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Original article

Subconjunctival Bevacizumab Versus Mitomycin-C as an Adjunctive Therapy to Trabeculectomy in Open Angle Glaucoma

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Abstract:

Background: Glaucoma is one of the leading causes that lead to blindness worldwide. **Purpose:** To compare the outcomes of sub-scleral trabeculectomy (SST) with subconjunctival Bevacizumab versus Mitomycin-C (MMC) in cases with bilateral primary open angle glaucoma (POAG). Study design: case series comparative study. **Methods:** We collected data from 60 eyes of 30 patients that were diagnosed as POAG and treated with SST and adjunctive therapy was used either with subconjunctival bevacizumab or topical intraoperative mitomycin-C, in the period from January 2021 to February 2022. We analyzed outcomes of this procedure as intraocular pressure (IOP), glaucoma medications reduction and bleb related complications. **Results:** The preoperative IOP improved significantly from 29.86±4.86 mm Hg to 11.8±2.17 mm Hg at 6th month and to 12.03±1.99mm Hg at the last follow-up in the bevacizumab group, and from 31.3±4.03 mm Hg to 10.8±2.24 mm Hg at 6th month and to 11.4±2.91 mm Hg after one year of follow-up in the MMC group. Both arms showed a significant decrease in the number of antiglaucoma eye drops used at 6 months compared with the preoperative data. In both groups, bleb show a horizontal extension of 2-3 hours, low to moderate height and mild to moderate vascularization. **Conclusions:** Trabeculectomy with adjunctive Bevacizumab is an effective and safe procedure in patients with POAG. The outcome of SST with MMC and with Bevacizumab was similar in lowering IOP. The complication rates were higher in MMC group than the Bevacizumab group. Bevacizumab is preferred in high risk bleb failure cases.

Keywords: Glaucoma, Bevacizumab, Anti-VEGF, Mitomycin-C. **Abbreviations and acronyms:** IOP = Intra-ocular pressure; MMC= Mitomycin-C, SST= subscleral trabeculectomy.

Introduction

Glaucoma is one of the leading causes that lead to blindness worldwide. Although controlling the intraocular pressure (IOP) is attainable in most of cases using topical medications, there is still a need for surgery to warrant the appropriate results in cases with poor patient compliance even with maximum lines of medications, and progressive disease. Trabeculectomy is needed in such cases with recurrence in some situations that targeting a more reduction in the IOP (1).

The success rate of the surgical intervention is related to the healing process to achieve long term results and healthy operating blebs. (1, 2) Antimetabolite agents are widely used to limit fibrosis that leads to bleb failure, two agents have been studied such as mitomycin (MMC) and 5-fluorouracil. Although, success rate is higher using antimetabolites according to previous reports (2), several adverse effects have been reported such as toxicity to the surrounding tissues as corneal endothelium (3), over filtration, bleb infection and panophthalmitis (4).

Vascular endothelial growth factors (VEGFs) have been investigated to have an important role in the healing process in glaucoma surgery (5). It has been found that VEGFs induce fibrosis in human tissues (6). VEGFs have been found in a higher concentration in the anterior chamber after glaucoma surgery. Several reports demonstrated that anti-VEGFs may reduce fibroblastic activity and healing scarring at the surgical site in trabeculectomy operation. Several anti-VEGF agents are available now, bevacizumab is still widely used for economic reasons in many developing countries. It is a monoclonal antibody that used as a systemic treatment in cancer colon (5- 7).

In this study, we aimed to compare the outcomes of trabeculectomy with intraoperative subconjunctival single dose Bevacizumab with trabeculectomy with intraoperative topical Mitomycin-C (MMC) in patients with bilateral primary open angle glaucoma (POAG).

Methods:

This is a single-center retrospective case-series comparative study that was carried out in Benha University Hospital from January 2021 to February 2022, on 60 eyes of 30 patients with bilateral primary open angle glaucoma with uncontrollable glaucoma with maximal medical therapy or intolerance for antiglaucoma medications. In this research article, eyes were divided into 2 groups each patient was represented in each group with one eye: Group 1 included 30 eyes with medically uncontrolled POAG in which subscleral trabeculectomy (SST) with intraoperative subconjunctival single dose of bevacizumab (2.5 mg/0.1 mL) was done.

Group 2 included 30 eyes with medically uncontrolled POAG in which SST with intraoperative mitomycin-C (0.3mg/1ml) topical application was done.

