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Original Article

# Intraocular Pressure Control after Trabeculectomy with Adjunctive Use of Mitomycin-C versus Bevacizumab: A Hospital Based Study

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## ABSTRACT

**Purpose:** To compare the control of intra ocular pressure (IOP) after trabeculectomy with adjunctive use of Mitomycin–C (MMC) versus Bevacizumab.

**Study Design:** Quasi experimental study.

**Place and Duration of Study:** Al-Ibrahim Eye Hospital, Isra Postgraduate Institute of Ophthalmology, Karachi, from August 2017 to August 2019.

**Methods:** One hundred and six patients of either gender, fulfilling the inclusion criteria were planned for trabeculectomy with adjunctive use of Mitomycin-C (MMC) or Bevacizumab. Each group consisted of 53 patients (53 Eyes). The patients diagnosed with Primary Open Angle Glaucoma (POAG) with IOP  21 mm Hg and not controlled with topical anti-glaucoma medication were selected. Data were analyzed by using SPSS Version 22.0. Independent sample t test was used to check significance between two drugs. Paired sample t test was used to check significance of pre and post-operative IOP.

**Results:** Mean age of patients was 56.67±7.34 years. Mean preoperative IOP was 31.51 ± 9.66 mm Hg in MMC group and 29.21 ± 7.69 mm Hg in Bevacizumab group. At first postoperative day, mean IOP after use of MMC was 14.75 ± 9.46 mm Hg and for Bevacizumab was 15.07 ± 6.47 mm Hg (p-value 0.001). Similarly, at one year follow-up, mean IOP for MMC group was 11.26 ± 2.31 mm Hg and for Bevacizumab was 11.73 ± 2.12 mm Hg (p-value 0.001).

**Conclusion:** There was significant reduction in IOP in both MMC and Bevacizumab groups. However, the difference between the two groups was not statistically significant at mean follow-up of one year.

**Key Words:** Primary Open Angle Glaucoma, Mitomycin–C, Intraocular Pressure, Bevacizumab, Trabeculectomy.

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## INTRODUCTION

Glaucoma is a vision-threatening condition characterized by progressive optic neuropathy and visual field loss with raised intraocular pressure (IOP) in majority of the patients. There were 60.5 million people with glaucoma worldwide in 2010 and it is was estimated that this number would be more than 79.6 million people by 2020.[1] Trabeculectomy was introduced by Cairns in 1968 and is considered to be

the gold standard to reduce IOP in patients with pharmacologically uncontrolled IOP.[2] Failure of trabeculectomy is associated with postoperative scarring of conjunctiva and tenon capsule at the site of filtering bleb due to inflammatory response associated with healing.[3] This inflammatory response includes fibroblasts migration and proliferation leading to formation of adhesions between epi-sclera and conjunctiva, decreasing aqueous outflow with a resultant increase in IOP.[4] To overcome this problem, several antimetabolites like Mitomycin-C and 5-flurouracil have been used. These are antifibrotic agents that have been used successfully in trabeculectomy to delay the wound healing process. However, due to inconsistent findings in terms of IOP control, there has been need for further studies.[5-7]

Mitomycin C (Kowa, Japan) is an antineoplastic/ antibiotic agent isolated from soil bacterium Streptomyces Caespitosus. It inhibits the fibroblast proliferation by acting as a deoxyribonucleic acid cross-linker. It is used in medicine as a chemotherapeutic agent in treatment of a variety of cancers. Its use in glaucoma filtration surgery is a common practice because of its modulatory effects on wound healing.[8] Chen et al. used MMC in patients with refractory glaucoma with successful outcome in control of IOP. Since then it is routinely used in trabeculectomy. MMC inhibits the postoperative epi-scleral fibrosis thus enhancing the successful outcome regarding the control of IOP.[9]

