a quarter of patients developed cystic bleb, defined as area of marked conjunctival thinning and avascularity. The higher incidence of cystic bleb in their case series compared with current study could be attributed to several factors such as higher concentration (0.02% in 68% of cases) of MMC, 5 min duration of tissue contact before washing and ‘milking out’ MMC and longer follow-up.^[11]

In our study, there was no difference in IOP and number of AGM between injection and sponge application. This is consistent with a single report on intra-tenon injection of MMC during trabeculectomy that showed the injection group had a similar result and had lower mean IOP and need for fewer glaucoma medications.^[15]

Limitations of this study include its small sample size, surgeons factor, and a relatively short follow-up period (limited to 1 year). While IOP tends to stabilize 6 months postoperatively,^[27] many complications of MMC occur even years after operation.^[28] Studies with longer follow-up period are needed to evaluate long-term side effects of subconjunctival MMC. Further study in a prospective, long-term, larger cohort is necessary to further assess the efficacy and safety of this modality.

Conclusion

In conclusion, injection of MMC may be as safe and as effective as conventional sponge application of MMC with comparable estimated complete treatment success with relatively lower complication rates. Surgeons may consider intraoperative injection of MMC in patient cohorts given comparable safety and efficacy and several advantages over traditional sponge application.

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Conflicts of interest

There are no conflicts of interest.

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