IJMA

International Journal of Medical Arts

Volume 6, Issue 3, March 2024

P- ISSN: 2636-4174
E- ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main Subject [Ophthalmology]

Original Article

Evaluation of The Efficacy of Aflibercept versus Mitomycin C in Trabeculectomy in Cases of Primary Open Angle Glaucoma

Abd Elmaksoud Hussien Abd Elmaksoud *[1], Younis Alsaied Abd Elhafez [1], Sayed Abbas Sayed [2], Ali A. Ghali [1]

[1] Department of Ophthalmology, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt
[2] Department of Ophthalmology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Article information

Received: 19-10-2023

Accepted: 21-11-2023

DOI: 10.21608/IJMA.2023.243536.1843.

*Corresponding author

Email: dr.abozahra87@gmail.com

Citation: Abd Elmaksoud AH, Abd Elhafez YA, Sayed SA, Ghali AA. Evaluation of The Efficacy of Aflibercept versus Mitomycin C in Trabeculectomy in Cases of Primary Open Angle Glaucoma. IJMA 2024 March; 6 [3]: 4196-4207. doi: 10. 21608/IJMA.2023.243536.1843.

ABSTRACT

Background: Post-operative scarring at the bleb site is a major factor in whether or not a trabeculectomy is successful. Mitomycin C and anti-vascular endothelial growth factor drugs like Aflibercept have been frequently used as supplementary treatments to trabeculectomy.

Aim of the Study: This study aims to compare the efficacy of aflibercept and mitomycin c in trabeculectomy in patients with primary open-angle glaucoma.

Patients and Methods: This prospective interventional study was carried out in Al-Azhar University Hospital in New Damietta from 2021 to 2023 on 40 patients with uncontrollable bilateral primary open angle glaucoma. Patients were divided into 2 groups each patient was represented in each group with one eye: Group 1, Included 20 eyes with medically uncontrolled primary open-angle glaucoma in which sub scleral trabeculectomy with intraoperative mitomycin C [0.3mg/1ml] topical application was done. Group 2, Included 20 eyes with medically uncontrolled primary open-angle glaucoma in which subscleral trabeculectomy with intraoperative subconjunctival single dose of Eylea [2 mg / 0.05 mL] was done.

Results: According to the IOP, we found a statistically significant reduction in the IOP from 25 [23-28] mmHg in group 1 and 25 [23-28] mmHg in group 2 at the baseline to 14 [13-15] mmHg in group 1 and 16 [15-16] mmHg in group 2 at 12 months postoperative [P = 0.001]. In terms of the Bleb evaluation, the Mainz score was used for the Bleb assessment all over the follow-up periods. It consists of seven main domains, bleb height, peripheral vascularity, central vascularity, transparency, microcyst formation, and conjunctival mobility. We found no statistically significant difference between the 2 groups as regards all Mainz domains over the follow-up periods [P > 0.05 for all].

Conclusion: The use of intraoperative subconjunctival single-dose Aflibercept in trabeculectomy is safe effective and comparable to the use of MMC in terms of the advantage of avoiding the potentially dangerous complications related to MMC use.

Keywords: Aflibercept; Eylea; Mitomycin c; Trabeculectomy; Primary open-angle glaucoma.

INTRODUCTION

Glaucoma is a chronic and progressive optic neuropathy that leads to distinct morphological alterations at the optic nerve head and in the retinal nerve fiber layer [1].

The prevalence of glaucoma among those aged 40 years and above ranges from 2% to 3%, with a significant proportion of cases, potentially up to 50%, remaining untreated. It ranks as the second most prevalent cause of visual impairment globally. Primary open-angle glaucoma [POAG] is the prevailing variant observed among individuals of Caucasian descent [2].

According to published guidelines for the management of POAG, medical intervention, such as the administration of topical eye drops, is seen as a viable initial course of treatment [3].

Topical medical therapy has demonstrated efficacy in reducing intraocular pressure [IOP]; however, it is not without limitations and drawbacks. These include financial implications, potential local and systemic adverse effects, challenges related to patient adherence and persistence, physical obstacles to self-administration [such as tremors or arthritis], and the requirement for long-term daily medication adherence [4].

Cairns first described his breakthrough trabeculectomy treatment for treating glaucoma in 1968. By cutting away some of the trabecular meshwork and the iris, a trabeculectomy creates an artificial passageway between the anterior chamber and the subconjunctival area. By draining out of the eye through this opening, aqueous humor [AH] forms a subconjunctival filtration bleb, which reduces intraocular pressure [5].

Histological analyses suggest that fibroblast growth in the subconjunctiva, thought to play a significant role in bleb failure, occurs on days 3–5 [6].

Filtration failure, caused by scarring at the level of the conjunctiva-tenon's-episcleral interface, the sclera flap, or the internal ostium, may impair long-term intraocular pressure control after glaucoma surgery [6].

The primary factor contributing to unsuccessful filtration procedures is the natural postoperative process of wound healing and scar development. Non-functional fistulas can develop as a result of scar tissue brought on by fibroblast growth following trabeculectomy [7].

Mitomycin C [MMC] has been found to effectively inhibit the proliferation of fibroblasts, hence preventing the formation of scar tissue in filtration blebs [8].

Trabeculectomy outcomes are highly correlated with postoperative scar management around the bleb development site. Mitomycin C and 5-fluorouracil are two examples of antimetabolite medicines commonly used in conjunction with trabeculectomy to improve wound healing. Complications such as corneal endothelial cell toxicity, hypotony, phlebitis, and endophthalmitis are present alongside the medicines' beneficial effects on the long-term outcome of trabeculectomy [9].

Bevacizumab, a humanized nonselective monoclonal antibody targeting vascular endothelial growth factor [VEGF], is anticipated to play a role in the suppression of scar formation and fibrosis by suppressing angiogenesis [10].

Patients who underwent a trabeculectomy exhibited higher levels of vascular endothelial growth factor [VEGF], which were subsequently lowered considerably with the administration of bevacizumab. Therefore, it is possible that bevacizumab could be effective in the context of trabeculectomy [11].

VEGF Trap-Eye/Aflibercept [EYLEA®-Regeneron Pharmaceuticals, Inc., Tarrytown, New York, NY, and Bayer Healthcare Pharmaceuticals, Berlin, Germany] represents a newly developed anti-VEGF drug with a molecular weight of 115-kDa. The fusion protein has been created utilizing the "trap technology" approach, wherein the extracellular binding domains of VEGF receptor [VEGFR] -1 and -2 are merged with the Fc portion of the human immunoglobulin-G1 backbone [12].

Aflibercept, like ranibizumab and bevacizumab, binds to all VEGF-A isomers. The binding of aflibercept to VEGF-B and placental growth factor has led to the speculation that the drug's efficacy can be improved by inhibiting these factors [12].