Vascular endothelial growth factor (VEGF) is a cytokine with multiple effects on wound healing. It stimulates the scar formation through collagen deposition, angiogenesis and epithelialization. VEGF has been shown to be elevated in glaucoma patients and is suggested that it might be playing a role in the scar formation after filtering surgery. Bevacizumab (Avastin, Roche Pakistan) is a full-length humanized monoclonal antibody that binds to all isoforms of VEGF. It has been approved by the US Food and Drug administration for intravenous treatment of metastatic colorectal cancer. It is used off label in various choroidal and retinal vascular disorders universally. There has been some evidence that it reduces filtering bleb failure after sub-conjunctival injections.[10]

Multiple publications in literature has suggested different results with the use of Bevacizumab in trabeculectomy. Akkan and colleagues conducted a study in Turkey and found that post-operative IOP target was achieved in 71% of eyes in MMC group while 33% success in patients in Bevacizumab group ($p = 0.02$), at 12 months follow-up.[11] Nilforushan et al. reported a study from Iran where they found statistically significant difference in IOP control between the two groups; 34% in Bevacizumab and 56% in MMC group ($p = 0.32$)[12]. Sengupta and coworkers however reported that Bevacizumab group had better success rate than MMC group (90% versus 60%; $p = 0.04$).[13]

As there is limited number of studies on Bevacizumab use in glaucoma filtering surgery with inconsistent findings, we conducted this prospective study to compare the frequency of controlled IOP after trabeculectomy with the adjunctive use of MMC and Bevacizumab. The primary end-point was control of IOP of □ 18 mm Hg without any added anti-glaucoma drug or 30% reduction in IOP from baseline at one-year follow-up. The secondary outcomes were; associated adverse effects with each drug and any change in visual acuity. We also evaluated the bleb morphology in both drugs.

## METHODS

This study was carried out in Glaucoma department of Al-Ibrahim Eye Hospital/Isra Postgraduate Institute of Ophthalmology, Karachi from August 2017 to August 2019. The study commenced after clearance from the hospital Research Ethical Committee and was carried out in accordance with declaration of Helsinki. Sample size was calculated with Open Epi sample calculator, using success of 94.4% of MMC group with 95% confidence interval and 5% margin of error.[12] The final sample size was 106 patients with 53 patients in MMC group and 53 patients in the Bevacizumab group. Patients were divided by non-probability consecutive sampling. All participants were given information about the study and an informed consent was taken. Patients > 40 years of age and having a diagnosis of primary open angle glaucoma (POAG) with intraocular pressure (IOP) of more than 21 mmHg, uncontrolled medically and having glaucomatous optic disc cupping were included in the study. We excluded patients with angle closure glaucoma, secondary glaucoma, corneal diseases, uveitis (or history of uveitis) and with a history of any intraocular surgery.

A detailed history was taken from all patients regarding any comorbids, ocular trauma, anti-glaucoma medications with dosage and duration.

Patients were also inquired about any addiction and family history of glaucoma.

Before surgery, all patients had detailed ocular examination including best-corrected visual acuity (BCVA), slit lamp bio-microscopic examination of anterior segment with recording of IOP using Goldman Applanation Tonometer (GAT). Gonioscopy was performed using Goldman two-mirror lens. Dilated fundus examination was carried out with +90 diopter Volk lens. Every patient had visual field examined on Humphrey Field Analyzer, Central Corneal Thickness (CCT) was determined and optical coherence tomography (OCT) was performed for Retinal Nerve Fiber Layer (RNFL) thickness and macular analysis.

Pre-operative blood pressure and blood sugar of all the patients were recorded. Intravenous Mannitol 1gram/Kg body weight was given 1 hour before surgery whenever required. Pupil was miosed preoperatively with single drop of pilocarpine 2% to prevent lens damage and to facilitate peripheral iridectomy.

