Outcome of Trabeculectomy with Intraoperative Subtenon Injection of Mitomycin C

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Research Article

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Abstract

Purpose: To evaluate the efficacy of trabeculectomy with intraoperative subtenon injection of Mitomycin C (MMC) in terms of control of Intraocular pressure post-operatively.

Study design: Observational study

Methods: A total of 49 patient's medical records who underwent trabeculectomy with intraoperative subtenon injection of MMC with diagnosis of Primary Open Angle Glaucoma (POAG) from January 2017 to December 2018 were evaluated to see the post-operative outcomes in terms of control of intraocular pressure (IOP) with 12 months follow-up. The medical records were retrieved using the hospital information system. Age, gender, pre-operative IOP, Best-Corrected Visual Acuity (BCVA), co-morbids, previous surgery, Central Corneal Thickness (CCT), fundus findings, number of glaucoma medications and postoperative complications were obtained by using a proforma.

Results: Total 72 eyes of 49 patient records were evaluated to see post operative outcomes at three, six and twelve months follow up. The mean IOP preoperatively was 24.68±13.66 mm Hg with maximum anti-glaucoma treatment. After the surgery the mean IOP was 13.69±6.68 mmHg at 3 months follow-up, and 12.68±4.04 and 13.33±4.8 mmHg at 6 and 12 months respectively (P-value 0.001). Preoperatively mean CCT was 529.81±28.75 and at 12 months follow-up after surgery was 530.45±29.43 with P-value 0.245. Best Corrected Visual Acuity outcomes were seen at each follow-up and results were found to be statistically significant (P value $\leq$ 0.05).

Conclusions: Twelve months follow-up of trabeculectomy show that intraoperative subtenon injection of MMC is effective in terms of control of IOP postoperatively with minimal complications in patients with POAG.

Introduction:

Glaucoma is the second leading cause of blindness worldwide effecting as many as 6 million individuals[1]. Almost 60% of the world total glaucoma cases are from Asia[2]. According to one estimate there are more than two million people suffering from this disease in Pakistan[3]. Long-term control of intraocular pressure (IOP) is the mainstay of glaucoma treatment and trabeculectomy still remains the surgical procedure of choice to reduce IOP[4]. A steady rate of failure has been reported after this surgical modality because of scarring external to the scleral flap.[5] The antifibrotic agent such as Mitomycin C (MMC) has therefore been used to enhance its success rate.[6] MMC is an antineoplastic/antibiotic agent isolated from soil bacterium Streptomyces caespitosus.[7]It inhibits the fibroblast proliferation by acting as a deoxyribonucleic acid cross-linker. It is used universally in medicine as a chemotherapeutic agent to treat a variety of cancers. Its use and implementation in ophthalmology is common practice because of its modulatory effects on wound healing.[8]

Chen and coworkers[9] were the first one to use MMC topically in a group of patients with refractory glaucoma. Since then it has been regularly used during trabeculectomy. MMC inhibits the postoperative episcleral fibrosis, thus enhancing the successful outcome regarding the control of IOP.[10,11,12]

Traditionally sponges soaked in MMC are applied over the sclerotomy site before or after the scleral flap formation. However, there is no uniformity among the surgeons on this approach in several ways. The concentration of MMC which is being used ranges from 0.1mg/ml to 0.5mg/ml among different patients. The exposure time of MMC is also variable from 1 minute to 5 minutes duration. There are different types of material used for sponges ranging from weck-cell to filter paper and cotton sticks with each material having different absorption property. The size of sponge used is also not uniform. The efficacy of MMC can also be effected if accidentally exposed to light in the operating room.[13] Moreover the amount of irrigating the site of MMC application with Balanced Salt Solution (BSS) is also variable.[14] All these factors contribute to surgeon's inability to determine the exact amount of drug delivered to the tissue. Mehel and colleagues estimated that actual dose delivered in sponge soaked with MMC 0.2mg/ml varied between 1.9 to 17.3 microg.[15]

Lee and colleagues rather than using sponge on scleral surface, injected MMC into subtenon tissue at the beginning of the trabeculectomy.[16] Further investigations have shown that this technique of delivering uniform dose of MMC results in good outcome in controlling the IOP with minimal adverse effects.[17,18]

We conducted this study to evaluate the outcomes of trabeculectomy procedure after the use of intraoperative subtenon injection of MMC rather than MMC soaked sponges in cohort of patients with diagnosis of Primary Open Angle Glaucoma (POAG). The primary end point was control of IOP at one year postoperatively with success defined as IOP of $\leq$ 15 mmHg without any additional anti-glaucoma drops and secondary outcomes were change in Central Corneal Thickness (CCT) and in the Best Corrected Visual Acuity (BCVA).