The aim of this study is to compare the efficacy of aflibercept and mitomycin c in trabeculectomy in patients with primary open-angle glaucoma.

PATIENTS AND METHODS

This prospective interventional study was carried out in Al-Azhar university hospital in New Damietta from 2021 to 2023 on 40 patients with uncontrollable bilateral primary open angle glaucoma with maximal medical therapy or intolerance for antiglaucoma medications. Our study followed the Helsinki declaration principles. Ethical approval was obtained from the ethical approval committee of Al-Azhar University. Signed informed consent was obtained from every patient before the recruitment. Patients were divided into 2 groups each patient was represented in each group with one eye: Group 1, Included 20 eyes with medically uncontrolled primary open angle glaucoma in which sub scleral trabeculectomy with intraoperative mitomycin C [0.3 mg/1 ml] topical application was done. Group 2, Included 20 eyes with medically uncontrolled primary open angle glaucoma in which sub scleral trabeculectomy with an intraoperative subconjunctival single dose of Eylea [2 mg / 0.05 mL] was done.

The Exclusion criteria were: [1] Angle closure glaucoma, [2] Secondary open angle glaucoma [post-traumatic, uveitic, neovascular, or dysgenetic glaucoma or pseudoexfoliative glaucoma], [3] Patients with previous ocular surgery, [4] Preliminary conjunctival damage [trauma, vitreoretinal surgery, previous glaucoma surgery, and other], and [5] Under 18 years of age.

Data collection: Complete medical history and general examinations were done for every patient at the time of recruitment. Ophthalmological examination was done in the form of, Anterior segment examination using slit lamp biomicroscopy to exclude other causes of secondary glaucoma e.g. Keratic precipitates [KPs], Iris neovascularization, and Pseudoexfoliation material, Best corrected Visual acuity [BCVA] measurement 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], Gonioscopy using the Goldman 3-mirror contact lens, to assess: [1] Angle grade using the Schaffer grading system, [2] Any abnormal angle structures suggesting secondary open angle glaucoma e.g. neovascularization, hyper-pigmentation. Dilated fundus examination using indirect ophthalmoscope and the 90 diopter Volk lens to assess, [1] C/D ratio, [2] Peri-papillary area. For each patient, we used the Humphrey Field Analyzer 750 [Humphrey-Zeiss Instruments, Dublin, CA] to perform a visual field perimetry [Swedish Interactive Threshold Algorithm Standard 24-2].

Surgical techniques

Under local peribulbar anesthesia, and sterilization by instillation of Povidine Iodine 5% in the conjunctival cul de sac and wash out. A 7/0 virgin silk superior corneal traction suture was inserted. At the superior limbus and the selected site of loose healthy conjunctiva fornix-based conjunctival 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 [Figure 1].

Only in eyes in the MMC group, A cellulose microsponge, which had been immersed in a solution containing 0.3 mg/mL of Mitomycin-C Kyowa® [manufactured by Kyowa Hakko kogyo, Tokyo, Japan], was utilized for a duration of 3 minutes. This application was performed underneath the scleral flap and within the space between the sclera and Tenons capsule. Subsequently, the sponge was extracted and the entire area was gently and generously cleansed using irrigating saline [Figure 2].

Tenon's capsule over the scleral flap was excised. The anterior chamber was entered with a MVR through the limbus. A surgical procedure known as trabeculectomy, including the use of Vanna's scissors, was conducted to create an incision measuring 2 × 2 mm. Additionally, a peripheral iridectomy was performed as part of the procedure. The closure of the scleral flap was achieved with two 10-0 Nylon sutures, with one stitch placed at each corner. The conjunctiva was securely closed with 8/0 Vicryl® sutures, specifically Vicryl® polyglactin 910, manufactured by Ethicon Inc, a subsidiary of Johnson & Johnson, located in Somerville, NJ, USA.

Only in the Eylea group A single administration of Aflibercept [2 mg/ 0.05 mL] [Aflibercept ®; Genentech, San Francisco, CA, USA] was performed using a blunt cannula, which was inserted via the securely closed conjunctiva. It was applied near the flap edges and into the posterior conjunctival space beyond its upper edge.

Bleb evaluation: Bleb was evaluated using the Mainz Bleb Appearance Grading System [MaBAGS], which consists of evaluation of the central and peripheral vascularity, microcysts, bleb transparency, area, height, mobility of bleb conjunctiva, and Seidel test [13].

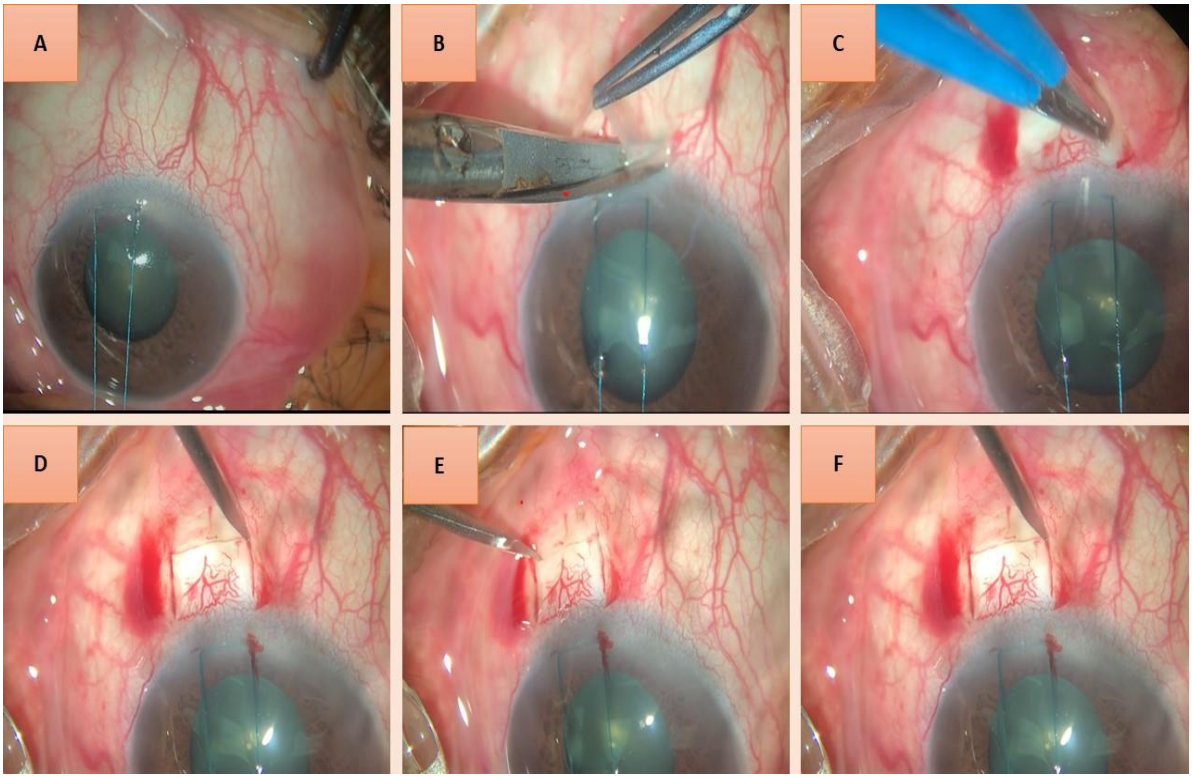

Figure [1]: [A]: Traction suture, [B]: Conjunctival incision, [C]: Scleral cautery, [D and E]: Scleral incision, [F]: Scleral discission