All surgeries were performed using retrobulbar 2% xylocaine local anesthesia. Surface anesthesia was achieved with topical Proparacaine drops (Alcaine – Alcon, Belgium). The operated eye was prepped and draped. Each patient underwent a fornix-based trabeculectomy. A 6/0 vicryl traction suture was inserted onto superior cornea. A fornix based flap of conjunctiva and tenon capsule was fashioned superiorly. Episcleral tissue was cleared and major vessels cauterized with wet-field bipolar cautery. Incision was made for 50% scleral thickness, to create a trapdoor lamellar scleral flap. The flap was triangular in shape of about 4 × 4 mm. In group one, Mitomycin-C was applied in sponge form on sclera and under the scleral flap for 3 minutes duration and then washed with 20 ml of balanced salt solution (BSS) for 30 seconds. Paracentesis was done on temporal side and anterior chamber was maintained with 1% Sodium Hyaluronate viscoelastic (Provisc – Alcon, Belgium). A peripheral iridectomy was performed and corneo-scleral block was removed measuring about 1 × 1 mm. Scleral flap and conjunctiva were closed with 10/0 nylon sutures.

In patients receiving Bevacizumab, same steps were taken for trabeculectomy without using MMC soaked sponges. However, at the end of procedure, 0.1 ml (2.5 mg) of Bevacizumab was taken in 1 ml syringe with 30 gauge needle. The needle was introduced sub-conjunctively away from the scleral flap site and forwarded over the flap with deposition of the drug. The point of needle entry was pressed with cotton applicator to avoid reflux of the drug.

Our postoperative treatment regimen included Moxifloxacin 0.3 % drops (Vigamox – Alcon, Belgium) every hour for first 24 hours, 2 hourly for next 3 days followed by 4 times a day for 4 weeks. We used Dexamethasone 0.1% drops (Maxidex – Alcon, Belgium) every hour for 24 hours, 2 hourly for 4 weeks, then 4 times a day for another 6 weeks. All patients were examined on day 1, one week, 4 weeks, 3 months, 6 months and 12 months postoperatively.

Data were analyzed by using SPSS Version 22.0. Mean and standard deviation was calculated for quantitative variables like age and IOP (pre and post treatment). Frequencies with percentages were presented for qualitative variables like complications, gender and type of glaucoma. Independent sample t test was used to check significance between two drugs. Paired sample t test was used to check significance of pre and post-operative IOP.

## RESULTS

A total of 106 patients (106 eyes) including 63 (59.43%) male and 43 (40.56%) female were recruited in the study. Mean age of the patients was 56.67 ± 7.34 years (range 40–70 years). Patients were divided into two groups based on drug prescribed by an ophthalmologist. Nine patients in MMC group and eleven patients in Bevacizumab group were lost to followup at the end of 1 year. Therefore, 44 patients in MMC group and 42 patients in Bevacizumab group were available for the final analysis.

Pre-operatively mean IOP in MMC group was 31.51 ± 9.66 mm Hg. This was reduced to 11.26 ± 2.31 mm Hg at one-year postoperatively with a p-value of 0.001. In Bevacizumab group, preoperatively mean IOP was recorded as 29.21 ± 7.69 mm Hg and was dropped to 11.73 ± 2.12 mm Hg at one-year follow-up with a p-value 0.001 respectively **(Table 1).**

At day 1, 41 (77.3%) out of 53 patients had controlled IOP ( 18 mm Hg) in MMC group. While after the use of Bevacizumab, frequency of controlled IOP of  18 mm Hg was noticed in 48 (90.56%) patients at first day post-operatively. Similarly, at one year, all 44 (100%) patients who completed follow-up had IOP of  18 mm Hg after the use of MMC.

Whereas in case of Bevacizumab, all attended 42 (100%) patients had controlled IOP **(Table 2).**

**Table 1:** *Post-operative Comparison of Mean IOP Between Mitomycin – C & Bevacizumab Groups*

| | MMC Group | | Bevacizumab Group | |
|---|---|---|---|---|
| **IOP** | **Mean** | **P-value** | **Mean** | **P-value** |
| Pre op IOP | 31.51 ± 9.66 | – | 29.21 ± 7.69 | - |
| First Day | 14.75 ± 9.46 | 0.001 | 15.07 ± 6.47 | 0.001 |
| Sixth Week | 14.90 ± 7.84 | 0.001 | 16.27 ± 6.59 | 0.001 |
| Third Month | 13.73 ± 7.18 | 0.001 | 15.02 ± 6.15 | 0.001 |
| Sixth Month | 12.06 ± 3.95 | 0.001 | 12.87 ± 3.68 | 0.001 |
| One Year | 11.26 ± 2.31 | 0.001 | 11.73 ± 2.12 | 0.001 |

*IOP = Intraocular pressure *MMC = Mitomycin C

Comparative analysis of IOP reduction in both groups after trabeculectomy is given in **Table 3** and **Figure 1**.

