

Comparison of Surgical Outcomes of Sponge Application versus Subconjunctival Injection of Mitomycin-C during Combined Phacoemulsification and Trabeculectomy Surgery in Asian Eyes

Wenqi Chiew¹, Xiner Guo¹, Bryan Chin Hou Ang^{2,3}, Angela Pek Hoon Lim², Leonard Wei Leon Yip²

¹Yong Loo Lin School of Medicine, National University of Singapore, Singapore, ²Department of Ophthalmology, National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore, ³Department of Ophthalmology, Woodlands Health Campus, Singapore

Abstract

Purpose: To compare the outcomes of combined phacoemulsification–trabeculectomy surgery with intraoperative sponge-applied versus subconjunctival injection of mitomycin-C (MMC) in Asian eyes.

Methods: This was a retrospective review of 95 eyes that consecutively underwent combined phacoemulsification–trabeculectomy surgery in a tertiary eye center in Singapore from January 2013 to June 2014. Data collected included intraocular pressure (IOP), best corrected visual acuity, and number of glaucoma medications. Outcome measures included postoperative IOP and complications at various timepoints up to 12 months after surgery.

Results: Twenty eyes (21.1%) received 0.2 mg/ml subconjunctival MMC injection (“Group 1”) and 75 (78.9%) received 0.4 mg/ml sponge-applied MMC (“Group 2”). There was no difference between groups in demographics, IOP, and number of glaucoma medications preoperatively. There was a reduction in IOP at postoperative month (POM) 1, 6, and 12 in both the groups (POM12: Group 1, -2.8 ± 5.36 mmHg, $P < 0.001$; Group 2, -5.8 ± 6.29 mmHg, $P = 0.054$). At POM1, Group 2 showed a trend toward greater IOP reduction (-5.89 ± 7.67 mmHg vs. -1.55 ± 5.68 mmHg, $P = 0.061$). However, at both POM6 and POM12, there was no statistically significant difference in IOP reduction between the two groups. At POM12, complete success, defined as achieving an IOP of between 6 and 15 mmHg without the use of antiglaucoma medications, was achieved in 11 (55%) eyes in Group 1 and 48 (64%) in Group 2 ($P = 0.9$). There was a lower rate of postoperative hypotony in the Group 1 (0%) compared to Group 2 (8%) ($P = 0.34$).

Conclusion: Combined phacoemulsification–trabeculectomy with subconjunctival MMC injection has comparable outcomes to that with sponge-applied MMC, with a similar reduction in IOP at 1, 6, and 12 months postoperatively and a lower postoperative complication rate.

Keywords: Asian, Glaucoma, Mitomycin-C, Trabeculectomy

Address for correspondence: Bryan Chin Hou Ang, National Healthcare Group Eye Institute, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, 308433 Singapore. E-mail: drbryanang@gmail.com

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INTRODUCTION

Glaucoma and cataract are the two leading causes of blindness worldwide.¹ While intraocular pressure (IOP)-lowering medications and laser treatment are first-line treatment modalities in glaucoma management, filtering surgery may

be required to achieve adequate IOP control in advanced or significantly progressing disease.

Combined phacoemulsification and trabeculectomy surgery (“phaco-trabeculectomy”) is often performed in

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patients with co-existing glaucoma and cataract.² Although phacoemulsification alone may reduce IOP, phaco-trabeculectomy has a higher success rate, requires fewer postoperative IOP lowering medications,^{3,4} and is more cost-effective long term.⁵ Combined surgery has advantages over staged cataract and glaucoma surgery – standalone trabeculectomy increases the risk of development of visually significant cataract,^{6,7} while phacoemulsification after trabeculectomy has been associated with an increased risk of bleb failure.^{8,9}

Despite the emergence of minimally invasive glaucoma surgery, trabeculectomy surgery is still acknowledged to be the most efficacious in terms of IOP-lowering.¹⁰ However, its long-term effectiveness remains limited by conjunctival scarring, which leads to surgical failure. While antimetabolites, most commonly mitomycin-C (MMC), are now routinely administered during surgery to inhibit scarring and reduce the risk of bleb failure,¹¹ there is currently no consensus on its most effective route of application. MMC may be administered either by subconjunctival injection or by topical application with MMC-soaked sponges. Studies in Caucasian populations have attempted to compare the results of both methods of MMC application;^{12,13} however, comparative data remain lacking in Asian eyes. Determining the most optimal route of application of intraoperative MMC remains critical in improving long-term survival rates of trabeculectomy surgery.