Materials And Methods:

This observational study with retrospective data collection was carried out in section of ophthalmology, Aga Khan University Hospital, Karachi, Pakistan. The permission of study was granted by hospital Ethical Research Committee and was carried out in accordance with declaration of Helsinki.

The charts of all consecutive patients with diagnosis of POAG, who underwent trabeculectomy with intraoperative subtenon injection of MMC from January 2017 to December 2018 were included. The patients with corneal, retinal pathologies and diagnosis of other than POAG were excluded. The calculated sample size was 49 patients (72 eyes) using World Health Organization (WHO) software, taking 95% confidence level and 5% margin of error. The medical records were retrieved using hospital's information system. Patient's age, gender, Best Corrected Visual Acuity (BCVA) associated comorbid, previous surgery, preoperative applanation IOP, pachymetry, gonioscopy, fundus findings, number of glaucoma medications and postoperative complications were obtained by using a proforma. Patient follow up was assessed at 3, 6 and 12 months postoperatively.

All surgeries were performed by the same surgeon (PSM) using peribulbar 2% xylocaine local anesthesia. Surface anesthesia was achieved with topical proparacaine (Alcaine – Alcon, Belgium). A 6 - O vicryl traction suture was inserted into clear cornea superiorly. A small snip incision was given in limbal conjunctiva at 11'O clock position with introduction of blunt 30 guage canula mounted on tuberculin syringe. MMC (Mitomycin-C, Kyowa – Japan) was injected in dose of 0.1 ml (0.2 mg/ml) given in subtenon space 10 mm away from the limbus. A cotton tip applicator was applied over the conjunctival opening to stop any reflux of the drug. With weck-cell sponge, MMC was distributed over the large surface of conjunctiva superiorly. Peritomy was carried out immediately from 11'O clock to 1'O clock position with undermining of conjunctiva. The exposed scleral surface was irrigated with 10 ml of BSS. After light cauterization of any bleeding point, a triangular scleral flap measuring 4 X 4 mm was fashioned. Before creating 1 X 1 mm deeper corneo-sclerotomy with Kelly's punch, anterior chamber was filled and maintained with 1% sodium hyaluronate (Provisc – Alcon, Belgium). After peripheral iridectomy, scleral flap was closed with 10 – 0 nylon suture one at apex and one on either side. The patency of flap was checked with BSS pushed through the paracentesis site. Conjunctiva was closed on either side with 10 – O nylon suture and one mattress suture was applied in the central area holding conjunctiva to cornea avoiding any leakage and to prevent conjunctival retraction postoperatively.

The postoperative care consisted of Moxifloxacin 0.3 % (Vigamox – Alcon, Pakistan) every hourly for first 24 hours, 2 hourly for next 3 days followed by 4 times a day for 3 weeks. We used Dexamethasone drops 0.1 % (Maxidex – Alcon, Pakistan) every hourly for 24 hours, 2 hourly for 4 weeks followed by 4 times a day for another 6 weeks. All conjunctival nylon sutures were removed at 3 weeks postoperatively.

Statistical analysis:

Data was entered and analyzed by using SPSS V.19.0 (IBM Corp, Armonk, NY). Categorical data were reported as frequencies and percentages and quantitative data as means and standard deviation. Paired sample t-test was applied to compute proportions for continuous variable like IOP and Pachymetry whereas Chi-square test was applied to compute proportions for categorical variables like BCVA. P-value ≤ 0.05 was considered as statistically significant.

Results:

A total 72 eyes (49 patients) underwent trabeculectomy with subtenon injection of MMC. Out of 49 patients, 30(61.2%) were male and 19(38.8%) were female. The mean age was 52 ± 15 years. In 72 eyes, 37(51.4%) were right and 35(48.6%) were left eyes. Basic characteristic of all patients are given in (Table – I).