Mean postoperative BCVA (log MAR) was 0.68 + 0.40 and 0.63 + 0.41 in MMC and Bevacizumab groups respectively at first day postoperatively with no significant difference. (p-value 0.538). Whereas at one-year follow-up, mean postoperative BCVA (log MAR) was 0.50 + 0.39 and 0.38 + 0.27 in MMC and Bevacizumab groups respectively with significant difference (p-value 0.01) (**Table 4)**

Regarding bleb morphology, 28 (52.8%) and 35 (66.03%) patients had elevated bleb for MMC and Bevacizumab group at day 1 postoperatively. Similarly, at one-year follow-up, 42 (79.24%) and 39 (73.58%) patients had elevated bleb in MMC and Bevacizumab groups respectively. At first day postoperatively, 48 (90.56%) and 51 (96.22%) patients had vascularized bleb for MMC and Bevacizumab, respectively. However, at one-year follow-up, only 8 (15.09%) and 15 (28.30%) patients had vascularized bleb for MMC and Bevacizumab group.

Needling was done in one case 1 (1.88%) in both MMC and Bevacizumab groups at third month post operatively. Suture lysis with argon laser was carried out at 6 weeks postoperatively in 13 (24.5%) and 16 (30.1%) patients in MMC and Bevacizumab groups.

At first day post operatively, hyphema was observed in 2 (3.77%) eyes in MMC group and none in Bevacizumab group. Hyphema was transient and disappeared in next 3 days without any added treatment. Similarly, 10 (18.8%) and 4 (7.54%) patients had flat anterior chamber for MMC and Bevacizumab group at first day postoperatively. Two patients in MMC group developed hypotomy (IOP □ 6 mm Hg) after 3 months of surgery. One patient in each group had conjunctival leak postoperatively. All these complications resolved conservatively without any added procedure.

**Table 2:** *Comparison of Controlled IOP after Use of MMC and Bevacizumab Post-operatively.*

| Post-Operative Follow-ups | MMC Group | | | BEVACIZUMAB Group | | |
|---|---|---|---|---|---|---|
| | IOP Controlled < 18 | IOP Uncontrolled > 21 | Patients Come on Followup | IOP Controlled < 18 | IOP Uncontrolled > 21 | Patients Come on Followup |
| IOP at 1st day | 41 (77.35%) | 12 (22.64%) | 53 (100%) | 48 (90.56%) | 5 (9.43%) | 53 (100%) |
| IOP at 6th week | 42 (80.76%) | 10 (19.23%) | 52 (100%) | 42 (82.35%) | 9 (17.64%) | 51 (100%) |
| IOP at 3rd month | 43 (87.75%) | 6 (12.24%) | 49 (100%) | 45 (91.83%) | 4 (8.16%) | 49 (100%) |
| IOP at 6th month | 46 (95.83%) | 2 (4.16%) | 48 (100%) | 47 (95.91%) | 2 (4.08%) | 49 (100%) |
| IOP at One year | 44 100%) | 0 (0%) | 44 100%) | 42 100%) | 0 (0%) | 42 (100%) |

*IOP = Intraocular pressure *MMC = Mitomycin C

**Table 3:** *Pre and Postoperative Changes in Mean IOP in Mitomycin – C Versus Bevacizumab Groups.*

| Intraocular Pressure | Mitomycin C | Bevacizumab | P-value |
|---|---|---|---|
| First day | 14.75 ± 9.46 | 15.07 ± 6.47 | 0.839 |
| Sixth week | 14.90 ± 7.84 | 16.27 ± 6.59 | 0.340 |
| Third month | 13.73 ± 7.18 | 15.02 ± 6.15 | 0.076 |
| Sixth month | 12.06 ± 3.95 | 12.87 ± 3.68 | 0.293 |
| One year | 11.26 ± 2.31 | 11.73 ± 2.12 | 0.364 |