This study aims to retrospectively compare the outcomes of phaco-trabeculectomy with intraoperative sponge-applied versus subconjunctival injection of MMC in an Asian population.

METHODS

The design of the study followed the tenets of the Declaration of Helsinki and the ethics approval was obtained from the Institution's Ethics Review Committee, the National Healthcare Group Domain Specific Review Board (NHG DSRB 2018/00082).

Clinical data were collected from all eyes which had consecutively undergone phaco-trabeculectomy surgery in a tertiary eye center in Singapore from January 1, 2013, to June 30, 2014. All the surgeries were performed by fellowship-trained glaucoma surgeons or by residents and fellows supervised by consultant-grade glaucomatologists. Patients who underwent phaco-trabeculectomy with either subconjunctival MMC injection or topical MMC sponge applied and completed at least 1 year of follow-up postoperatively were included. The indication for combined phaco-trabeculectomy surgery included the presence of both visually significant cataract and glaucomatous optic neuropathy with corresponding visual field defect, with eyes having IOP controlled on two or more glaucoma medications or IOP uncontrolled despite maximal medical therapy.

Data were collected retrospectively from pre and postoperative clinical charts. Baseline Goldmann applanation IOP, best

corrected visual acuity (BCVA), and the number of glaucoma medications were recorded from the most recent visit prior to the surgery, until the postoperative month (POM) 12. Postoperative outcome measures included IOP measurements recorded at POM1, POM6, and POM12, as well as complications after surgery.

Standardized definitions of postoperative complications were used during the data collection process.¹⁴ Hypotony was defined as IOP <6 mmHg on at least one follow-up within the 12-month postoperative period. Shallow anterior chamber (AC) was defined as iridocorneal contact extending to within 1 mm of the pupil. Malignant glaucoma was defined by a persistently elevated IOP of >21 mmHg, accompanied by a shallow AC in an eye with a patent peripheral iridotomy. Hyphema was recorded if macroscopic blood was observed in the AC. Bleb leak was documented when leaking aqueous could be directly visualized from the bleb, and/or when subtle, a Seidel's test was done and proved positive.

The broad surgical steps for phaco-trabeculectomy in this institution are as follows. Peri-bulbar or topical anesthesia is administered and 5% povidone-iodine is instilled into the eye. A lid speculum is inserted, followed by traction sutures with 7/0 Vicryl placed on the superior cornea. The route of administration of MMC is decided based on individual surgeon preference. Eyes that receive a subconjunctival injection of MMC receive 0.1 ml of 0.2 mg/mL of MMC, which is injected into the subconjunctival space posterior to the anticipated conjunctival flap location, before the creation of the conjunctival peritomy.

A fornix-based conjunctival flap is then created and a partial-thickness rectangular 4 mm × 3 mm scleral flap is raised. However, in eyes that receive MMC-soaked sponges, the sponges soaked in 0.4 mg/ml MMC solution are inserted into the subconjunctival pocket after the conjunctival peritomy is performed, for 3–5 min, with the specific duration of application depending on the glaucoma subtype and indication for surgery. After removing the sponges, 40 ml of balanced saline solution is used to flush the site. Phacoemulsification with intraocular lens implantation is then performed at a second site, through a separate corneal incision. Thereafter, sclerotomy and surgical peripheral iridectomy is performed. The scleral flap is closed with 10/0 nylon by fixed sutures or a combination of fixed and releasable sutures, depending on individual surgeon preference. The trabeculectomy site is inspected and tested for integrity. Finally, the conjunctival flap is closed with an 8/0 Vicryl suture, followed by the administration of intracameral cefazolin and topical or subconjunctival gentamicin and dexamethasone.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics (Version 23, IBM Corp., New York, USA). To present patient demographics, descriptive statistics such as mean, standard deviation, median, range, frequency, and percentage values were used. To evaluate the differences between both

groups, we used *t*-test, Mann–Whitney test, and Chi-square test as appropriate. To compare the two study groups adjusted for baseline values, analysis of covariance tests was performed. To assess changes within each study group from baseline to POM 1, 6, and 12, a linear mixed model analysis was performed. $P < 0.05$ was considered statistically significant.

