

Subconjunctival Bevacizumab as an Adjunct to 5-Fluorouracil Enhanced Trabeculectomy: 1 Year Outcomes

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ABSTRACT

Purpose: To compare the results of trabeculectomy with subconjunctival Bevacizumab and 5-Fluorouracil (5-FU); with trabeculectomy with 5-FU alone; in terms of intraocular pressure (IOP) lowering, bleb formation, and complications, in the long term.

Study Design: Quasi experimental study.

Place and Duration of Study: Fauji Foundation Hospital, Rawalpindi, from December 2013 to August, 2019.

Methods: A total of 30 eyes (15 in each group) with glaucoma were recruited. Exclusion criteria were previous trabeculectomy, congenital, traumatic, uveitic, neovascular glaucomas, aphakia, or ocular surface disease. Trabeculectomy with 5FU was performed in both groups. In one group, subconjunctival Bevacizumab was injected into the bleb at the end of surgery. The patients were observed for IOP control, bleb configuration, and complications for 1 year.

Results: Primary open angle glaucoma was the predominant diagnosis in 17 (56.7%) eyes. The mean pre-operative IOP in the 5-FU group was 30.8 ± 17.03 mmHg, & in the 5-FU+Bevacizumab group it was 28.9 ± 18.9 mmHg. The mean IOPs of the 5-FU group at 1 Year was 14.5 ± 5.04 mmHg. In 5-FU+Bevacizumab group, mean IOPs at 1 year was 12.7 ± 4.38 mmHg. The differences between pre-operative and post-operative IOPs in both groups at 6, 9 and 12 months were statistically significant. However, differences in mean IOPs between the two groups, bleb morphology and complications were not statistically significant.

Conclusion: No added benefit of subconjunctival Bevacizumab used as an adjunct to 5-FU enhanced trabeculectomy was found at the end of 1 year follow-up.

Key Words: Trabeculectomy, 5-Fluorouracil, Bevacizumab, Glaucoma, Intraocular pressure.

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INTRODUCTION

Glaucoma envelops a group of disorders characterized by progressive optic neuropathy and consequential

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visual field loss, in which intraocular pressure (IOP) is a primary modifiable risk factor.¹ According to the World Health Organization, glaucoma accounts for greater than 12% of the burden of global blindness, with around 4.5 million people blinded worldwide by it.² It is the leading cause of irreversible blindness³, and surgery is often necessary when topical therapy, laser or all else fails in controlling the IOP.

Trabeculectomy still remains the gold standard incisional surgery for IOP reduction. It involves the creation of a fistula between the anterior chamber and

sub-tenon/sub-conjunctival space, beneath a partial thickness scleral flap, from where aqueous humor passes into a filtering bleb, from where it is absorbed into surrounding structures. Hence, a functional filtering bleb is vital for surgical success.⁴⁻⁷

The success of glaucoma filtration surgery (GFS) is hindered by scarring and fibrosis. Antimetabolites used intraoperatively or postoperatively, prevent this scarring. Conventionally, 5-Fluorouracil (5-FU) and mitomycin C (MMC) are the most commonly used agents to modulate the healing response post-surgery, by prevention of the activation, proliferation and migration of fibroblasts. However, these may cause collateral damage. Angiogenesis, mediated by the vascular endothelial growth factor (VEGF), plays a primary role in wound modulation leading to granulation tissue formation. VEGF also directly promotes inflammatory mediator migration and fibroblast activity. These hypotheses lead to researchers to investigate the role of anti-VEGF agents like bevacizumab (BVZ) as adjuvants in GFS to enhance its success rates and safety profile.^{1,8}

The rationale of our study is to compare the effect of subconjunctival BVZ as an adjunct to 5-FU enhanced trabeculectomy to the effect of 5-FU alone; in terms of IOP lowering, bleb formation, and complications, in the long term and to see if it gives an additional benefit.