The mean intraocular pressure preoperatively was 24.68 ± 13.66 mm Hg with maximum anti-glaucoma treatment which comprised of latanoprost 0.005%, combined timolol 0.5% with dorzolamide 2% and brimonidine 0.2%. After the surgery the mean IOP was 13.69 ± 6.68 mmHg at 3 months follow-up, and 12.68 ± 4.04 and 13.33 ± 4.8 mmHg at 6 and 12 months respectively (P-value 0.001). (Table –II). This IOP was achieved without addition of any topical anti-glaucoma drops.

One eye postoperatively had a conjunctival leak with positive seidle sign and 3 eyes had shallow anterior chamber during 1st week of surgery which were all settled with appropriate medical treatment. No other unwanted side effects were seen throughout the entire 12 months follow-up involving cornea or sclera.

Preoperatively mean CCT was 529.81 ± 28.75 microns and at 12 months follow-up after surgery was 530.45 ± 29.43 microns having no significant difference (P-value 0.245). (Table – III)

BCVA outcomes were seen at each follow-up. There was a positive change noticed at third month follow-up as most of the patients moved towards good vision with a significant difference. (p-value 0.001). Similarly, improvement in visual acuity was also seen at sixth and 12 months follow-up as the frequency of patients with good vision increased and results were found to be statistically significant with a P-value 0.045 and 0.032 respectively. (Table – IV)

Although postoperatively patient's visual fields and optical coherence tomography (OCT) did not show any significant change from the preoperative results, we attribute the change in visual acuity mainly due to improved tear film stability with clearing of cornea because of discontinuation of anti-glaucoma drops.

Discussion:

MMC augmented trabeculectomy is the common filtration procedure routinely performed in patients with uncontrolled IOP after maximum medical treatment or when routine use of anti-glaucoma drops cannot be guaranteed due to financial or compliance issues. Weck-cell sponges soaked in MMC

applied over the scleral surface has been the standard practice with majority of the glaucoma surgeons. Due to the variation in sponge size, material and MMC concentration and exposure time, subtenon injection of MMC offers a technique where surgeons ensure exact amount of antimetabolite distributed over wide sub-conjunctival area.

Lee et al[16] injected MMC into subtenon tissue at the beginning of the procedure. They injected 0.15 ml of MMC in variable dose of 0.2 mg / ml to 0.5 mg / ml depending on the risk of bleb failure determined preoperatively, over superior part of the conjunctiva using 23-gauge needle. After 5 minutes, the perilimbal conjunctiva was opened and saline was injected to milk out the residual amount of MMC. This was followed with conventional fornix based trabeculectomy. Their 12 months outcome data showed reduction of IOP from preoperative value of 23.6 ± 5.8 mm Hg to 12.2 ± 3.9 mm Hg in 70 % of their patients. The range of complications in their cohort of 108 patients included hypotony (n = 23, 21%), hyphema (n = 16, 15%) and choroidal detachment (n = 17, 16%) which were all managed conservatively. Pakravan and colleagues[19] in comparative analysis used subtenon injection of MMC in dose of 0.1 ml in 40 patients while another group of 40 patients received MMC soaked sponges (0.2 mg / ml) for 1 to 3 minutes. The injection group received subtenon injection of MMC into superior conjunctiva diffused with blunt canula followed by peritomy 1 minute later. Both groups had successful reduction of IOP in 82.5% of patients. They found the drainage bleb more diffuse, less vascularized and shallow in injection group. Both groups did not show any significant difference with regard to adverse effects. Khouri and colleagues[20] in retrospective analysis of 2 groups of patients with POAG receiving either injection or MMC soaked sponges concluded that the injection group had overall low postoperative IOP and comparative treatment success defined as achieving > 30% IOP reduction without glaucoma medication.

Though MMC soaked sponges are traditionally used during glaucoma drainage surger,y the advantage of intraoperative subtenon injection of MMC includes a standard dosage of drug delivered to the surgical site. The wider area of application results in diffuse bleb formation, as the localized drainage bleb created by sponge application tends to be functionally limited by encapsulation described by Khaw[21] as a ring of steel. Another advantage of this technique is easy dissection of conjunctiva and tenon capsule reducing any damage or button hole of conjunctiva. By injecting the MMC, one also eliminates the risk of intraoperative sponge loss[22]. One of the concerns raised by Grower et al[23] for injection technique was that by using the fine needle to inject MMC superiorly, one can pierce the sclera or this may cause conjunctival leak postoperatively. In our surgical method as we enter with blunt canula at limbus, these complications are bypassed.

The limitation of our study is that it is single centered and retrospective in nature with small sample size and without any control group.