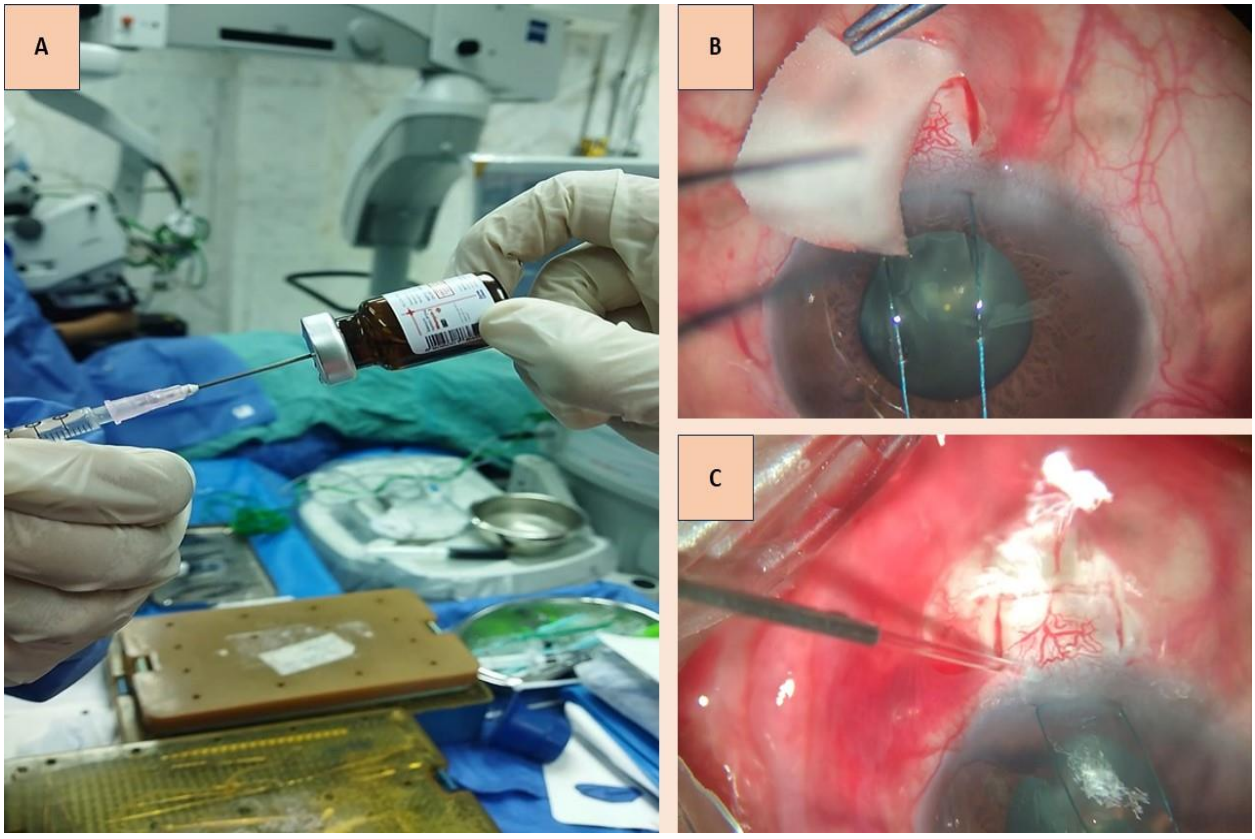

Figure [2]: [A]: Mitomycin C preparation, [B]: MMC soaking, [C]: Irrigation after MMC soaking

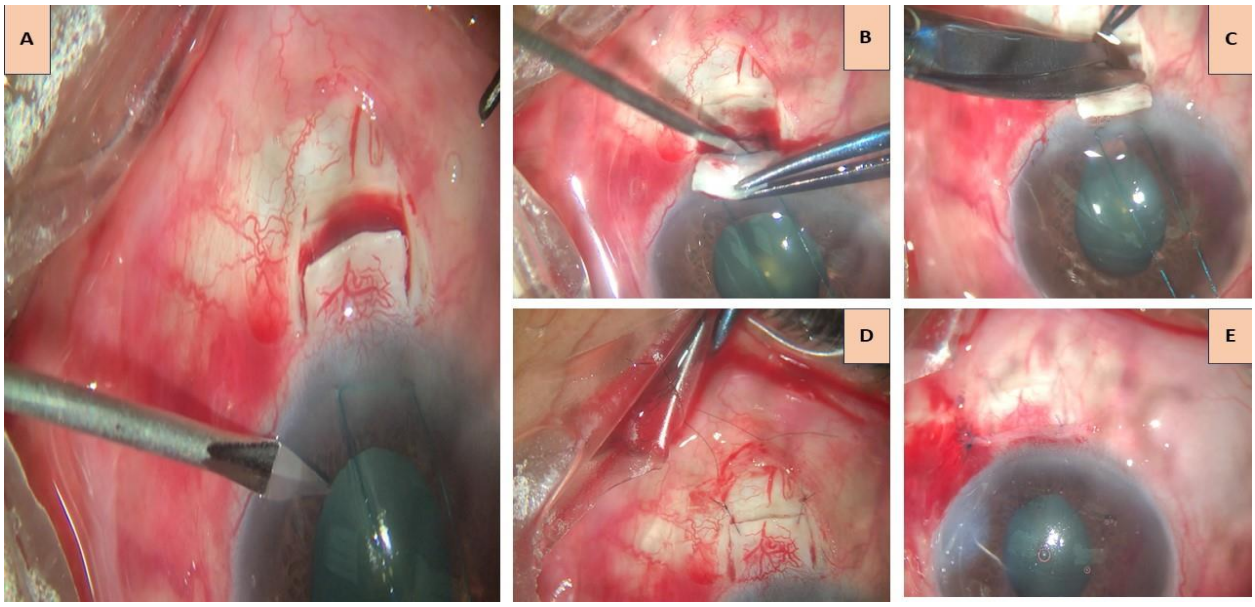

Figure [3]: [A]: Side port incision, [B]: Trabeculectomy, [C]: Iridectomy, [D]: Closure of the scleral Flab, [E]: Conjunctival suture and Bleb formation