An eye was considered to have achieved “complete success” if it achieved a postoperative IOP of between 6 and 15 mmHg, without the use of antiglaucoma medications. “Qualified success” was defined as also achieving a postoperative IOP of between 6 and 15 mmHg but with the use of antiglaucoma medications.¹⁴

RESULTS

Data were collected from a total of 108 phaco-trabeculectomy surgeries. Of these, 13 (12.0%) were excluded because the postoperative follow-up duration of these eyes was <1 year. Data from 95 eyes of 95 patients were included in the final data analysis. Of the 95 eyes, 20 (21.1%) received 0.2 mg/ml subconjunctival MMC injection (“Group 1”) and 75 (78.9%) received 0.4 mg/ml sponge-applied MMC (“Group 2”). Baseline characteristics of the patients are summarized in Table 1. There was no difference between both groups. In both groups, there was a reduction in IOP at 1, 6, and 12 months postoperatively [Table 2; 12 months: Group 1,

-2.8 ± 5.36 mmHg, $P < 0.001$; Group 2, -5.8 ± 6.29 mmHg, $P = 0.054$]. At POM1, Group 2 showed a trend toward greater IOP reduction compared to Group 1 (-5.89 ± 7.67 mmHg vs. -1.55 ± 5.68 mmHg, $P = 0.061$). However, at POM6 and POM12, there was no statistically significant difference in IOP reduction between both groups [Table 2]. There was no statistically significant difference in BCVA improvement between both groups [Table 3]. At POM12, complete success was achieved in 11 (55%) eyes in Group 1 and 48 (64%) in Group 2, while qualified success was achieved in 3 (15%) eyes in Group 1 and 1 (1.3%) eye in Group 2 [Table 4]. Using the Chi-square test, there was no significant difference between both groups in terms of surgical success or failure.

Kaplan–Meier survival analysis was used to compare the cumulative probability of success at 12 months of follow-up between Group 1 and Group 2 [Figure 1]. The mean duration of survival was 7.80 ± 1.1 months and 9.81 ± 0.5 months in Groups 1 and 2, respectively ($P = 0.313$). Postoperative bleb manipulation procedures (bleb needling, flap lift, bleb revision) were required in 2 (10%) eyes in Group 1 and 9 (12%) eyes in Group 2 [Table 5]. No eyes in Group 1 and 6 (8%) eyes in Group 2 had hypotony postoperatively [Table 5]. No eyes in Group 1 and 3 (4%) eyes in Group 2 had shallow AC postoperatively [Table 5]. One eye in Group 2 developed malignant glaucoma 1 week postoperatively that was refractive to medical treatment, YAG capsulotomy or anterior

Table 1: Baseline clinical characteristics of subconjunctival mitomycin-C (MMC) injection (“Group 1”) and sponge-applied MMC (“Group 2”)

	Group 1 Injection ($n=20$), n (%)	Group 2 Sponge ($n=75$), n (%)	<i>P</i>
Age, median (IQR)	74.5 (67, 78.3)	71 (65, 77)	0.275 [§]
Sex			
Female	12 (60)	35 (46.7)	0.324 [†]
Male	8 (40)	40 (53.3)	
Race			
Chinese	17 (85)	70 (93.3)	0.191 [†]
Indian	1 (5)	1 (1.3)	
Malay	1 (5)	1 (1.3)	
Others	1 (5)	3 (4)	
Type of glaucoma			
POAG	12 (60)	45 (60)	>0.999 [‡]
CACG	5 (25)	19 (25.3)	
Others	3 (15)	11 (14.7)	
Diabetes mellitus			
No	12 (60)	42 (56)	0.804 [†]
Yes	8 (40)	33 (44)	
Previous surgery			
No	16 (80)	52 (69.3)	0.415 [†]
Yes	4 (20)	23 (30.7)	
BCVA (logMAR), median (IQR)	0.3 (0.18, 0.48)	0.4 (0.18, 0.6)	0.191 [§]
IOP, mean±SD	16.8±4.93	18.89±5.53	0.128 [*]
Antiglaucoma medications, median (IQR)	3 (2-3)	3 (2-3)	0.772 [§]

**T*-test, [†]Chi-square test, [‡]Fisher’s exact test, [§]Mann–Whitney U-test. SD: Standard deviation, BCVA: best corrected visual acuity, IOP: Intraocular pressure, IQR: Interquartile range, CACG: chronic angle-closure glaucoma, POAG: Primary open-angle glaucoma