Currently a pilot study is undergoing by Caprioli and colleagues[24] at university of California Los Angeles. This compares preoperative injection of MMC at bleb site 3–4 weeks prior to trabeculectomy vs intraoperative injection of MMC vs topical application of MMC as conventionally used. We await results of this study with great interest.

Conclusions:

The technique of application of subtenon injection of Mitomycin C is quick and easy to perform during trabeculectomy and is alternate to use of sponges. The 12-months follow-up showed this technique to be effective in terms of control of IOP in patients with POAG. However, further prospective randomized studies on large population and long term follow-up are needed to clarify the efficacy of this technique.

Declarations:

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Conflict of Interest:

Conflict of interest none with any of the authors.

Competing Interest:

None

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References:

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of Glaucoma and projections of Glaucoma burden through 2040. Ophthalmol 2014;121(11):2081-2090.
2. Chan EW, Li X, Tham YC, Liao J, Wong TY, Aung T, Cheng CY. Glaucoma in Asia: regional prevalence variations and future projections. Br J Ophthalmol 2016;100:78-85.
3. Hassan B, Ahmed R, Li B, Noor A, Hassan Z. A comprehensive study capturing vision loss burden in Pakistan (1990-2025): Findings from the Global Burden of Disease (GBD) 2017 study. PLoS ONE 14(5):e0216492. https://doi.org/10.1371/journal.pone.0216492.
4. Kirwan JF, Lockwood AJ, Shah P, Macleod A, Broadway DC, King AJ, McNaught AI, Agarwal P. Trabeculectomy in the 21st Century: A Multicenter Analysis. Ophthalmol 2013;120(12):2532-2539.
5. Broadway DC and Chang L. Trabeculectomy, risk factors for failure and the preoperative state of the conjunctiva. J Glaucoma 2001;10(3):237-249.
6. Mearza AA, Aslanides IM. Uses and complications of mitomycin C in ophthalmology. Expert Opin Drug Saf. 2007;6(1):27–3.
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. Lama PJ, Fechtner RD. Antifibrotics and wound healing in glaucoma surgery. Surv Ophthalmol. 2003;48(3):314–346.
9. Chen CW, Huang HT, Bair JS, Lee CC. Trabeculectomy with simultaneous topical application of Mitomycin – C in refractory glaucoma. J Ocul Pharmacol 1990;6(3):175-182.
10. Wilkins M, Indar A, Wormald R. Intra-operative mitomy-cin C for glaucoma surgery. Syst Rev. 2001;2(2):28–97.
11. Kyprianou I, Nessim M, Kumar V, O'Neill E. Long-term results of trabeculectomy with mitomycin C applied under the scleral flap. Int Ophthalmol. 2007 Dec;27(6):351–355.
12. Romero P, Hirunpatravong P, Alizaden R, Kim EA, Mahdavi KN, Morales E, Law SK, Caprioli J. Trabeculectomy with Mitomycin – C: Outcomes and risk factors for failure in Primary Angle-Closure Glaucoma. J Glaucoma 2018;27(2):101-107.
13. Cumurcu T. Mitomycin-C use and complications in ophthalmology. Int J Clin Exp Ophthalmol 2017;1:029-032.
14. Habash AA, Aljasim LA, Owaidhah O and Edward DP. A Review of the efficacy of mitomycin – C in glaucoma filtration surgery. Clin Ophthalmol 2015;9:1945-1951.
15. Mehel E, Weber M, Stark L, Pechereau A. A novel method for controlling the quantity of Mitomycin – C applied during filtering surgery for glaucoma. J Ocul Pharmacol Ther 1998;14(6):491-496.
16. Lee E, Doyle E and Jenkins C. Trabeculectomy surgery augmented with intra-Tenon injection of Mitomycin – C. Acta Ophthalmol 2008;86:866-870.
17. Onol M, Aktas Z, Hasanreisoglu B. Enhancement of the success rate in trabeculectomy: large-area Mitomycin – C application. Clin Exp Ophthalmol 2008;36(4):316-322.
18. Lim MC. A comparison of trabeculectomy surgery outcomes with Mitomycin – C applied by intra-Tenon injection versus sponge method. American Glaucoma Society 23rd Annual Meeting 2013, San Francisco, CA.
19. Pakravan M, Esfandiari H, Yazdani S, Douzandeh A, Amouhashemi N, Yaseri M, Pakarvan P. Mitomycin – C augmented trabeculectomy: Subtenon injection versus soaked sponges: a randomised clinical trial. Br J Ophthalmol 2017;101(9):1275-1280.
20. Khouri AS, Huang G, Huang LY. Intraoperative injection vs Sponge-applied Mitomycin – C during Trabeculectomy: One-year study. J Curr Glaucoma Pract 2017;11(3):101-106.
21. Khaw PT, Doyle JW, Sherwood MB, Grierson I, Schultz G & McGorray S. Prolonged localized tissue effects from 5-minute exposures to Fluorouracil and Mitomycin – C. Arch Ophthalmol 1993;111:263-267.
22. Guivaraes ME, Bezerra BPS, Cordeiro FM, Carvalho CH, Danif DN, Prata TS, Dorairaj SK, Kanadani FN. Glaucoma surgery with soaked sponges with Mitomycin C vs sub-tenon injection: Short-term outcomes. J Curr Glaucoma Pract 2019;13(2):50-54.
23. Grover DS, Kornmann HL and Fellman RL. Historial considerations and innovations in the preioperative use of Mitomycin C for Glaucoma filtration surgery and Bleb revisions. J Glaucoma 2020;29(3):226-235.