METHODS

A total of 30 eyes in patients with glaucoma presenting to the eye out patient department, were included in this prospective, interventional study. Thirty eyes were grouped into two (15 in each group). The study was carried out in the Department of Ophthalmology, Fauji Foundation Hospital, Rawalpindi, which is a tertiary care, teaching hospital affiliated with Foundation University Medical College; from 18th December, 2013 to 16th August, 2019. Approval from the ethical committee was taken prior to the study. Convenience sampling was done. Inclusion criteria were patients above 40 years of age with primary open or angle closure glaucoma, pseudoexfoliative glaucoma, or pseudophakic glaucoma who had uncontrolled IOP with maximally tolerated medical therapy, or non-compliance, or advanced glaucomatous damage at presentation, or as a combined procedure for cataract and glaucoma, if on multiple medications. Patient preference for trabeculectomy was also respected if on

2 or more topical anti-glaucoma medications. Exclusion criteria were young patients with glaucoma, congenital, juvenile, secondary, uveitic, traumatic, neovascular, aphakic glaucoma or the presence of ocular surface disease. Pre-operatively, thorough ocular examination with slit lamp examination of the anterior and posterior segments, Goldmann applanation tonometry, Pachymetry and Gonioscopy was done. The patients were assessed and monitored for glaucomatous progression by serial Humphrey perimetry and optical coherence tomography (OCT) of the optic nerve head and retinal nerve fiber layer.

All surgeries were performed under local anaesthesia by the author using a standardized technique for facial nerve and retrobulbar blocks. The fornix based approach for trabeculectomy was used in all cases with a limbal conjunctival peritomy performed, and then a triangular superficial scleral flap was fashioned measuring 4 x 4 mm with a blade No.15, then 5-FU (50 mg/ml) was applied above and below the superficial flap with cotton pledgets for 5 minutes. After thorough washing of the 5-FU, a paracentesis was performed, and a deep scleral window was made 1.5 x 2 mm in size with a blade No. 11. Peripheral iridectomy was performed using the Vannas scissors. The superficial flap was then approximated to the sclera with 10/0 nylon sutures one at the apex, and one on the right side, with the left side being left un-sutured. The conjunctiva was then sutured with 8-0 silk or 6-0 vicryl on the right side ensuring a water-tight closure. Fluid was injected through the paracentesis to ensure bleb formation and patency of the filtration procedure. In cases of subconjunctival bevacizumab (Avastin®) injection (2.5 mg in 0.1 ml), the injection was performed from the left side with a bent needle of a 1 cc (30 G) syringe, horizontally into the bleb, about 8mm from the limbus. A subconjunctival antibiotic and steroid injection was given at the end of the surgery. In case of combined phaco-trabeculectomy, after peritomy and fashioning of superficial flap, phacoemulsification with an intraocular lens (IOL) implantation was performed, following which the trabeculectomy was then completed. Post-operatively the patients were given a topical antibiotic-steroid combination and cycloplegics, eventually tapered off at 6 weeks' time.

The patients were examined by the operating surgeon on the post-operative visits at Day 1, 1 week, 1 month, and then monthly for 1 year. Visual acuity, Goldmann tonometry, and slit lamp examination with

fundus assessment was done as routine post-operative examination. Bleb assessment using a simple grading system was done after healing of the conjunctiva, according to which blebs were classified into four types; Type 1: thin-walled, polycystic (well-functioning), Type 2: Diffuse, flatter and thicker (good functioning), Type 3: Flattened bleb with scarring and little or no function, and Type 4: Encapsulated (Tenon’s cyst) with engorged blood vessels and poor function.

The data was analyzed on SPSS version 20. Frequencies and percentages were calculated for all the variables. Unpaired and paired samples t-tests were used for the data analysis as the case may be. The Wilcoxon signed-rank test was used to assess the types of bleb formation between the two groups, and the complications between the two groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 30 eyes of 24 patients were included in this study, with 15 eyes in each group. Majority of the patients were females accounting for 29 (96.7%) eyes. Primary open angle glaucoma was the predominant diagnosis in 17 (56.7%) eyes, primary angle closure in 10 (33.3%) eyes, pseudoexfoliative glaucoma in 2 (6.7%) eyes, and pseudophakic glaucoma in 1 (3.3%) case only (Table 1). In 22 (73.3%) eyes, Enhanced trabeculectomy with 5-FU alone or combined 5-FU with subconjunctival Bevacizumab was performed and Phaco-Trabeculectomy was performed in 8 (26.7%) eyes.

The difference of means of pre-operative IOP between the groups was not statistically significant [P = 0.730]. IOP differences were analyzed at Month 6, Month 9 and 1 Year, to assess the long term effects of the drugs and were compared with pre-operative IOP as well as between the two groups (Tables 2, 3). The differences between pre-operative and post-

operative IOP in the 5-FU group was significant at both Month 6 (p = 0.003), Month 9 (p = 0.003), and 1 Year (p = 0.003), thus pointing to its surgical success in the long term period. In case of the 5-FU + Bevacizumab group, the differences between pre-operative and post-operative IOP in the 5-FU + Bevacizumab group was also statistically significant at Month 6 (p = 0.007), Month 9 (p = 0.007) and 1 year (p = 0.009). Comparison of differences in the mean IOP between the two groups did not reveal a significant difference between the two groups; either at Month 6 (p = 0.277), Month 9 (p = 0.564) or at 1 year (p = 0.256); although the mean IOP in the 5-FU + Bevacizumab group was lower on all occasions.