Exclusion criteria:

Cases with angle closure glaucoma, secondary open angle glaucoma (post-traumatic, uveitic, neovascular, or dysgenetic glaucoma or pseudoexfoliative glaucoma). Patients with previous ocular surgery, preliminary conjunctival damage (trauma, vitreo-retinal surgery, previous glaucoma surgery, and other) and cases under 18 years of age.

All participants were subjected to: Full history taking, past history of topical anti-glaucoma medications (The number of antiglaucoma treatment was calculated as the total number of all antiglaucoma eye drops. For the combined eye drops, a score of 2 was calculated). History of systemic diseases e.g., Diabetes, hypertension, family history of glaucoma…….

Ophthalmological examination:

Full ophthalmological examination was done as follows: Best Corrected Visual Acuity (BCVA) using Snellen's chart, refraction using an auto-refractometer to assess astigmatism for more accurate

applanation reading. Intraocular pressure (IOP) measurement using Goldman applanation tonometer (AT 900, Haag-Streit AG, Könitz, Switzerland), anterior segment examination using slit lamp biomicroscoy- to exclude other causes of secondary glaucoma e.g., Keratic precipitates (KPs), Iris neovascularization, Pseudoexfoliation material. Gonioscopy using the Goldman 3-mirror contact lens, to assess: Angle grade using the Schaffer grading system and any abnormal angle structures suggesting secondary open angle glaucoma. Dilated fundus examination using indirect ophthalmoscope and the 90 diopter Volk lens to assess cup/disc (C/D) ratio.

Investigations were done to all subjects as follows:

Visual field examination was done by (Swedish Interactive Threshold Algorithm Standard test of central 24-2) using the Humphrey Field Analyzer 750 (Humphrey-Zeiss Instruments, Dublin, CA).

This study followed the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of Faculty of Medicine, Benha University, EGYPT (RC-8-2012).

Surgical techniques:

The procedure was done by the same surgeon (M.A) as follows: Regional peribulbar anesthesia, instillation of Povidine Iodine 5% in the conjunctival sac and wash out. A 7/0 virgin silk superior corneal traction suture was inserted at the superior limbus and at the selected site of loose healthy conjunctival fornix-based flap was dissected. Hemostasis was achieved with wet field cautery. A (4×4 mm) half-thickness scleral flap was created and dissected until reaching the clear cornea. Only in eyes in the MMC group, a cellulose microsponge was dipped in MMC solution which was diluted to be in 0.3 mg/mL concentration (Mitomycin-C Kyowa®; Kyowa Hakko kogyo, Tokyo, Japan) then it was applied for 3 minutes under the scleral flap and in between the sclera and Tenons capsule, then the microsponge was removed the surgical field washed well with irrigating balanced salt saline. Tenon's capsule over the scleral flap was excised. The anterior chamber was entered with a micro vitreoretinal (MVR) blade at 9 o'clock or 3 o'clock site via the limbus. A trabeculectomy with a flap width diameter of 2 × 2 mm was performed using a Vanna's scissors, then a using scissors a peripheral iridectomy was performed. The flap was closed with two 10-0 Nylon suture one at each corner of the flap. The conjunctiva was tightly closed with 8/0 Vicryl® sutures (Vicryl® polyglactin 910; Ethicon Inc, Johnson & Johnson, Somerville, NJ, USA).

Only in bevacizumab group single subconjunctival bevacizumab (2.5 mg/0.1 mL) (Avastin®; Genentech, San Francisco, CA, USA) was injected by cannula near the flap edges and towards the posterior conjunctiva.

Post-operative management:

All patients were treated with, prednisolone acetate 1% and gatifloxacin 0.3%, eye drops were administered five times daily for 3 weeks, and cyclopentolate 1% eye drops 3 times daily for 2 weeks.

Post-operative visits were scheduled at day 1, day 7, 1 month, 3 months, 6 months and 12 months.

At each visit, IOP, slit lamp biomicroscopy and complications including the need for anti-glaucoma

medications or surgical intervention were recorded.

The primary outcome was the IOP. Secondary outcome included the number of antiglaucoma medications, postoperative interventions, complications, and bleb evaluation.

Efficacy was defined as reduction in postoperative IOP.

(a) IOP lower than 21 mmHg without any antiglaucoma eye drops was defined as *"Complete successes"*.