24. Caprioli J. Comparing preoperative injection of Mitomycin-C vs Intraoperative injection of Mitomycin-C vs Topical application of Mitomycin-C (Conventional use) in Trabeculectomy. ClinicalTrial.gov Identifier: NCT03875911.

Tables:

Table- I: Basic Characteristics of Patients:

Age distribution:			**Gender distribution:**			**Eye Status:**		
Age groups	Frequency	Percent	Gender	Frequency	Percent	Eye	Frequency	Percent
20-30 yrs	1	2	Male	30	61.2	RE	37	51.4
>30-40	3	6.1						
>40-55	16	32.7	Female	19	38.8	LE	35	48.6
>55-65 yrs	20	40.8						
>65 yrs	9	18.4	Total	49	100	Total	72	100
Total	49	100						
Diabetes				**Hypertension**				
Status	Frequency		Percent	Status	Frequency		Percent	
Yes	31		63.3	Yes	22		44.9	
No	18		36.7	No	27		55.1	
Total	49		100	Total	49		100	

Table – II: Intraocular Pressure (IOP) Status Before and After Surgery:

Descriptive	No.of Eyes	Mean	Std. Deviation	P-value
Baseline IOP (mm Hg)	72	24.68	13.66	
Three months IOP (mm Hg)	72	13.69	6.86	0.001
Six months IOP (mm Hg)	72	12.68	4.04	0.001
Twelve months IOP (mm Hg)	72	13.33	4.8	0.001

Table – III: Central Corneal Thickness (CCT) Status:

Descriptive	No.of Eyes	Mean	Std. Deviation	P-value
Baseline CCT (micron)	72	529.81	28.75	
CCT at 12 months (micron)	72	530.45	29.43	0.245

Table – IV: Best corrected Visual Acuity (BCVA) from baseline to 12 months' follow-up:

Baseline BCVA			BCVA at three months			P-value	BCVA at six months			P-value	BCVA at twelve months			P-value
BCVA	Count	Percent	BCVA	Count	Percent		BCVA	Count	Percent		BCVA	Count	Percent	
20/20	1	1.39	20/20	6	8.33	0.001	20/20	9	12.50	0.045	20/20	19	26.39	0.032
20/25	2	2.78	20/25	9	12.50		20/25	15	20.83		20/25	24	33.33	
20/30	4	5.56	20/30	14	19.44		20/30	20	27.78		20/30	16	22.22	
20/50	4	5.56	20/50	11	15.28		20/50	9	12.50		20/50	4	5.56	
20/60	2	2.78	20/60	4	5.56		20/60	3	4.17		20/60	2	2.78	
20/100	15	20.83	20/100	7	9.72		20/100	4	5.56		20/100	2	2.78	
20/200	23	31.94	20/200	12	16.67		20/200	7	9.72		20/200	3	4.17	
CF	4	5.56	CF	3	4.17		CF	2	2.78		CF	1	1.39	
NFI	17	23.61	NFI	6	8.33		NFI	3	4.17		NFI	1	1.39	
Total	72	100	Total	72	100		Total	72	100		Total	72	100	

C.F = Counting fingers

N.F.I = No further improvement