Statistical Methods

To test for normal distribution frequency, data was plotted against a 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 the significance of the difference between the two groups and the significance of the difference between pre and postoperative values in the same group. The 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

A total of 40 patients diagnosed with primary open-angle glaucoma and submitted for trabeculectomy with either MMC [Group 1] or Eylea [Group 2] were included in this study. The median and IQR age of the studied patients was 59.5 [55.25-66] years with no statistically significant difference between the two groups [P = 0.2]. The two groups were comparable regarding their gender [P = 0.1], with the percentage of males being higher than males [60% vs 40%]. As regards the patients' comorbidities, the percentage of DM and HTN were significantly higher in group 2 than in group 1 [P = 0.03]. In the present study, all patients were on antiglaucoma medications preoperatively, 7.5% of the patients were on single treatment, 30% were on double treatment, and 62.5% were on tribble treatment [Table 1].

As regards the BCVA, there was no significant improvement in the visual acuity in each of the two groups between the preoperative and all the postoperative follow-up periods [P > 0.05 for all]. However, the BCVA was significantly better in group 2 than in group 1 at the baseline and at all follow-up periods [P < 0.05 for all] [Table 2].

According to the IOP, we found a statistically significant reduction in the IOP from 25 [23-28] mmHg in group 1 and 25 [23-28] mmHg in group 2 at the baseline to 14 [13-15] mmHg in group 1 and 16 [15-16] mmHg in group 2 at 12 months postoperative [P = 0.001] [Table 3].

In the present study, the overall complication rate was 17.5% including the following 5% failure rate in each group, 10% leakage in each group, and 5% flat bleb in group 1 only.

In terms of the Bleb evaluation, the Mainz score was used for the Bleb assessment all over the follow-up periods. It consists of seven main domains, bleb height, peripheral vascularity, central vascularity, transparency, microcysts formation, and conjunctival mobility. We found no statistically significant difference between the 2 groups as regards all Mainz domains all over the follow-up periods [P > 0.05 for all] [Tables 4-9].

Table [1]: Demographics and clinical data of the studied patients

Variables		Total [n=40]	Group 1 [n=20]	Group 2 [n=20]	P value
Age [years]	Median [IQR]	59.5 [55.25-66]	60 [58-62.5]	58 [51-67]	**0.2**[a]
	Range	43-79	48 - 75	43- 79	
Gender. N [%]	Male	24 [60%]	14 [70%]	10 [50%]	**0.1**[b]
	Female	16 [40%]	6 [30%]	10 [50%]	
Comorbidities	DM	1 [%2.5]	1 [5%]	0 [0%]	**0.03***[b]
	Hypertension	12 [30%]	2 [10%]	10 [50%]	
	DM + HTN	6 [15%]	3 [15%]	3 [15%]	
Antiglaucoma. N [%]	Single	3 [7.5%]	1 [5%]	2 [10%]	**0.5**[b]
	Double	12 [30%]	5 [25%]	7 [35%]	
	Tribble	25 [62.5%]	14 [70%]	11 [55%]	
Gonio. N [%]	Grade 1	0 [0%]	0 [0%]	0 [0%]	**0.14**[b]
	Grade 2	0 [0%]	0 [0%]	0 [0%]	
	Grade 3	2 [5%]	2 [10%]	0 [0%]	
	Grade 4	38 [95%]	18 [90%]	20 [100%]	
C/D ratio.	Median [IQR]	0.9 [0.8-0.9]	0.9 [0.8-0.9]	0.8 [0.7-0.9]	**0.11**[a]
	Range	0.5-1	0.6 - 1	0.5 – 0.9	

Table [2]: BCVA of the studied patients

BCVA	Group 1 [n=20]	P value [b]	Group 2 [n=20]	P value [b]	P value [c]
Preoperative	0.9 [0.5-1.1]	-	0.4 [0.3-0.5]	-	0.02*
1 day postoperative	1[0.6-1.1]	0.2	0.4 [0.4-0.6]	0.06	0.01*
1 week postoperative	0.9 [0.5-1.1]	0.7	0.4 [0.4-0.6]	0.5	0.01*
1 month postoperative	0.9 [0.5-1]	0.8	0.4 [0.3-0.5]	0.3	0.01*
3 months postoperative	0.9 [0.4-1]	0.4	0.4 [0.3-0.5]	0.7	0.02*
6 months postoperative	0.8 [0.4-1.1]	0.3	0.4 [0.3-0.6]	0.03	0.01*
12 months postoperative	0.9 [0.4-1]	0.2	0.4 [0.3-0.6]	0.09	0.01*
P value [a]	0.01		0.01		-

Table [3]: IOP of the studied patients

TOP	Group 1 [n=20]	P value [b]	Group 2 [n=20]	P value [b]	P value [c]
Preoperative	25 [23-28]	-	25 [23-28]	-	0.9
1 day postoperative	9 [8-10]	0.001*	10 [10-11]	0.001*	0.02*
1 week postoperative	10 [9-11]	0.001*	11 [11-12]	0.001*	0.02*
1 month postoperative	11 [10-12]	0.001*	12 [12-13]	0.001*	0.004*
3 months postoperative	12 [11-13]	0.001*	13 [13-14]	0.001*	0.02*
6 months postoperative	13 [12-14]	0.001*	14 [14-15]	0.001*	0.004*
12 months postoperative	14 [13-15]	0.001*	16 [15-16]	0.001*	0.009*
P value [a]	0.001*		0.001*		

Table [4]: Bleb height of the studied patients

Bleb height. N [%]		Group 1 [n=20]	Group 2 [n=20]	P value [a]
1 day postoperative	Grade 0 [Flat]	0 [0%]	0 [0%]	0.1
	Grade 1	13 [65%]	16 [80%]	
	Grade 2	3 [15%]	3 [15%]	
	Grade 3 [High]	4 [20%]	1 [5%]	
1 week postoperative	Grade 0 [Flat]	0 [0%]	0 [0%]	0.3
	Grade 1	10 [50%]	15 [75%]	
	Grade 2	6 [30%]	4 [20%]	
	Grade 3 [High]	4 [20%]	1 [5%]	
1 month postoperative	Grade 0 [Flat]	0 [0%]	0 [0%]	0.2
	Grade 1	8 [40%]	14 [70%]	
	Grade 2	8 [40%]	4 [20%]	
	Grade 3 [High]	4 [20%]	2 [10%]	
3 months postoperative	Grade 0 [Flat]	0 [0%]	0 [0%]	0.8
	Grade 1	8 [40%]	10 [50%]	
	Grade 2	8 [40%]	8 [40%]	
	Grade 3 [High]	4 [20%]	2 [10%]	
6 months postoperative	Grade 0 [Flat]	0 [0%]	0 [0%]	0.8
	Grade 1	7 [35%]	8 [40%]	
	Grade 2	8 [40%]	9 [45%]	
	Grade 3 [High]	5 [25%]	3 [15%]	
12 months postoperative	Grade 0 [Flat]	0 [0%]	0 [0%]	0.9
	Grade 1	8 [40%]	7 [35%]	
	Grade 2	7 [35%]	8 [40%]	
	Grade 3 [High]	5 [25%]	5 [25%]	