Table 2: Changes in intraocular pressure in subconjunctival mitomycin-C (MMC) injection ("Group 1") and sponge-applied MMC ("Group 2")

	Group 1 (n=20)		Group 2 (n=75)		P
	Mean±SD	Median (range)	Mean±SD	Median (range)	
Baseline IOP (mmHg)	16.8±4.93	16.5 (10-30)	18.89±5.53	19 (8-35)	
POM 1					
IOP (mmHg)	15.25±4.01	15 (8-22)	13±6.49	12 (2-36)	0.079*
Change in IOP from baseline (mmHg)	-1.55	-1.5	-5.89	-7	0.061†
Change in IOP from baseline (%)	-9.2	-9.1	-31.2	-36.8	
P value within group‡	<0.001		0.02		
POM 6					
IOP (mmHg)	13.8±3.68	14 (6-20)	12.65±4.52	12 (3-24)	0.221*
Change in IOP from baseline (mmHg)	-3	-2.5	-6.24	-7	0.164†
Change in IOP from baseline (%)	-17.9	-15.2	-33.0	-36.8	
P value within group‡	<0.001		0.048		
POM 12					
IOP (mmHg)	14±3.32	13.5 (10-22)	13.09±4.67	13 (3-32)	0.233*
Change in IOP from baseline (mmHg)	-2.8	-3.5	-5.8	-6	0.119†
Change in IOP from baseline (%)	-16.7	-21.2	-30.7	-31.6	
P value within group‡	<0.001		0.054		

*T-test, †Analysis of covariance, adjusted for baseline, ‡Linear mixed model, adjusted for the multiple comparisons by Bonferroni method. SD: Standard deviation, IOP: Intraocular pressure, POM: Postoperative month

Table 3: Changes in best corrected visual acuity in subconjunctival mitomycin-C (MMC) injection ("Group 1") and sponge-applied MMC ("Group 2")

	Group 1 (n=20)		Group 2 (n=75)		P
	Mean±SD	Median (range)	Mean±SD	Median (range)	
Baseline BCVA (logMAR)	0.47±0.58	0.3 (0-2)	0.45±0.36	0.4 (0-2)	
Month 1					
BCVA (logMAR)	0.29±0.3	0.18 (0-1.3)	0.32±0.28	0.3 (0-2)	0.208*
Change in BCVA from baseline	-0.18	-0.12	-0.13	-0.1	0.609†
P value within group‡	<0.199		0.034		
Month 6					
BCVA (logMAR)	0.22±0.22	0.18 (0-0.88)	0.21±0.18	0.18 (0-0.9)	0.947*
Change in BCVA from baseline	-0.25	-0.12	-0.24	-0.22	0.909†
P value within group‡	0.081		0.008		
Month 12					
BCVA (logMAR)	0.27±0.46	0.1 (0-2)	0.25±0.35	0.18 (0-2)	0.379*
Change in BCVA from baseline	-0.20	-0.2	-0.2	-0.22	0.915†
P value within group‡	0.212		0.018		

*Mann-Whitney U-test, †Analysis of covariance, adjusted for baseline, ‡Linear mixed model, adjusted for the multiple comparison by Bonferroni method. SD: Standard deviation, BCVA: Best corrected visual acuity

Table 4: Surgical outcomes for subconjunctival mitomycin-C (MMC) injection ("Group 1") and sponge-applied MMC ("Group 2") at postoperative month 12 (P=0.90*)

	Group 1 (n=20), n (%)	Group 2 (n=75), n (%)
Failures	6 (30)	26 (34.7)
Successes	14 (70)	49 (65.3)
Complete successes	11 (55)	48 (64)
Qualified successes	3 (15)	1 (1.3)

*Chi-square test

hyaloidotomy, and only resolved after vitrectomy surgery. Using the Fisher's exact test, there was no significant difference between both groups in the frequency of postoperative interventions and complication rates.