(b) IOP lower than 21 mmHg with topical antiglaucoma was defined as "*Qualified successes*".

(c) "*Failure*" was defined when an IOP was measured higher than 21 mmHg in 2 subsequent visits, even with topical antiglaucoma eye drops or when adding more lines is needed or further surgery.

(d) IOP < 5mmHg was defined as *"Hypotony"*.

Bleb photos were obtained at months 3, 6 and 12 months follow up visits. Bleb photos at the last follow-up were graded to compare this study outcomes with benchmark released before on 2003 as which was the Indiana Bleb Appearance Grading Scale (IBAGS), which is based on extent, height, vascularization and seidel test (7).

Statistical methods

To test for normal distribution frequency, data was plotted against normal distribution curve and one sample Kolmogorov-Smirnov test was used. Parametric statistical methods were used. Mean and standard deviation were used to describe data. Fisher exact test (FET) was used to test for significance of difference between each two groups and for significance of difference between pre and postoperative values in the same group. P value was considered significant if less than 0.05. These tests were run on an IBM compatible personal computer using the Statistical Package for Social scientists (SPSS) version 16b for windows (SPSS Inc., Chicago, IL, USA).

Results:

In this study we analyzed the outcomes of 60 eyes with bilateral open angle glaucoma that underwent trabeculectomy and were divided into 2 groups: Group A: (30 eyes) that were treated with subscleral trabeculectomy (SST) with intraoperative subconjunctival single dose of bevacizumab. Group B: (30 eyes) that were treated with SST and intraoperative mitomycin-C topical application.

Demographic data:

There were no demographic characteristics difference between the two groups as all included patients had bilateral POAG, and every patient was represented in group (A) with one eye and in group (B) with the other eye.

IOP reduction:

There were no statistical differences have been reported between both groups in the preoperative mean IOP (Table 2) or the number needed for antiglaucoma topical drops (Table 1).

The preoperative IOP improved significantly from 29.86±4.86 mmHg to 11.8±2.17 mmHg at the 6th month and to 12.03±1.99 mmHg after 12 months of follow-up in the bevacizumab group, and from 31.3±4.03 mm Hg to 10.8±2.24 mm Hg at month 6 and to 11.4±2.91 mm Hg after 12 months of follow-up in the MMC group (Figure 1).

As regards IOP reduction in bevacizumab group (Table 3) there was a significant reduction of IOP in all postoperative measurement as compared to preoperative, and non-significant difference between

postoperative IOP reductions in all follow up visits.

As regards IOP reduction in MMC group (Table 4) there was a significant reduction of IOP in all postoperative measurement as compared to preoperative, and non-significant difference between postoperative IOP reductions in all follow up visits.

Table (1) Demonstrates the number of preoperative anti-glaucoma medications for studied groups.

No of patients	*Group A Bevacizumab (N=30)*	*Group B MMC (N=30)*
Three medications	***25 (83.3%)***	***24(80%)***
Two medications	***3 (10%)***	***5(6.7%)***
one medication	***2 (6.7%)***	***1(3.3%)***
no medication	***0***	***0***
Test of significant	***X2=0.85***	
P value	***0.65***	

Table (2): Comparing IOP measurement between both studied groups.

		Group A Bevacizumab (N=30)	*Group B MMC (N=30)*	*P-value*
preoperative		29.86±4.86	31.3±4.03	0.2
postoperative	1 D	10.76±3.51	9.9±3.32	0.3
	1 W	11.5±3.35	10.00±3.02	0.07
	1 M	11.8±2.94	10.46±3.03	0.08
	3 M	11.66±2.73	10.56±2.54	0.11
	6 M	11.8±2.17	10.8±2.24	0.08
	12 M	12.03±1.99	11.4±2.91	0.33

MMC= mitomycin-C Fisher exact test (FET) was used to test for significance of difference between each two groups and for significance of difference between pre and postoperative values in the same group. P value was considered significant if less than 0.05.

Table (3) The mean reduction in IOP in bevacizumab group.

	Preoperative	*postoperative*				
	1D	***1 W***	***1 M***	***3 M***	***6 M***	***12 M***
Preoperative	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***
postoperative ***1D***		***0.4***	***0.22***	***0.27***	***0.17***	***0.09***
1 W			***0.7***	***0.8***	***0.6***	***0.4***
1 M				***0.8***	***1.00***	***0.7***
3 M					***0.8***	***0.5***
6 M						***0.6***
12 M						

Table (4) The mean reduction in IOP in MMC group.