Table 1: Baseline patient characteristics.

Age	
Years (Mean ± SD)	62.6±7.35
Range, years	50 – 84
Gender N (%)	
Male	1 (3.3)
Female	23 (96.7)
Eye N (%)	
Right	18 (60)
Left	12 (40)
Glaucoma Diagnosis N (%)	
POAG [×]	17 (56.7)
PACG ^Σ	10 (33.3)
PXF [¶]	2 (6.7)
Pseudophakic	1 (3.3)
Pre-op Antiglaucoma Drugs	
5-FU^ø group	
Mean ± SD	3.87 ± 0.35
Range	(3-4)
5-FU + Bevacizumab group	
Mean ± SD	3.93 ± 0.26
Range	(3-4)
Surgical Procedure N (%)	
Enhanced Trabeculectomy	22 (73.3)
PhacoTrab	8 (26.7)

× Primary open angle glaucoma
 Σ Primary angle closure glaucoma
 ¶ Pseudoexfoliative glaucoma
 ø 5-fluorouracil

Table 2: IOP[§] at different time periods.

	IOP mmHg (Mean ±SD) and Range at different times			
	Pre-operative Baseline	Month 6	Month 9	1 Year
Trabeculectomy with 5-FU^ø	30.8 ± 17.03	14.33 ± 4.57	13.86 ± 4.22	14.5 ± 5.04
Mean	[Maximum 68] [Minimum 15]	[8-25]	[6-23]	[6-28]
Trabeculectomy with 5-FU^ø + S/C[‡] Bevacizumab	28.9 ± 18.9	12.8 ± 3.89	12.8 ± 3.89	12.7 ± 4.38
Mean	[Maximum 78] [Minimum 14]	[5-18]	[5-18]	[4-20]

ø 5-fluorouracil § Intraocular pressure ‡ subconjunctival

Table 3: Paired samples t-Test in the 5-FU group (IOP)& in the Bevacizumab + 5-FU group (IOP).

		Mean	Std. Deviation	Std. Error Mean	Paired Differences		
					Lower	Upper	
Pair 1	Pre-Op IOP in 5FU group - IOP at 6 months 5-FU group	16.46	17.71	4.57	6.65	26.27	.003
Pair 2	Pre-Op IOP in 5FU group - IOP at 9 months 5-FU group	16.93	18.45	4.76	6.71	27.15	.003
Pair 3	Pre-Op IOP in 5FU group - IOP at 1 year 5-FU group	16.26	17.78	4.59	6.41	26.11	.003
Pair 4	Pre-Op IOP in BVZ+5-FU group - IOP at 6 months BVZ+5-FU group	16.13	19.65	5.07	5.24	27.01	.007
Pair 5	Pre-Op IOP in BVZ+5-FU group - IOP at 9 months BVZ+5-FU group	15.86	19.68	5.08	4.96	26.76	.007
Pair 6	Pre-Op IOP in BVZ+5-FU group - IOP at 1 year BVZ+5-FU group	16.20	20.76	5.36	4.70	27.69	.009