Table 5: Bleb central vascularity of the studied patients

Bleb central vascularity. N[%]		Group 1 [n=20]	Group 2 [n=20]	P value [a]
1 day postoperative	Grade 0 [Avascular]	7 [35%]	5 [25%]	0.5
	Grade 1	8 [40%]	10 [50%]	
	Grade 2	4 [20%]	2 [10%]	
	Grade 3 [severe]	1 [5%]	3 [15%]	
	Corkscrew blood vessel	0 [0%]	0 [0%]	
1 week postoperative	Grade 0 [Avascular]	7 [35%]	4 [20%]	0.3
	Grade 1	5 [25%]	5 [25%]	
	Grade 2	6 [30%]	11 [55%]	
	Grade 3 [severe]	2 [10%]	9 [45%]	
	Cork screw blood vessel	1 [5%]	3 [15%]	
1 month postoperative	Grade 0 [Avascular]	7 [35%]	1 [5%]	0.14
	Grade 1	4 [20%]	6 [30%]	
	Grade 2	5 [25%]	10 [50%]	
	Grade 3 [severe]	4 [20%]	3 [15%]	
	Corkscrew blood vessel	1 [5%]	3 [15%]	
3 months postoperative	Grade 0 [Avascular]	4 [20%]	0 [0%]	0.16
	Grade 1	6 [30%]	5 [25%]	
	Grade 2	7 [35%]	8 [40%]	
	Grade 3 [severe]	3 [15%]	7 [35%]	
	Cork screw blood vessel	2 [10%]	4 [20%]	
6 months postoperative	Grade 0 [Avascular]	2 [10%]	1 [5%]	0.6
	Grade 1	8 [40%]	5 [25%]	
	Grade 2	6 [30%]	7 [35%]	
	Grade 3 [severe]	4 [20%]	7 [35%]	
	Cork screw blood vessel	2 [10%]	4 [20%]	
12 months postoperative	Grade 0 [Avascular]	1 [5%]	0 [0%]	0.4
	Grade 1	11 [55%]	12 [60%]	
	Grade 2	4 [20%]	3 [15%]	
	Grade 3 [severe]	4 [20%]	5 [25%]	
	Cork screw blood vessel	2 [10%]	6 [30%]	

Table [6]: Bleb Peripheral vascularity of the studied patients

Bleb Peripheral vascularity. N[%]		Group 1 [n=20]	Group 2 [n=20]	P value [a]
1 day postoperative	Grade 0 [Avascular]	7 [35%]	5 [25%]	0.9
	Grade 1	9 [40%]	11 [55%]	
	Grade 2	3 [15%]	3 [15%]	
	Grade 3 [severe]	1 [5%]	1 [5%]	
	Cork screw blood vessel	0 [0%]	0 [0%]	
1 week postoperative	Grade 0 [Avascular]	7 [35%]	5 [25%]	0.8
	Grade 1	6 [30%]	5 [25%]	
	Grade 2	6 [30%]	9 [45%]	
	Grade 3 [severe]	1 [5%]	1 [5%]	
	Cork screw blood vessel	0 [0%]	0 [0%]	
1 month postoperative	Grade 0 [Avascular]	6 [30%]	3 [15%]	0.5
	Grade 1	6 [30%]	4 [20%]	
	Grade 2	4 [20%]	9 [45%]	
	Grade 3 [severe]	4 [20%]	4 [20%]	
	Cork screw blood vessel	0 [0%]	0 [0%]	
3 months postoperative	Grade 0 [Avascular]	5 [25%]	3 [15%]	0.7
	Grade 1	7 [35%]	5 [25%]	
	Grade 2	5 [25%]	6 [30%]	
	Grade 3 [severe]	3 [15%]	6 [30%]	
	Cork screw blood vessel	0 [0%]	0 [0%]	
6 months postoperative	Grade 0 [Avascular]	3 [15%]	3 [15%]	0.51
	Grade 1	9 [45%]	6 [30%]	
	Grade 2	5 [25%]	5 [25%]	
	Grade 3 [severe]	3 [15%]	6 [30%]	
	Cork screw blood vessel	0 [0%]	0 [0%]	
12 months postoperative	Grade 0 [Avascular]	2 [10%]	1 [5%]	0.4
	Grade 1	10 [50%]	8 [40%]	
	Grade 2	5 [25%]	9 [45%]	
	Grade 3 [severe]	3 [15%]	2 [10%]	
	Cork screw blood vessel	0 [0%]	0 [0%]	

Table 7: Bleb transparency of the studied patients

Bleb transparency		Group 1 [n=20]	Group 2 [n=20]	P value [a]
1 day postoperative	Transparent	16 [80%]	16 [80%]	1
	Non transparent	4 [20%]	4 [20%]	
1 week postoperative	Transparent	15 [75%]	16 [75%]	0.12
	Non transparent	5 [25%]	4 [25%]	
1 month postoperative	Transparent	16 [80%]	14 [70%]	0.4
	Non transparent	4 [20%]	6 [30%]	
3 months postoperative	Transparent	16 [80%]	15 [75%]	0.5
	Non transparent	4 [20%]	5 [25%]	
6 months postoperative	Transparent	16 [80%]	14 [70%]	0.1
	Non transparent	4 [20%]	6 [30%]	
12 months postoperative	Transparent	16 [80%]	14 [70%]	0.4
	Non transparent	4 [20%]	6 [30%]	

Table [8]: Bleb microcysts of the studied patients

Bleb microcysts		Group 1 [n=20]	Group 2 [n=20]	P value [a]
1 day postoperative	None	10 [50%]	12 60[%]	0.5
	1	7 [35%]	7 [35%]	
	2 [many]	3 [15%]	1 [5%]	
1 week postoperative	None	10 [50%]	11 [55%]	0.3
	1	6 [30%]	8 [40%]	
	2 [many]	4 [20%]	1 [5%]	
1 month postoperative	None	7 [35%]	5 [25%]	0.6
	1	8 [40%]	11 [55%]	
	2 [many]	5 [25%]	4 [16%]	
3 months postoperative	None	4 [20%]	5 [25%]	0.6
	1	9 [45%]	6 [30%]	
	2 [many]	7 [35%]	9 [45%]	
6 months postoperative	None	4 [20%]	5 [25%]	
	1	7 [35%]	3 [15%]	0.3
	2 [many]	9 [40%]	12 [60%]	
12 months postoperative	None	5 [25%]	3 [15%]	0.12
	1	15 [75%]	15 [75%]	
	2 [many]	0 [0%]	2 [10%]	