		Preoperative	*postoperative*				
			1D	***1 W***	***1 M***	***3 M***	***6 M***	***12 M***
Preoperative			***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***
postoperative	***1D***			***0.9***	***0.4***	***0.3***	***0.22***	***0.06***
	1 W				***0.55***	***0.43***	***0.25***	***0.07***
	1 M					***0.8***	***0.63***	***0.22***
	3 M						***0.7***	***0.24***
	6 M							***0.37***
	12 M							

Fisher exact test (FET) was used to test for significance of difference between each two groups and for significance of difference between pre and postoperative values in the same group. P value was considered significant if less than 0.05.

Anti-glaucoma medications:

Both groups in this study showed a significant decrease in the number of topical IOP lowering medications used at 6 months when compared to the preoperative ones (Table 1). On the 6th month visit, 28(93.3%) of the eyes in group with MMC were stopped using topical IOP lowering medications, compared to the 27(90%) in the bevacizumab group. There were no significant changes between both groups in the number of topical eye drops at the 3rd month (P=0.49) and 6th month (P=0.6) (Figure 2) and (Table 5).

Bleb characteristics at the 12 months of follow-up in both groups is shown in (Table 6). Bleb characteristics showed statistically non-significant difference between both groups in scores on IBAGS. In both groups' bleb showed a horizontal extension of 2-3 hours (p=0.3), low to moderate height (p=0.9) and mild to moderate vascularization (p=0.16) (Figure 3).

Figure (4) shows example of cases in group A and B illustrating the surgical steps of the procedure.

According to intraoperative and post-operative complications the difference of incidence between both study groups was statistically non-significant, however, blebitis and encysted bleb occur more with MMC group.

Table (5) The mean number of prescribed anti-glaucoma medications used preoperatively and post-operatively in both studied groups.

No of patients	*preoperative*		*Postoperative 3 m*		*Postoperative 6 m*	
	Group A (n=30) Bevacizumab	***Group B (n=30) MMC***	***Group A (n=30) Bevacizumab***	***Group B (n=30) MMC***	***Group A (n=30) Bevacizumab***	***GroupB (n=30) MMC***
Three medications	***25(83.3%)***	***24(80%)***	***0***	***0***	***0***	***0***
Two medications	***3 (10%)***	***5(6.7%)***	***1(3.3%)***	***0***	***2(6.7%)***	***2 (6.7%)***
one medication	***2 (6.7%)***	***1 (3.3%)***	***2 (6.7%)***	***1 (3.3%)***	***1 (3.3%)***	***0 (0%)***
no medication	***0***	***0***	***27 (90%)***	***29 (96.7%)***	***27 (90%)***	***28 (93.3%)***
Test of significant	***X2=0.85***		***X2=1.4***		***X2=1.01***	
P value	***0.65***		***0.49***		***0.6***	

MMC= mitomycin-C

Fisher exact test (FET) was used to test for significance of difference between each two groups and for significance of difference between pre and postoperative values in the same group. P value was considered significant if less than 0.05.

Table (6) The different bleb scores in both groups.

Variables	Group A Bevacizumab N=30	Group B MMC N=30	P value
Extent	2.12±0.51	1.99±0.48	0.3
Height	1.78±0.45	1.79±0.5	0.9
vascularity	2.5±0.52	2.3±0.57	0.16

MMC= mitomycin-C

Fisher exact test (FET) was used to test for significance of difference between each two groups and for significance of difference between pre and postoperative values in the same group. P value was considered significant if less than 0.05.