*Intraocular pressure *MMC = Mitomycin C

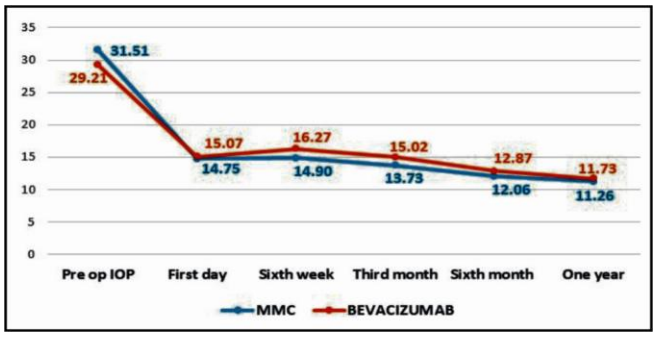


**Figure I:** Mean IOP Comparison between Mitomycin – C and Bevacizumab. *IOP = Intraocular pressure *MMC = Mitomycin C

**Table 4:** *Post-operative Mean Changes in BCVA (LogMar) between MMC and Bevacizumab*.

| BCVA | MMC | Bevacizumab | P-value |
|---|---|---|---|
| First day | 0.68 ± 0.40 | 0.63 ± 0.41 | 0.538 |
| Sixth week | 0.57 ± 0.41 | 0.42 ± 0.35 | 0.067 |
| Third month | 0.51 ± 0.36 | 0.36 ± 0.29 | 0.034 |
| Sixth month | 0.51 ± 0.36 | 0.35 ± 0.23 | 0.01 |
| One Year | 0.50 ± 0.39 | 0.38 ± 0.27 | 0.01 |

*IOP = Intraocular pressure *MMC = Mitomycin C
*BCVA = Best corrected visual acuity

## DISCUSSION

The main cause of failure of trabeculectomy is excessive postoperative conjunctival scarring at the site of filtering bleb due to inflammatory reaction. To overcome this problem, several antimetabolites like 5 – fluorouracil and MMC had been used successfully with filtration surgery. Over last few years, anti-VEGF agents such as Bevacizumab has been introduced as a potent adjunct in trabeculectomy with good outcome in control of IOP. The fibroblasts of tenon capsule, which produce collagen and elastin are the most important mediators of ocular scar formation after filtration surgery. Various in vitro studies have shown effectiveness of anti-VEGF agent on corneal and conjunctival fibroblast.[14-15]

In this particular study, we compared IOP control after trabeculectomy with the adjunctive use of MMC and Bevacizumab. We report a significant reduction of IOP in both groups at one year (p = 0.001), with a reduction in IOP values of about 83% and 79% respectively. Both the groups were comparable in terms of IOP control at one year. In terms of bleb characteristics, we noticed increase in bleb vascularity in Bevacizumab group as compared to MMC group i.e., 34% and 19%, at one year followup. Postoperative complication rates were slightly higher in MMC group, although statistically not significant. There was no difference in number of anti-glaucoma medications required at one year after surgery between the two groups.

Kahook et al. reported that Bevacizumab prevented excessive scar formation after needle bleb revision in failed trabeculectomy, a finding similar to our study.[16] A study conducted by Sengupta et al. showed that sub-conjunctival Bevacizumab was equally effective in reducing IOP, with a better safety profile compared with MMC. The mean IOP was 16.2 ± 4.3 mm Hg in their patients receiving MMC and 16.2 ± 3.7 mm Hg in Bevacizumab group at six months follow-up.[13] Grewal et al. reported on the efficacy of a single postoperative injection of 1.25 mg/ 0.05 ml of Bevacizumab in 12 glaucomatous eyes that underwent trabeculectomy.[17] Their findings showed a reduction in mean IOP from 24.4 mm Hg to 11.6 mmHg (52%) at six months' follow-up. In another study conducted by Jaya Kaushik and associates, adjunctive Bevacizumab in trabeculectomy was found to be effective and comparable to MMC for controlling IOP in POAG patients at one-year follow-up (p = 0.43). However, there was statistically significant difference in peripheral bleb vascularity with Bevacizumab group exhibiting a low degree of vascularity at one year (p = 0.029).[18] This finding is different from our study where we found increased bleb vascularity in Bevacizumab group at one year.