Table [9]: Bleb conjunctival mobility of the studied patients

Bleb conjunctival mobility		Group 1 [n=20]	Group 2 [n=20]	P value [a]
1 day postoperative	Immobile	3 [15%]	3 [15%]	0.6
	Slightly mobile	17 [85%]	17 [85%]	
	Tenon cyst	0 [0%]	0 [0%]	
1 week postoperative	Immobile	3 [15%]	6 [30%]	0.2
	Slightly mobile	17 [85%]	14 [70%]	
	Tenon cyst	0 [0%]	0 [0%]	
1 month postoperative	Immobile	4 [20%]	9 [45%]	0.05
	Slightly mobile	16 [80%]	9 [45%]	
	Tenon cyst	0 [0%]	2 [10%]	
3 months postoperative	Immobile	4 [20%]	9 [45%]	0.05
	Slightly mobile	16 [80%]	9 [45%]	
	Tenon cyst	0 [0%]	2 [10%]	
6 months postoperative	Immobile	5 [25%]	5 [25%]	0.3
	Slightly mobile	15 [80%]	13 [15%]	
	Tenon cyst	0 [0%]	2 [10%]	
12 months postoperative	Immobile	5 [25%]	3 [15%]	0.2
	Slightly mobile	15 [80%]	15 [75%]	
	Tenon cyst	0 [0%]	2 [10%]	

DISCUSSION

The terrible effects of glaucoma are shown by a global analysis. The World Health Organization [WHO] conducted a comprehensive evaluation of international literature and arrived with an annual incidence estimate of 2 400 000 new cases of POAG [14]. An estimated 5.2 million people are visually impaired due to glaucoma, with 3 million of those suffering from POAG alone. It has been estimated that glaucoma accounts for 15% of all cases of blindness, making it the second leading cause of blindness worldwide behind cataracts [15].

Trabeculectomy is a clinically proven surgical intervention that has demonstrated efficacy in the management of glaucoma. One of the key determinants for achieving successful Trab is the mitigation of excessive wound healing reactions, predominantly driven by the migration and proliferation of fibroblasts [16].

The primary cause of filtering surgery failure is the multiplication of fibroblasts and the consequent creation of scar tissue at the operative site. Antimetabolites, such as mitomycin C and 5-fluorouracil, have been used to modify the wound healing response and to prevent bleb failure [17].

Glaucoma experts are very interested in finding safe ways to stop scars from forming in GFS and make surgery more likely to work. Antime tabolites, like 5-fluorouracil [5-Fu] and mitomycin-C [MMC], change the way the body heals and make operations more likely to work. Even though these drugs work, they can cause thin-walled filtering bleb, which is linked to a high chance of leak age, hypotony, and endophthalmitis [18].

Antibodies that fight vascular endothelial growth factor [VEGF] are well known to be an alternative way to stop cell growth and angiogenesis. connected to the exact effect at wound tuning of the filtering bleb and with fewer bad effects [19].

There is sufficient proof that VEGF influences fibroblastic activity both indirectly [via angiogenesis] and directly [20]. VEGF is recognized as a mediator and regulator that facilitates the infiltration of inflammatory cells into the core of the reparative process, hence enhancing the migration of fibroblasts. There is a positive correlation between the concentration of vascular endothelial growth factor [VEGF] in the aqueous humor of glaucoma patients who have had filtration surgery and the risk of scarring. Additionally, elevated levels of other cytokines in the aqueous humor are also associated with an increased risk of scarring [21].

Recent studies have provided evidence indicating that angiogenesis inhibitors have a notable effect on scar formation in the skin. This effect is achieved by the modulation of collagen deposition and the promotion of wound healing, ultimately leading to an enhanced density of blood vessels. This improvement is attributed to the increased presence of vascular endothelial growth factor [VEGF] [22, 23]. Hence, the efficiency of an anti-VEGF therapy is enhanced when it not only inhibits the production of new blood vessels [neovascularization], but also suppresses the development of scar tissue. In the study of **Ming *et al.*** [24], filtering blebs on the surface of vascularization in rats had an average survival time of 11.932.23 days.

At the same time, growing blood vessels were found upon the filtering bleb 7 days after surgery, and fusiform or star-shaped fibroblasts began multiplying 5 days after surgery. These results informed the decision to administer the medication subconjunctivally on postoperative day 5 in order to reduce vascularization and fibroblast growth. Anti-VEGF medications, such as bevacizumab and ranibizumab, were also associated with fewer problems after subconjunctival injection than anti-proliferative drugs. **Akkan and Cilsim** [25] have reported that there exists an inhibitory effect on scar development of filtering blebs subsequent to filtration surgery in glaucoma patients. Nevertheless, it is an indisputable fact that the cost of these medications is prohibitively high.

One example of an antimetabolite is Aflibercept [Eylea], which functions as a vascular endothelial growth factor [VEGF] inhibitor. The qualities of this substance result in the suppression of the pathogenic process involved in the construction of new blood vessels and their excessive permeability. Additionally, it leads to a reduction in leukocyte infiltration and inflammation [26].

In our study we aimed to compare between the efficacy of aflibercept and mitomycin c in trabeculectomy in patients with primary open angle glaucoma. Complete success was defined in the present study as an IOP constantly lower than 21 mmHg without any antiglaucoma

medication. However, the failure was defined as when IOP was higher than 21 mmHg in two subsequent follow-up visits, despite topical antiglaucoma therapy or need for further glaucoma surgical interventions. The success rate in the current study was 95% in each study group with no significant difference between them.

In the current study the median [IQR] IOP was reduced from 25 [23-28] mmHg in the MMC group preoperatively to 14 [13-15] mmHg at 12 months post operatively [P = 0.001]. In the Eylea group the median [IQR] IOP was reduced from 25 [23-28] mmHg preoperatively to 16 [15-16] mmHg at the end point of the study [P = 0.001]. Although the postoperative IOP in both groups was in the normal range, the difference between them at 12 months postoperative was statistically significant [P = 0.009]. This slight difference may be due to the slight difference in the time of application of the MMC and Eylea, also, it may be due to the difference in the patients' clinical characteristics as we found that in the Eylea group, 50% of the patients were hypertensive in comparison to 10% of the patients in MMC group.