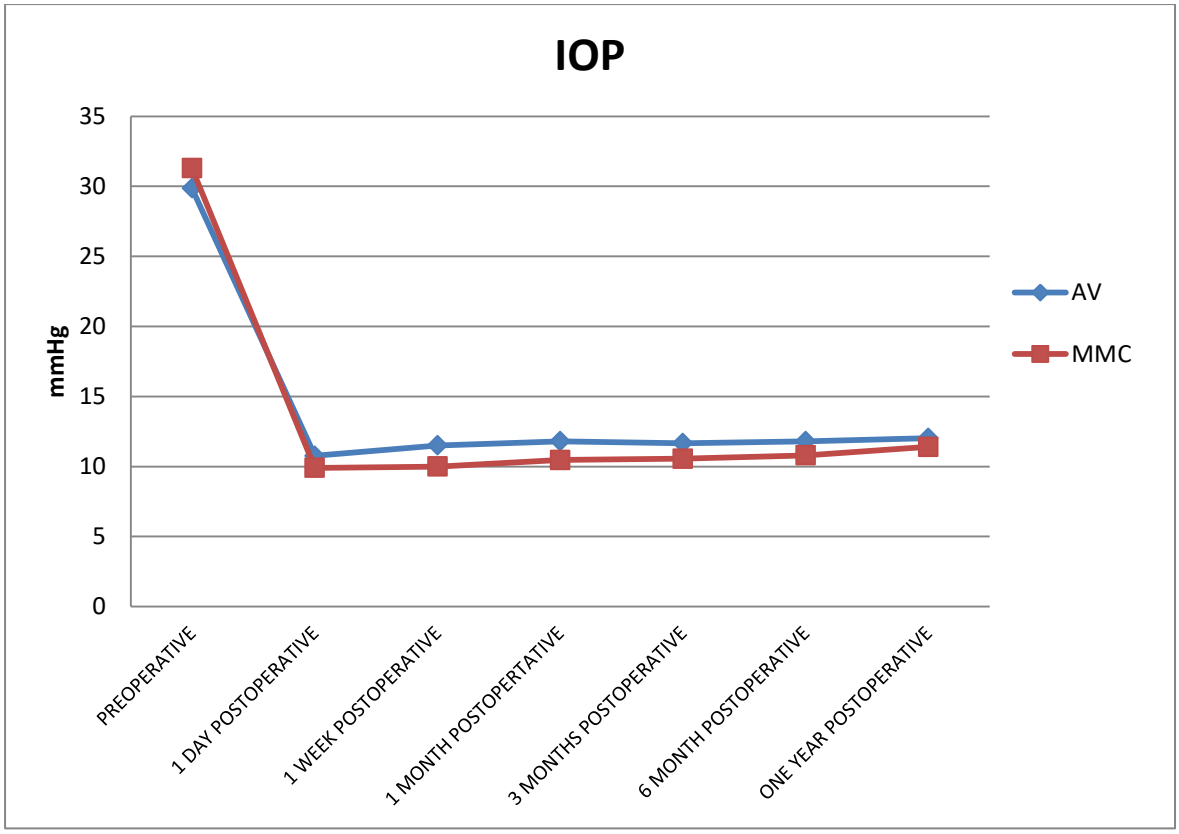

Figure (1) IOP measurement and p values at each follow-up visit in study groups.