Akkan et al. showed the frequency of IOP control after one year in 41% and 46% of their patients receiving Bevacizumab and MMC, respectively.[11] Nilforushan et al, reported that 2.5 mg/0.1 ml subconjuctival Bevacizumab application after primary trabeculectomy provided effective IOP control, but when compared to the MMC administered group, it was less effective.[12] They observed a 56% fall of IOP in the MMC group, and 34% in the Bevacizumab group, after an average followup of 7 months. However, this study had a small sample size and short follow-up period that may be the reason for findings different from our study.

Xiaoyan Liu and associates found that Bevacizumab was an effective adjunct in trabeculectomy concerning the complete success rate, IOP and anti-glaucoma medications reduction when compared with placebo. However, its use increased the risk of bleb leakage and encysted bleb formation compared with MMC.[19] This study had a shorter follow-up period of six months that may explain findings different from our study.

Kopsinis et al compared the effects of intracameral Bevacizumab to sub tenon Mitomycin C in trabeculectomy. They concluded that average IOP and glaucoma medications decreased significantly in both groups at all follow-up points compared to baseline (p < 0.001), without significant difference between groups at 3 years.[20] Bilgic et al, compared the outcomes of trabeculectomy using two different routes of Bevacizumab administration as an adjunct in patients with primary open angle glaucoma. A significant reduction was observed in the IOP post trabeculectomy in all patients in both groups (paired t-

test, P < 0.001, both groups), a change that had persisted at one-year follow-up.[21] Another report found that Bevacizumab along with Mitomycin C in trabeculectomy was not superior to trabeculectomy with Mitomycin C or trabeculectomy with Mitomycin C and intracameral Bevacizumab. However, both groups showed a statistically significant reduction in IOP after 6 and 12 months (p-0.001).[22] Nadeem S, published her work of 30 patients who underwent trabeculectomy with adjunctive use of 5 – Fluorouracil (5 – FU) applied topically for 5 minutes. In half of the eyes, Bevacizumab was injected over scleral flap at the end of the procedure. After 3 months follow-up, IOP control and bleb appearance was indifferent between the two groups. The author concluded no added benefit of sub-conjunctival Bevacizumab.[23]

Limitations of our study are that 9 patients lost to follow-up in MMC group and 11 in Bevacizumab group at the end of one year. Secondly, followup was limited to one year. However, this study is a significant contribution to the available literature regarding glaucoma, particularly in Pakistan.

## CONCLUSION

Adjunctive use of Mitomycin-C (MMC) or Bevacizumab with trabeculectomy are equally effective in reducing IOP in patients with diagnosis of primary open angle glaucoma. Though, vascularity of bleb was slightly increased in Bevacizumab group as compared to MMC group at one year followup, whereas postoperative complications were slightly lower in Bevacizumab group. These findings were statistically not significant.

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### Ethical Approval

The study was approved by the Institutional review board/Ethical review board (A-00093).

### Conflict of Interest

Authors declared no conflict of interest.

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## Authors Designation & Contribution

P. S. Mahar; Professor & Dean: *Concepts, Design, Manuscript preparation.*

Sobia Tabassum; Senior Registrar: *Data acquisition, Data analysis.*

Mujahid Inam; Associate Professor: *Manuscript review.*

Muhammad Faaz Malik; Senior Registrar: *Literature Search.*

Tauseef Mahmood; Statistician: *study Design. Statistical Analysis.*