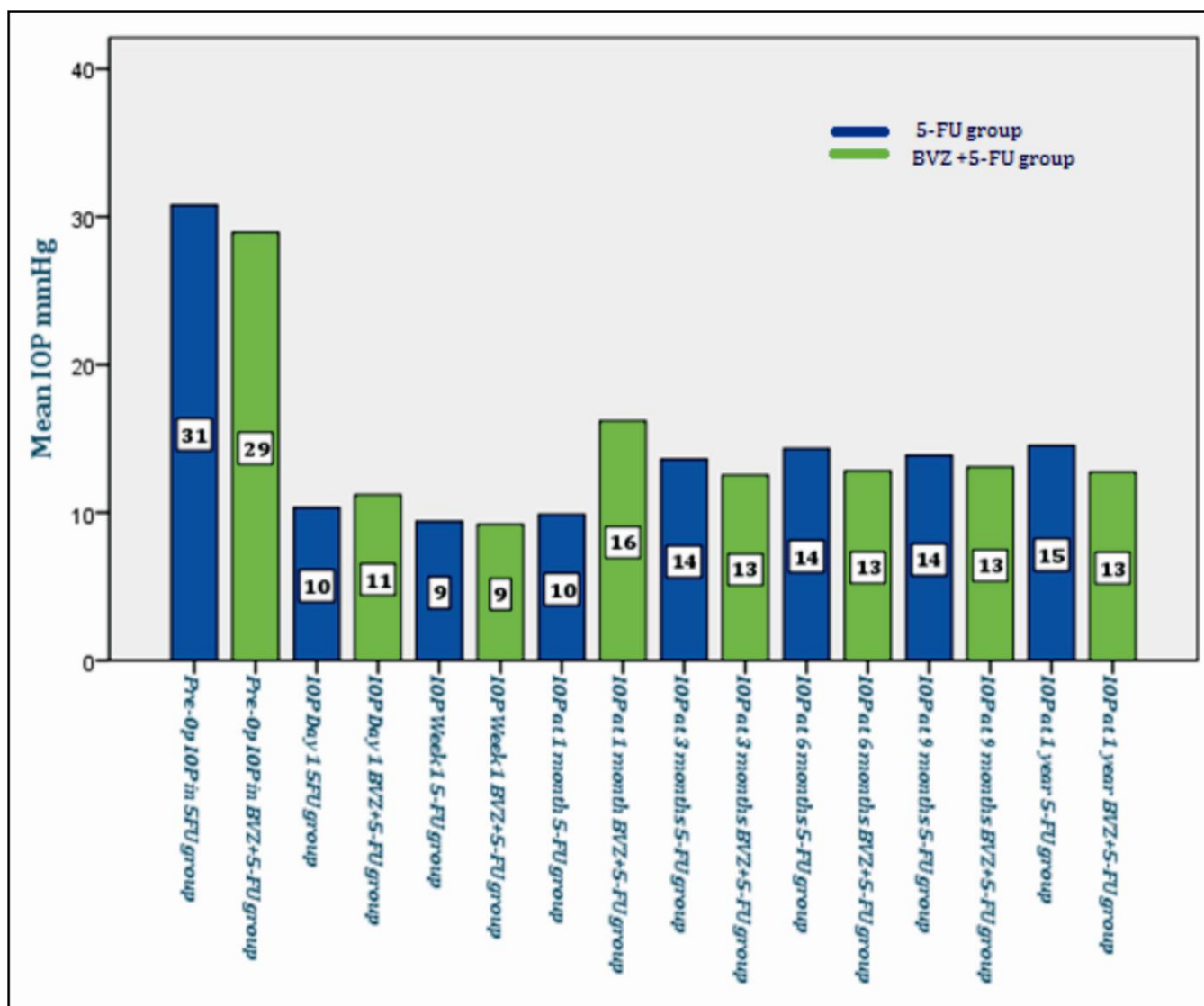


Fig. 1: Bar chart depicting the comparison of means of IOP over time in both groups.

Bleb morphology analysis and comparison between the two groups, revealed a slightly higher frequency of cystic bleb formation in the 5-FU + Bevacizumab group in 5 (16.7%) eyes, as compared to 4 (13.3%) eyes in the 5-FU group, with 1 (6.7) case of an encapsulated bleb, in the later, for which needling of the bleb was required. However, bleb morphology comparison between the two groups did not reveal statistically significant differences ($P = 0.366$) using the *Wilcoxon signed ranks test* (Table 4).

Table 4: *Bleb Analysis.*

Type of Bleb	Trabeculectomy with 5-FU N (%)	Trabeculectomy with 5-FU + S/C Bevacizumab N (%)
Type 1 Cystic	4 (13.3)	5 (16.7)
Type 2 Diffuse	10 (33.3)	10 (33.3)
Type 3 Flattened	0	0
Type 4 Encapsulated	1 (3.3)	0

Test Statistics^a

	Type of bleb Bevacizumab+5FU group - Type of bleb 5 FU group	a. Wilcoxon Signed Ranks Test
Z	-.905 ^b	b. Based on positive ranks.
Asymp. Sig. (2-tailed)	.366	