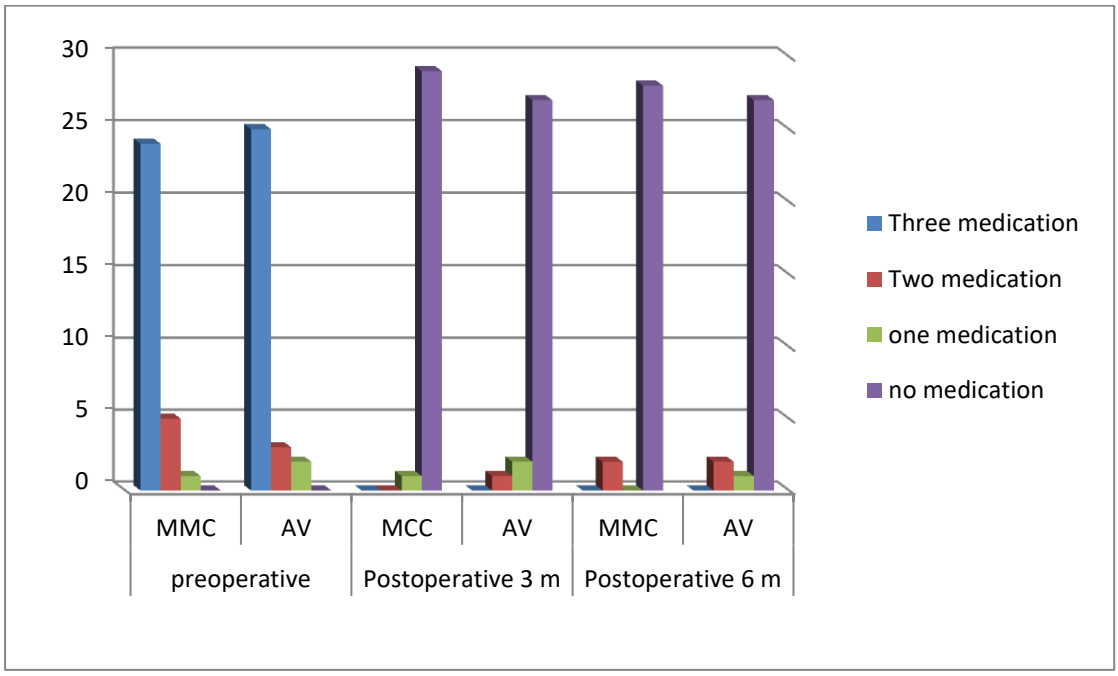

Figure (2) The mean number of prescribed anti-glaucoma medications used preoperatively and post-operatively in both groups.

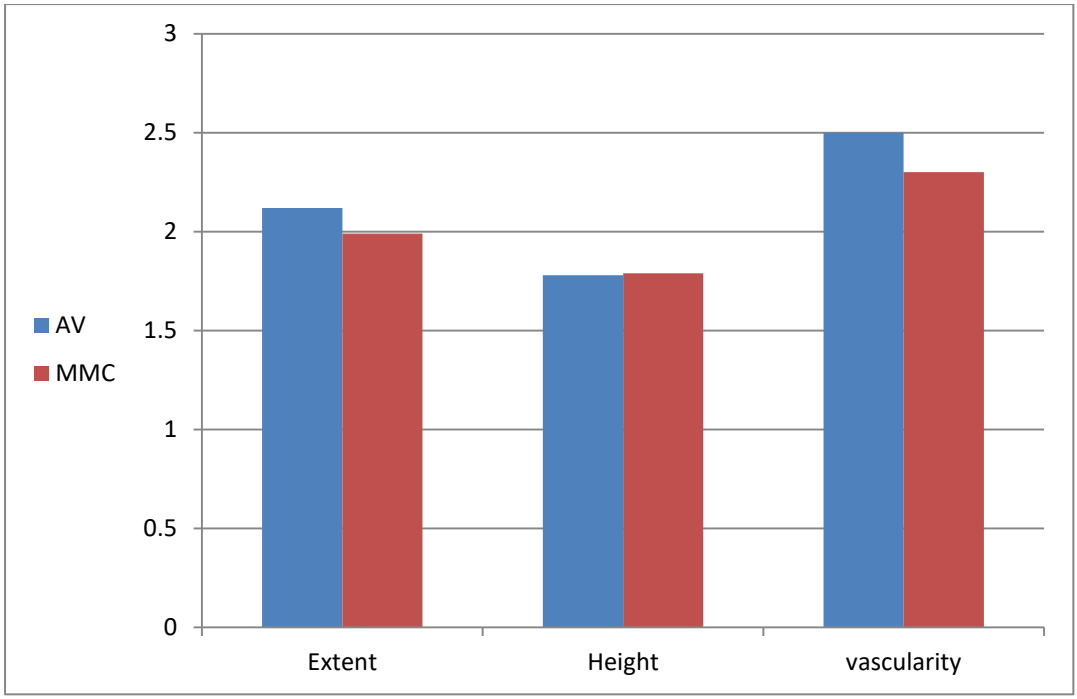

Figure (3) Represents IBAGS for the studied groups.