DISCUSSION

MMC ($C_{15}H_{18}N_4O_5$) is an antibiotic agent isolated from *Streptomyces caespitosus*. MMC undergoes metabolic activation via reduction into an alkylating agent and inhibits DNA synthesis by its cross-linking action at the N position of adenine and at the O6 and N position of guanine.¹⁵ This results

Table 5: Postoperative interventions and complications in subconjunctival mitomycin-C (MMC) injection ("Group 1") and sponge-applied MMC ("Group 2")

	Group 1 (n=20), n (%)	Group 2 (n=75), n (%)	P
Bleb needling	1 (5.0)	5 (6.7)	>0.999*
Flap lift	1 (5.0)	2 (2.7)	0.51*
Bleb revision	0	2 (2.7)	>0.999*
Hypotony	0	6 (8.0)	0.34*
Shallow AC	0	3 (4.0)	>0.999*
Malignant glaucoma	0	1 (1.3)	>0.999*
Hyphema	0	1 (1.3)	>0.999*
Leaking bleb	0	1 (1.3)	>0.999*
Total	2 (10)	21 (28)	0.14*

*Fisher's exact test. AC: Anterior chamber

in an antiproliferative effect on cells with high rates of mitosis. It is used as an antineoplastic agent in high concentrations and as an anti-fibrotic agent in low concentrations.¹⁶ In ophthalmology, MMC was first used topically in 1969 to treat recurrent pterygium.¹⁷ Since then, its modulatory effect on wound healing has been used in other areas of ophthalmology including glaucoma filtering surgery, corneal refractive surgery, ocular surface tumors, squint surgeries, dacryocystorhinostomy and allergic conjunctivitis.¹⁸

Topical MMC was first applied in trabeculectomy surgery by Chen¹⁹ in 1983. The use of intraoperative topical MMC has since been shown to improve outcomes in glaucoma filtration surgery and results in good long-term IOP control.²⁰ Conventionally, MMC is applied to the surgical site via MMC-soaked surgical sponges placed onto the scleral surgical site prior to creation of the ostomy, before or after formation of a partial-thickness scleral flap. The sponge is applied for a variable amount of time depending on disease severity and the health of the conjunctiva, ranging from 30 s to 5 min.²¹

Subsequently, Lee *et al.* described a novel technique of MMC application involving subconjunctival intra-Tenon injection of MMC during trabeculectomy surgery and reported favorable outcomes.²²

Subconjunctival MMC injection presents several advantages over the traditional method of sponge application. These include the reduced risk of unwanted exposure of areas of the conjunctiva and corneal epithelium to MMC, less conjunctival damage during manipulation of MMC-soaked sponges, and eliminating the risk of inadvertently retained sponge material.²³ In addition, subconjunctival MMC injection allows the administration of a more precise dose of MMC, unlike that when MMC is delivered via soaked sponges, which have been shown to have high intra and interobserver variability in quantification.^{24,25} The wider coverage area from subconjunctival dissipation of the MMC after subconjunctival injection²⁴ may result in better bleb morphology^{26,27} and filtering function.^{28,29} Esfandiari *et al.* studied 3-year outcomes of trabeculectomy with MMC-soaked

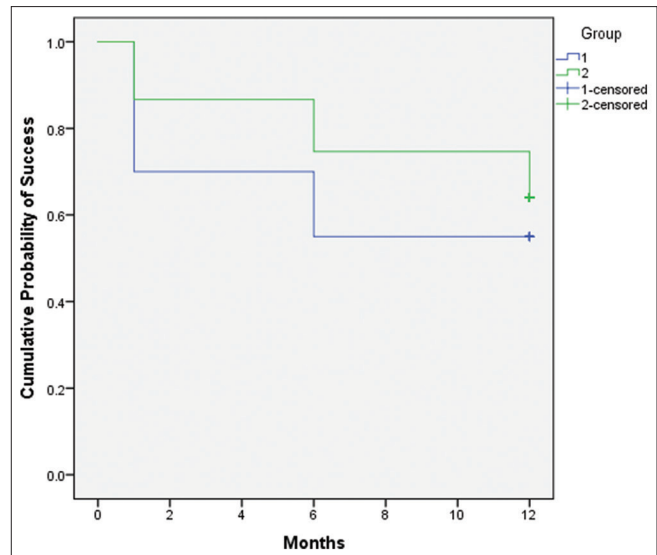


Figure 1: Kaplan-Meier plot showing cumulative probability of complete success between subconjunctival mitomycin-C (MMC) injection ("Group 1") and sponge-applied MMC ("Group 2"). Complete success was defined as a postoperative intraocular pressure between 6 and 15 mmHg without the use of antiglaucoma medications

sponges versus intra-Tenon injection of MMC in eyes with uncontrolled primary open-angle glaucoma and reported that although the complication rate and extent of IOP reduction were comparable between both techniques, bleb morphologic parameters were more favorable in trabeculectomies performed with intra-Tenon MMC injection.³⁰