To the best of our knowledge, it is the first study to compare the MMC and Eylea as antifibrotic agent in trabeculectomy surgery. A study was done by Zhang ***et al.***, [19] who included 36 eyes from 36 patients after OAG surgery divided randomly into conbercept and 5-FU groups. They injected with either concept [0.2 mL] or 5-FU [0.2 mL] on the 5th day post-operatively, and they found significant reductions of IOP 1d, 1wk, 1-, 3- and 6-months post-injection in comparison with preoperatively in the concept group. Also, they found a significant decrease in IOPs in the concept group in comparison with the 5-FU group 1-, 3-, and 6-months post-injection. Although, the difference between our study and **Zhang *et al.*** [19] in the type of injected materials and methods of injection, conbercept is considered as an Anti VEGF which is similar to aflibercept, which confirms our hypothesis that Anti VEGF is effective in preventing fibrosis after GFS with fewer side effects.

In a study done by **Sengupta *et al.*** [27]**,** They found that the group treated with bevacizumab demonstrated a complete success rate of 90%, which was significantly higher compared to the 60% complete success rate observed in each of the other two groups [P=0.04]. The percentage of success of the bevacizumab group which is Anti-VEGF is relatively similar to our Elea group despite the difference in the structure of both interventions, however, they are both Anti-VEGF, which agreed with our hypothesis that Anti VEGF is effective in preventing bleb fibrosis after trabeculectomy. However, The percentage of success of the MMC group in **Sengupta *et al.*** study is lower than our percentage [60% vs 90%]. This difference may be due to different sample sizes, the difference in the clinical characteristics of the patients as they included patients who presented with visually significant cataracts and concomitant primary open-angle glaucoma or chronic angle-closure glaucoma.

In an animal study [trabeculectomy mouse model], **Van Bergen *et al.*** [28] compared the intracameral injection of the placental growth factor [PlGF] inhibitor [5D11D4] to MMC or aflibercept and the combination of both compounds and they found that application of MMC together with PlGF inhibition may have complementary effects in the improvement of surgical outcome and is equally efficacious as the combined treatment of MMC and aflibercept.

In a systematic review and meta-analysis examining the efficacy and safety of mitomycin C [MMC] or no antimetabolite in cases of trabeculectomies, the findings revealed that following trabeculectomy, MMC demonstrated a statistically significant superiority over a placebo in reducing postoperative intraocular pressure [IOP] [29].

Lim *et al.* [30] retrospectively reviewed a cohort of 566 patients diagnosed with primary and secondary glaucoma who underwent trabeculectomy surgery with the use of mitomycin-C [MMC]. The researchers aimed to compare the efficacy of MMC administration via intra-Tenon injection versus sponge application during trabeculectomy surgery. The study findings indicated that the reduction in intraocular pressure [IOP] achieved through MMC injection was comparable to that achieved through sponge application in patients with glaucoma. Furthermore, the safety profiles of both techniques were found to be similar.

In the current study, the MMC concentration was 0.3 mg/ml. **Seol *et al.*** [31] compared the efficacy and safety of 0.2 mg/mL and 0.4 mg/

mL of MMC in eyes undergoing trabeculectomy, and they found that trabeculectomy with 0.2 mg/mL and 0.4 mg/mL of MMC showed similar IOP-control effects to those recorded in previous studies, along with a low rate of complications.

Although our study is considered the first one to compare Eylea with MMC in trabeculectomies, we have some drawbacks which is as follows; initially, it is important to note that the duration of the follow-up period was quite brief, hence limiting our ability to assess the long-term surgical prognoses. Additionally, in order to enhance the robustness of illustrating the safety of surgical complications that occur with low frequency, it is imperative to do an analysis on a larger cohort of patients.

Conclusion

The use of intraoperative subconjunctival single dose Aflibercept in trabeculectomy is safe and effective and comparable to the use of MMC in terms of the advantage of avoiding the potentially dangerous complications related to MMC use.

Financial and non-financial relations and activities of interest: None

REFERENCES

1. Mahabadi N, Foris LA, Tripathy K. Open Angle Glaucoma. 2022 Aug 22. In: StatPearls [Internet]. Treasure Island [FL]: StatPearls Publishing; 2024 Jan–. PMID: 28722917.
2. Allison K, Patel D, Alabi O. Epidemiology of Glaucoma: The Past, Present, and Predictions for the Future. Cureus. 2020 Nov 24;12[11]:e11686. doi: 10.7759/cureus.11686.
3. Li T, Lindsley K, Rouse B, Hong H, Shi Q, Friedman DS, Wormald R, Dickersin K. Comparative Effectiveness of First-Line Medications for Primary Open-Angle Glaucoma: A Systematic Review and Network Meta-analysis. Ophthalmology. 2016 Jan; 123[1]:129-40. doi: 10.1016/j.ophtha.2015.09.005.
4. Lamoureux EL, Mcintosh R, Constantinou M, Fenwick EK, Xie J, Casson R, *et al.* Comparing the effectiveness of selective laser trabeculoplasty with topical medication as initial treatment [the Glaucoma Initial Treatment Study]: study protocol for a randomised controlled trial. Trials. 2015 Sep 11;16:406. doi: 10.1186/s13063-015-0924-6.
5. Ang BCH, Lim SY, Betzler BK, Wong HJ, Stewart MW, Dorairaj S. Recent Advancements in Glaucoma Surgery-A Review. Bioengineering [Basel]. 2023 Sep 19;10[9]:1096. doi: 10.3390/bioengineering10091096.
6. Van Bergen T, Van de Velde S, Vandewalle E, Moons L, Stalmans I. Improving patient outcomes following glaucoma surgery: state of the art and future perspectives. Clin Ophthalmol. 2014 May 2;8:857-67. doi: 10.2147/OPTH.S48745.
7. Yamanaka O, Kitano-Izutani A, Tomoyose K, Reinach PS. Pathobiology of wound healing after glaucoma filtration surgery. BMC Ophthalmol. 2015 Dec 17;15 Suppl 1[Suppl 1]:157. doi: 10.1186/s12886-015-0134-8.
8. Merritt SR, Velasquez G, von Recum HA. Adjustable release of mitomycin C for inhibition of scar tissue formation after filtration surgery. Exp Eye Res. 2013 Nov;116:9-16. doi: 10.1016/j.exer.2013.07.005.
9. Fan Gaskin JC, Nguyen DQ, Soon Ang G, O'Connor J, Crowston JG. Wound Healing Modulation in Glaucoma Filtration Surgery-Conventional Practices and New Perspectives: The Role of Antifibrotic Agents [Part I]. J Curr Glaucoma Pract. 2014 May-Aug;8[2]:37-45. doi: 10.5005/jp-journals-10008-1159.
10. Liu X, Du L, Li N. The Effects of Bevacizumab in Augmenting Trabeculectomy for Glaucoma: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine [Baltimore]. 2016;95[15]: e3223. doi: 10.1097/MD.0000000000003223.
11. Landers JA, Mullany S, Craig JE. Intravitreal bevacizumab improves trabeculectomy survival at 12 months: the bevacizumab in trabeculectomy study-a randomised clinical trial. Br J Ophthalmol. 2023 Aug 4:bjo-2023-323526. doi: 10.1136/bjo-2023-323526.
12. Moradi A, Sepah YJ, Sadiq MA, Nasir H, Kherani S, Sophie R, Do DV, Nguyen QD. Vascular endothelial growth factor trap-eye [Aflibercept] for the management of diabetic macular edema. World J Diabetes. 2013 Dec 15; 4[6]:303-9. doi: 10.4239/wjd.v4.i6.303.
13. Hoffmann EM, Herzog D, Wasielica-Poslednik J, Butsch C, Schuster AK. Bleb grading by photographs versus bleb grading by slit-lamp examination. Acta Ophthalmol. 2020 Aug;98[5]:e607-e610. doi: 10.1111/aos.14335.
14. Greco A, Rizzo MI, De Virgilio A, Gallo A, Fusconi M, de Vincentiis M. Emerging Concepts in Glaucoma and Review of the Literature. Am J Med. 2016 Sep;129[9]:1000.e7-1000.e13. doi: 10.1016/j.amjmed.2016.03.038.
15. Nkum G, Lartey S, Frimpong C, Micah F, Nkum B. Awareness and Knowledge of Glaucoma Among Adult Patients at the Eye Clinic of a Teaching Hospital. Ghana Med J. 2015 Sep;49[3]: 195-9. doi: 10.4314/gmj.v49i3.11.