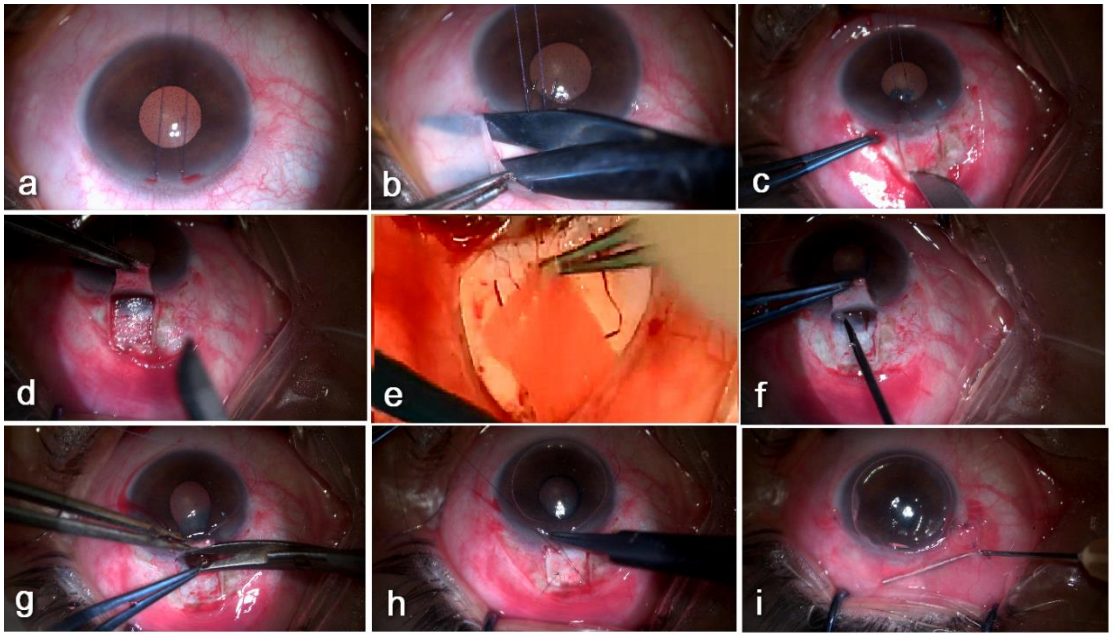

Figure (4) Intraoperative steps: **a)** Tractional suture**, b)** Dissection of conjunctiva, **c)** Creation of A (4×4 mm) half-thickness scleral flap**, d)** Dissection of scleral flap**, e)** MMC application**, f)** opening a trabeculectomy of 2 × 2 mm**, g)** peripheral iridectomy**, h)** The scleral flap was closed with two 10-0 Nylon suture**, i)** Injection of sub conjunctival bevacizumab.

Discussion:

Glaucoma is a chronic disease that may leads to persistent visual damage. In depth preview of the disease has been studied by the World Health Organization (WHO), which concluded that the incidence of new glaucoma cases that have been confirmed with the diagnosis of POAG is 2,400,000 per year (8). The blindness is the fate for advanced cases which is avoidable if the appropriate management is performed. The incidence of blindness among POAG cases is reported to be 3,000,000 cases (9).

SST is still the mainstay surgical intervention used for glaucoma. Several factors have been postulated for successful surgery as decreasing the wound healing response, which have been reported to be mediated by activation of fibroblasts proliferation (10, 11).

In this single-center study, we studied 60 eyes with POAG in patients with bilateral glaucoma. They were divided into 2 groups: Group A: Included 30 eyes treated with trabeculectomy with intraoperative subconjunctival single dose of bevacizumab. Group B: Included 30 eyes treated with trabeculotomy with intraoperative mitomycin C topical application.

In 2008, a pilot study was conducted on 12 cases with uncontrolled POAG. An adjunctive therapy was used in the form of sub-conjunctival injection of bevacizumab in a single dosage of 1.25 mg/0.05mL. Their results showed a mean IOP reduction of 52%, and at the 6th month of follow-up, a mean IOP of 11.6 mm Hg without any topical eye drops was reported. No reported systemic adverse effects related to bevacizumab, but their study had no control group to compare with (12, 13).

In 2012, a comparative prospective study based on randomized selection of the adjunctive therapy for POAG, there was an incidence of 34% in the bevacizumab arm that showed IOP reduction compared to baseline parameters, and on the other arm, 56% reduction among MMC group, the MMC showed significant better IOP effect (14).

Another study in 2011 compared the results of bevacizumab after SST as an adjunctive therapy versus injection of normal saline as a placebo, they concluded that the mean IOP was 28.4 mmHg at baseline which was reduced to a value of 12.1 mmHg on the first day and 15.1 mmHg after 3 months, but adding bevacizumab to SST didn't affect IOP reduction when compared to placebo (15).

The reduction in mean IOP from 29.86±4.86 to 12.03±1.99 at the last visit in bevacizumab group in our study is more than their study. The difference may be due to short follow up time in their study.