There was a significant long term reduction of drugs post-operatively in both groups. The comparison for the 5-FU group between the pre-operative drugs [3.87 ± 0.35] and the post-operative drugs at Month 6 [0.33 ± 0.48], Month 9 [0.60 ± 0.83] and 1 Year [0.73 ± 1.03] was statistically significant [$p = 0.000$]. For the 5-FU + Bevacizumab group, similarly the comparison between the pre-operative anti-glaucoma drugs [2.93 ± 0.26] and post-operative drugs at Month 6 [0.40 ± 0.83], Month 9 [0.53 ± 0.99] and 1 Year [0.60 ± 1.12] was statistically significant [$p = 0.000$]. The drugs used were dorzolamide HCL 2%, timolol maleate 0.5%, brimonidine tartarate 0.1% and latanoprost 0.005% or a combination of these agents only. The difference in anti-glaucoma agents between the two groups was not statistically significant either at Month 6 [$p = 0.499$], Month 9 [$p = 0.698$] or 1 Year [$p = 0.582$], although the number of post-operative drugs required was less in the 5-FU + Bevacizumab group, at Month 9 and 1 Year.

Early complications were encountered equally in both groups, summarized in Table 5. The differences between the two groups were not statistically significant ($p = 0.167$). Shallow anterior chamber (AC) was considered only if iris cornea touch was present in the mid-peripheral iris and this was present in 1 (3.3%) case each, which led to choroidal detachment in the 5-FU + Bevacizumab group, both of which were successfully treated with steroids and cycloplegics. One (3.3%) case of an imperforate peripheral iridectomy (PI) required Nd: YAG (neodymium: yttrium-aluminium-garnet) laser iridotomy post-operatively for completion, also in the same group. Bleb leaks were discovered in 2 (6.7%) cases of the 5-FU group, which were successfully managed with bandage contact lenses (Table 5).

Table 5: *Complications of Trabeculectomy.*

Complications	N (%)
Trabeculectomy with 5-FU	
HypHEMA	1 (3.3)
Shallow AC ^β	1 (3.3)
Failure of filtration	2 (6.7)
Bleb leak	2 (6.7)
Peaked pupil/other pupil abnormalities	1 (3.3)
Trabeculectomy with 5-FU + S/C Bevacizumab	
Epithelial defect	1 (3.3)
Imperforate PI ^α	1 (3.3)
HypHEMA	1 (3.3)
Shallow AC ^β & Choroidal detachment	1 (3.3)
Peaked pupil/other pupil abnormalities	1 (3.3)
Posterior synechiae	2 (6.7)

^α Peripheral iridectomy

^β anterior chamber

DISCUSSION

Wound healing in GFS requires four phases: hemostasis, inflammation, proliferation and remodelling of tissue. Controlled angiogenesis plays an integral part in the healing process. Glaucoma surgeons sought to use anti-VEGF agents as wound modulators to inhibit the healing response, which is vital to the success of GFS. Blockage of the fistula occurs by aggressive collagen accumulation, angiogenesis, and fibroblast activity and proliferation at the subconjunctival and episcleral level; all contributing to trabeculectomy failure and continued visual loss. Avascular blebs are associated with favourable outcomes and vascularization of the bleb is associated with loss of IOP control. Conventionally used antimetabolites like 5-FU and MMC can result in

bothersome hypotony, endothelial damage and thin blebs susceptible to leaks and infections. Although beneficial in neovascular glaucomas, Bevacizumab and Ranibizumab both have been tried for IOP control in traditional GFS but their effects are still limited and uncertain.⁸⁻¹¹

At the end of 1 year of follow-up, the results of our study indicated no significant additional benefit of subconjunctival bevacizumab used as an adjunct to 5-FU enhanced trabeculectomy; in comparison to 5-FU alone in glaucoma filtration surgery; considering hypotensive efficacy, bleb morphology or complication rate. In terms of IOP lowering, although mean IOP at 6 months, 9 months and 1 year was slightly lower in the 5-FU + Bevacizumab group on all three occasions, the differences between the two groups was not statistically significant. Previously, we reported¹² the short term results of our study, in which we did not observe any additional significant IOP lowering effect of BVZ, although at Month 3, the mean IOP in the 5-FU + Bevacizumab group was lower as compared to the 5-FU group. In both groups, the mean post-operative IOP at Month 6, Month 9 and at 1 year was significantly lower compared to the pre-operative baseline IOP, indicating surgical success of the glaucoma filtration surgery in both groups.