In our study, the efficacy of subconjunctival MMC injection appears similar to sponge application of MMC in phaco-trabeculectomy surgeries, with both groups having a comparable percentage of treatment success up to 12 months postoperatively. These results appear similar to published results from other groups.^{12,30} While our study demonstrated a lower percentage decrease in IOP of 20% in the subconjunctival MMC injection group as compared to other studies of 48.3%–58.7%, this could be due to the lower baseline IOP of 16.8 mmHg in our study, compared to the baseline IOPs in other studies which range from 21.9 mmHg to 28.8 mmHg.^{12,22,30}

The main complications of combined phacoemulsification and trabeculectomy with MMC include hyphema, shallow AC, and hypotony.³¹ Hypotony-related complications may further result in visual deterioration.³² In our study, the sponge-applied MMC group demonstrated a greater decrease in IOP in the 1st month, which correlated with a higher incidence of hypotony and shallow AC compared to the subconjunctival injection group. This could be due to a higher exposure of the area of the conjunctiva and corneal epithelium to MMC in the use of the sponge. MMC is known to be present on the ocular surface and absorbed into the sclera and aqueous humor despite copious irrigation.^{33,34} Ciliary body toxicity caused by MMC might play a role in the higher incidence of hypotony^{35,36} as compared to the subconjunctival injection group. However, this was not

observed in the other two studies. Khouri *et al.* reported a similar reduction in IOP in both groups in the 1st month, as well as a similar incidence of hypotony.¹² Esfandiari *et al.* reported a similar reduction in IOP and a similar incidence of shallow AC in both groups, in the first 12 months.³⁰

This study has several limitations. First, this was a retrospective, noncontrolled study where the patients were operated on and followed up by different surgeons postoperatively. This may contribute to variability in surgical skill and postoperative clinical management. Early IOP data were not compared prior to POM1 as different surgeons perform suture lysis at different timepoints postoperatively. Surgeries were performed either by fellowship-trained glaucoma surgeons or residents and fellows. However, this variability in surgical skill was mitigated in part, by every surgery either being performed, or at least supervised by a senior consultant glaucomatologist. Surgical techniques may also have differed in ways other than the method of MMC application – surgeons performing subconjunctival MMC injection may perform less extensive subconjunctival/sub-Tenon's dissection, compared to surgeons using sponge-applied MMC, who would typically aim to perform dissection over as large an area as possible to allow maximal surface area exposure of tissue to MMC. This variability in dissection may influence outcomes. In addition, differences in suturing and bleb manipulation techniques may influence surgical outcomes and should also be considered as a confounding factor. The patients in each group were unequal and unmatched, with more patients in the sponge ($n = 70$) compared to the injection group, which we acknowledge was limited in its sample size ($n = 20$). About 12% of our patients also defaulted their follow-up within 1 year of surgery and were excluded from the study analysis. Surgical outcomes and postoperative complication rates were not analyzed with respect to the dose and duration of MMC applied. Lee *et al.* used a relatively higher concentration of 0.15 ml of between 0.2 and 0.5 mg/ml of MMC and a longer sponge exposure time of 5 min. This appeared to correspond to a higher rate of postoperative complications – 19.4% of eyes demonstrated cystic bleb formation.²² Pakravan *et al.* used a lower concentration of 0.1 ml of 0.01% MMC over a shorter duration of 1 min and this corresponded with a lower rate of cystic bleb formation at 7.5%.¹³ Of note, the concentration and duration of MMC exposure did not affect the decrease in IOP at 12 months in both studies, which found a similar IOP reduction of approximately 50% at 12 months. Finally, we acknowledge that bleb morphology would be another worthwhile outcome measure to examine in future studies.

To the best of our knowledge, there has been no published literature to date comparing outcomes of subconjunctival injection versus sponge-applied MMC in combined phaco-trabeculectomy surgery in Asian eyes. Our study reports these outcomes over a reasonable follow-up period of 12 months and demonstrates that both groups have comparable IOP-lowering efficacy, with a lower hypotony-related complication rate in the subconjunctival MMC group.

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Conflicts of interest

There are no conflicts of interest.

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