In 2012, a study conducted on 38 cases with cataract and POAG and chronic narrow angle glaucoma which were randomized to 3 groups. 1st group received MMC (n=13); the 2nd group was received three bevacizumab sub-conjunctival injections in a dose of (1.25mg in 0.05 mL) (n=13); and the 3rd group received micro sponge soaked with bevacizumab on the sclera (concentration of 1.25mg in 0.05 mL) (n=12). Subjects were followed up to 6 months. They concluded that bevacizumab group had 90% significant success, when compared to 60% every other group. Their conclusion was that the bevacizumab was noted to be useful adjunctive therapy for raising the success rate after combined

cataract and glaucoma surgery. On the other hand, bevacizumab soaked in a sponge had no advantages over MMC results (16).

The results of our study are similar to their results, in the group of subconjunctival bevacizumab but better than it in other group, this may be due to the included non-effective bevacizumab soaked in sponges' group.

Another study in 2016, concluded that intracameral injection of bevacizumab with a dosage of 1.25 mg improved the success rate of SST significantly. Their study was done on 32 patients in bevacizumab group and the placebo group which included a number of 33 subjects. On their last visit, the IOP was 14.5±3.7 mmHg in the bevacizumab group and 18.55±3.64 mmHg in the placebo group. In their study complete success was found in 26 subjects (81.3%) of bevacizumab group and just 16 cases (48.5%) among placebo group (17).

The reduction in mean IOP from 29.86±4.86 to 12.03±1.99 at the last visit in bevacizumab group in our study is more than that in Fakhraie et al. Also, the complete success is higher in our study (90%), that may be due to the difference in administration rout of bevacizumab.

Regarding the bleb architecture at 12 M, in this study we had no significant differences in the bleb extent, height, and vasculature according to the reference scale *"indian bleb grading scale* (IBAGS)". The vascularity in bevacizumabe group is low at first 3 m then the bleb vascularity started to increase. Thus, explaining the prevention of cystic avascular blebs formation, which are clinically more prone to scar formation after SST. The only case which develops non infected babilitis was in the MMC group and start with mild leakage in central area of the bleb. That may be due to cellular toxicity of MMC. Two eyes develop encysted bleb in bevacizumab group and 3 eyes in MMC group.

Regarding to bleb morphology and scaling, there was no difference between our study results and other similar studies. Regarding to intraoperative and post-operative complications, there are no significant difference between the two groups of our study.

Only one eye (3.3%) in group MMC, had intraoperative buttonhole managed with suturing. Two eyes (6.7%) in MMC group, had shallow anterior chamber on the first postoperative day. One eye (3.3%) in MMC group after 10 months postoperative, had blebitis associated with hypopyon. The case was managed with systemic and topical antibiotics, with prophylactic intracameral and intravitreal injection of antibiotics, after one week of the follow up the condition start to improve then resolved within the next two weeks without need to any surgical intervention. One eye (3.3%) in bevacizumab group, had failed bleb, with IOP 24 mmHg, with flat bleb. The IOP stays 22mmhg with medical treatment so that trabeculectomy revision surgery was done.

Among three (10%) eyes in the MMC group, an encapsulated bleb was detected, which is a localized bleb formed but with a high IOP. On the other hand, among bevacizumab group, two (6.7%) eyes showed encapsulated bleb on the 3rd month and the 6^{th} month of follow up. However, all eyes with an encapsulated bleb were improved with needling procedure 1-time only.

In conclusion, SST with Bevacizumab is a safe and effective procedure in patients

with primary open angle glaucoma. The outcome of trabeculectomy with MMC and with Bevacizumab was similar in lowering IOP. The complication rates were higher in MMC group than the Bevacizumab group. Blebs in the group with Bevacizumab were less vascular compared with group with MMC only in the early follow up (3 month), but it become equal after that. Bevacizumab may for instance be preferred in patient with high risk of bleb failure and when IOP lowering and maximum safety are required, such as in high hyperopia, hemorrhagic risk, and monocularity.

Authors recommend the use of intraoperative subconjunctival single dose bevacizumab in SST for avoiding the potentially dangerous complications related to MMC use in the early follow-up period.

The limitations in this study are small sample size, didn't address the changes in corneal endothelium. Thus, further studies are recommended with longer follow-up period and larger sample size to strengthen the outcomes of this study.

Data availability:

The data of patients used to support the results of this study are limited by the Research Ethics Committee of the Faculty of medicine, Benha University. Data are available to researchers who meet the criteria for accessing confidential data at the request of Dr. Mohamed anany elsayed, lecturer of Ophthalmology, Benha University, Egypt. E-mail: anany71@hotmail.com.

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