16. Belkin A, Chaban YV, Waldner D, Samet S, Ahmed IIK, Gooi P, Schlenker MB. Gonioscopy-assisted transluminal trabeculotomy is an effective surgical treatment for uveitic glaucoma. Br J Ophthalmol. 2023 May;107[5]:690-697. doi: 10.1136/bjophthalmol-2021-320270.

17. Pakravan M, Miraftabi A, Yazdani S, Koohestani N, Yaseri M. Topical Mitomycin-C versus Subconjunctival 5-Fluorouracil for Management of Bleb Failure. J Ophthalmic Vis Res. 2011 Apr; 6[2]:78-86. PMID: 22454715.

18. Zuo L, Zhu S, Gu S, Xu X. Anti-scarring effects of conbercept on human Tenon's fibroblasts: comparisons with bevacizumab. BMC Ophthalmol. 2023 Apr 26;23[1]:183. doi: 10.1186/s12886-023-02914-4.

19. Zhang J, Vikash V, Wang P, Zheng T, Chen DL, Wang Q, Ke M. Effect of subconjunctival injection with conbercept as an adjuvant to filtration surgery for open angle glaucoma: a prospective randomized interventional 6-month follow-up study. Int J Ophthalmol. 2019 Feb 18;12[2]:235-240. doi: 10.18240/ijo.2019.02.08.

20. Park YM, Kim CD, Lee JS. Effect of Bevacizumab on Human Tenon's Fibroblasts Cultured from Primary and Recurrent Pterygium. Korean J Physiol Pharmacol. 2015 Jul;19[4]:357-63. doi: 10.4196/kjpp.2015.19.4.357.

21. Cheng G, Xiang H, Yang G, Ma J, Zhao J. Bevacizumab Inhibits Angiogenesis and Inflammation in Rat Filtration Surgery Model. Cell Biochem Biophys. 2015 Sep;73[1]:71-7. doi: 10.1007/s12013-015-0566-z.

22. Wang P, Jiang LZ, Xue B. Recombinant human endostatin reduces hypertrophic scar formation in rabbit ear model through down-regulation of VEGF and TIMP-1. Afr Health Sci. 2016 Jun; 16[2]:542-53. doi: 10.4314/ahs.v16i2.23.

23. Wang C, Wang Q, Gao W, Zhang Z, Lou Y, Jin H, *et al.* Highly efficient local delivery of endothelial progenitor cells significantly potentiates angiogenesis and full-thickness wound healing. Acta Biomater. 2018 Mar 15;69:156-169. doi: 10.1016/j.actbio.2018.01.019.

24. Peipei MI, Ling WA, Dabo WA, Xiaojing PA. Dynamic changes of morphology and histopathology of conjunctival filtering bleb after anti-glaucoma filtering surgery in rat. Chin J Exp Ophthalmol. 2014:886-90.

25. Akkan JU, Cilsim S. Role of subconjunctival bevacizumab as an adjuvant to primary trabeculectomy: a prospective randomized comparative 1-year follow-up study. J Glaucoma. 2015 Jan;24[1]:1-8. doi: 10.1097/IJG.0b013e318287abf3.

26. Adams BS, Sorhaitz W, Stringham J. Aflibercept. 2023 Jul 4. In: StatPearls [Internet]. Treasure Island [FL]: StatPearls Publishing; 2024 Jan–. PMID: 35881741.

27. Sengupta S, Venkatesh R, Ravindran RD. Safety and efficacy of using off-label bevacizumab versus mitomycin C to prevent bleb failure in a single-site phacotrabeculectomy by a randomized controlled clinical trial. J Glaucoma. 2012 Sep;21[7]:450-9. doi: 10.1097/IJG.0b013e31821826b2.

28. Van Bergen T, Jonckx B, Moons L, Feyen JH, Stalmans I. The Combination of PlGF Inhibition and MMC as a Novel Anti-Scarring Strategy for Glaucoma Filtration Surgery. Invest Ophthalmol Vis Sci. 2016 Aug 1;57[10]:4347-55. doi: 10.1167/iovs.16-19725.

29. Song ZH, Xu SS, Li GY, Wang ET, Li YM, Zhang C. Efficacy and Safety of the Intraoperative Application of Mitomycin in Glaucoma Patients with Trabeculectomy: A Systematic Review and Meta-Analysis. J Clin Pharm Ther. 2023 Feb 10; 2023. doi: 10.1155/2023/5249552.

30. Lim MC, Hom B, Watnik MR, Brandt JD, Altman AR, Paul T, Tong MG. A Comparison of Trabeculectomy Surgery Outcomes With Mitomycin-C Applied by Intra-Tenon Injection Versus Sponge. Am J Ophthalmol. 2020 Aug;216:243-256. doi: 10.1016/j.ajo.2020.03.002.

31. Seol BR, Lee SY, Kim YJ, Kim YK, Jeoung JW, Park KH. Comparison of the Efficacy and Safety of Trabeculectomy with Mitomycin C According to Concentration: A Prospective Randomized Clinical Trial. J Clin Med. 2020 Dec 26;10[1]:59. doi: 10.3390/jcm10010059.

IJMA

International Journal of Medical Arts

Volume 6, Issue 2, February 2024

P- ISSN: 2636-4174
E- ISSN: 2682-3780