Our study findings are similar to those of Suh et al¹³, who stated that BVZ did not exert additional effect when used in conjunction with 5-FU in trabeculectomy at 24 months. Jukowska-Dudzińska et al¹⁴ compared 5-FU to subconjunctival BVZ in trabeculectomy and also found no significant differences between the two groups at 12 months follow-up. However, contrary to our findings, more medical therapy was required in the BVZ group post-operatively for IOP control in their study. Elgin et al¹⁵ compared a single dose of subconjunctival BVZ + 5-FU to 5-FU alone in trabeculectomy in pseudoexfoliative glaucoma and found no added benefit at 6 months in terms of IOP lowering and reported successful GFS in both groups, similar to ours. Freiberg et al¹⁶ compared adjunctive subconjunctival BVZ injections with subconjunctival 5-FU to 5-FU injections alone, in patients who underwent trabeculectomy with MMC. They found a reduction in the number of 5-FU applications in eyes in which BVZ had been applied at the end of 12 months of follow-up. However, GFS success rates were comparable in their two groups.

Many other authors have compared BVZ to MMC

in GFS and have reported their outcomes. One year outcomes reported by Kaushik et al¹⁷, of comparison of BVZ to MMC enhanced trabeculectomy in primary open angle glaucoma patients yielded comparable results in IOP lowering terms. Akkan¹⁸ et al in their one-year study comparing BVZ to MMC, found MMC to show superior IOP control. Mahdy¹⁹ et al have reported a positive role of combined BVZ-MMC trabeculectomy in recurrent pediatric glaucomas. Similarly, Arish²⁰ et al have reported superior outcomes in GFS with a single application of BVZ in the short term. El-Kasaby²¹ reported comparable outcomes between BVZ and MMC enhanced trabeculectomy. Zarei²² et al also showed no superiority after 2 weeks of topical use post-operatively in GFS with MMC.

In terms of bleb morphology, our study demonstrated a slightly higher occurrence of cystic bleb formation in the 5-FU + Bevacizumab group as compared to the 5-FU group, with early bleb failure and one case of an encapsulated bleb in the later group, which required needling. However, statistically significant differences were not observed upon bleb comparison between the two groups. Kaushik¹⁷ et al found statistically significant bleb avascularity in comparison to MMC, whereas Bitelli²⁶ et al did not observe any avascular blebs in their patients. Akkan¹⁸ et al found a higher incidence of encapsulated blebs in the BVZ group, contrary to ours. Chua²³ et al found a higher incidence of bleb related complications in the BVZ-5-FU group when compared to 5-FU alone in GFS, but central bleb avascularity was not found to be statistically significant. Liu²⁴ et al in their meta-analysis revealed a significantly higher incidence of encysted blebs as compared to MMC.

In terms of complications; an equal number of complications was noted in both groups, and the differences between the two groups were not found to be statistically significant. Contrary to what is reported in research, early bleb leaks were present in two eyes of our 5-FU group, which required Bandage contact lens application. No late bleb leaks or sweating was observed at the end of one year.

Cheng¹⁰ et al in 2016, searched extensively in the electronic database for randomized controlled trials comparing subconjunctival bevacizumab to other antimetabolites, and concluded that there is inadequate and low quality evidence to recommend or negate its use for wound modulation in GFS. Chen and co-workers²⁵ in their meta-analysis in 2018, concluded

that adjunctive use of bevacizumab (1.25 mg/mL) with a regular concentration of antimetabolites (5-FU or MMC) did not show any advantage or detrimental effect when compared with using antimetabolites alone.

Strengths of our study is that equal allotment of cases has been ensured in the two groups and meticulous follow-up has been done. All procedures were performed by one surgeon.

Limitations of our study are small sample size. We are not a glaucoma facility and not every patient with glaucoma fulfils the criteria for undergoing trabeculectomy. Recruiting patients and following them up has taken a long time. The loss of follow-up of one patient led us to recruit another one, which has taken a longer time to report our results.

However, further randomized controlled trials with larger number of patients are needed to better assess the advantages and safety of bevacizumab in GFS.

CONCLUSION

Subconjunctival bevacizumab in conjunction with 5-fluorouracil enhanced trabeculectomy does not offer any significant additional benefit in terms of IOP lowering, bleb morphology or post-operative complications; when compared to 5-FU enhanced trabeculectomy alone, at the end of a 1 year follow-up.

Ethical Approval

The study was approved by the Institutional review board/ Ethical review board. (217/FF/FUMC/ERC)

Conflict of Interest

Authors declared no conflict of interest.

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Authors' Designation and Contribution

Sana Nadeem; Assistant Professor: *Concepts, Design, Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

