The Egyptian Journal of Hospital Medicine (October 2019) Vol. 77 (2), Page 4952-4955

Subconjunctival Bevacizumab versus Mitomycin C Adjunctive to Subscleral Trabeculectomy

Ekram R. Abdallah*, Mahmoud Abd El-badie Mohamed, Hossam Eldeen Saad Abou Saif
Department of Ophthalmology, Faculty of Medicine, Al-Azhar University (Assuit), Egypt
***Corresponding author:** Ekram R. Abdallah, **E-mail:** ekramragababdallah@gmail.com

ABSTRACT

Background: trabeculectomy was considered gold standard procedure for glaucoma treatment. Mitomycin C (MMC) and bevacizumab (BVZ) has been used to increase trabeculectomy success rates.

Objective: to compare the outcome of subscleral trabeculectomy with subconjunctival injection of BVZ with that of trabeculectomy with MMC.

Patients and Methods: a prospective, non-randomized, comparative study design was used. Thirty eyes from thirty patients with uncontrolled glaucoma were enrolled. Fifteen eyes underwent subscleral trabeculectomy with intraoperative use of MMC (0.2mg/ml for 3 minutes) (group I) and 15 eyes underwent subscleral trabeculectomy with subconjunctival bevacizumab injection (1.25mg/0.1ml) (group II). The outcome measures were the best-corrected visual acuity, intraocular pressure (IOP), number of IOP-lowering medications, complications, and bleb morphologic features (based on the Indiana Bleb Appearance Grading Scale).

Results: thirty eyes of thirty patients fulfilled inclusion criteria and assigned to one of two study groups. Each study group included fifteen eyes of fifteen patients. Participants were 14 males and 16 females. Mean ages of patients assigned to MMC and BVZ were 54.0±7.33 and5.7±6.9 years respectively. The difference in mean age was statistically insignificant among treatment groups (p=0.740). Mean number of pre-operative anti-glaucoma medications used by MMC and BVZ treatment groups were 2.47±0.52 and 2.47±0.52 with no significant difference among treatment groups (p=1.00). **Conclusions:** adjunctive subconjunctival bevacizumab with trabeculectomy is effective in controlling the IOP profile and the post-operative IOP reduction showed no statistically significant different in both group at all post-operative visits. Comparable success rates were achieved in the two groups.

Keywords: subscleral trabeculectomy, Bevacizumab, Mitomycin C, intraocular pressure.

INTRODUCTION

Trabeculectomy has been considered the gold standard procedure since 1968[(1)].The main cause of failure following trabeculectomyis the post-operative wound healing response thatleads to subconjunctival scarring in the filtering tract and bleb[(2)].

Anti-fibrotic agents such as Mitomycin C (MMC) has been used to modulate the wound healing process and increase surgical success. Among these several factors involved in this process, angiogenesis seems to play an important role providing a variety of mediators related to the healing process. Blocking angiogenesis by administration of anti-vascular endothelial growth factor (anti-VEGF) agents decreases fibroblast proliferation and scar tissue formation[(3)].

Intravitreal administration of bevacizumab (BVZ) (Avastin), one of the most commonly used anti-VEGF agents in ocular diseases, has been shown to improve trabeculectomy success rates in eyes with secondary glaucomas, more specifically, in those with neovascular glaucoma[(4,5)].

Objective of the study:

It is to compare the outcome of subscleral trabeculectomy with subconjunctival injection of BVZ (1.25mg/0.1ml) with that of trabeculectomy with MMC (0.2mg/ml for 3 minutes).

PATIENTS and METHODS

This prospective, comparative, non-randomized, interventional study was conducted at Al-Azhar University hospital in Assiut from June 2016 to March 2018. Thirty eyes of thirty patients were enrolled in the study.

Ethical and approval considerations:

Patients were enrolled after **the approval of Ethical Committee of Al-Azhar Faculty of Medicine in Assiut.** The risk benefits and alternatives to surgery were discussed with the patients and informed consents were assigned.

The study excluded patients with angle closure glaucoma, inflammatory, neovascular, traumatic glaucoma, history of prior failed trabeculectomy surgery, history of ocular infection in recent two weeks and patients with corneal ulcers or perforations, which prevent proper measurement of intraocular pressure (IOP). The study subjects underwent trabeculectomy surgery augmented by either MMC 0.2mg/ml or BVZ 1.25mg/0.05ml when they had uncontrolled IOP under maximum anti-glaucoma medications, or due to poor socio-economic status. The demographic data, function of bleb, and ocular examinations results, including measurements of best corrected visual acuity (BCVA) at a distance using Landolt C chart, refractive status using an autorefractometer (KR-8100; Topcon Corporation, Tokyo, Japan), IOP measured by Goldman applanation tonometry (CT-80; Topcon Corporation) and fundus bio-microscopy to assess retina and optic disc by + 90 D Volk non-contact lens.

Surgical procedure:

Sterilization was done by using betadine 10% for the surgical field. Betadine 5% eye drops was used for the conjunctival sac. Application of sterile drops was

Received: 20/8/2019
Accepted: 1/9/2019

done. An 8-0 nylon corneal traction suture was used. The conjunctiva was dissected at the supero-nasal quadrant. A 15knife was used to delineate and a crescent knife was used to dissect and create a half-thickness, 3.5×4.5 mm, rectangular-shaped scleral flap. Cellulose sponges soaked with MMC (0.2 mg/ml) were applied under the scleral flap, for 3 min and then the surgical area was dried and rinsed with 30 ml balance salt saline (BSS). A corneal paracentesis was made by a super blade knife. Sclerectomy was performed with a Kelly-Descemet's punch and the peripheral iridectomy was performed with a Vannas scissors. The scleral flap was approximated with three interrupted 10–0 nylon sutures. The conjunctiva was closed with interrupted 10-0 nylon sutures. Assessment of filtration was done by injecting lactated ringer solution into the anterior chamber (AC) through the paracentesis. BVZ was injected subconjunctivally adjacent to the temporal edge of the bleb over the scleral flap area, with a 30-G needle. The needle entrance was at least 8 mm away from the bleb to prevent any needle track leakage.

Post-operative care:

It included topical antibiotic, topical 1% prednisolone acetate and cycloplegic eye drops for 3 weeks. Ocular massage, antiglaucoma medications, depending on the target IOP.

Post-operative follow-up:

Post-operative follow-up was scheduled daily in the first week for early detection and management of early post-operative complications. Then follow-up visits were scheduled at 2 weeks, one month, and then monthly up to the 6th month. At each visit, slit lamp evaluation (to assess AC reaction and depth), IOP measurements, measurements of BCVA at a distance using Landolt C chart, fundus evaluation by + 90 D Volk non-contact lens, complications, and the need for anti-glaucoma medications, bleb morphology including bleb extent, height, leakage and vascularity at 6th month (evaluated according to Indiana Bleb Appearance Grading Scale[6] (IBGS) were recorded. In the first post-operative day, IOP was measured by Goldman applanation tonometer.

Definition of success and failure:

1- Complete success: It was defined as an IOP less than 21mmHg (from 5mmHg to 21mmHg) and at least 20% reduction in preoperative pressure, without any anti-glaucoma medications at 6th month follow up time.

2- Qualified success: It was defined as an IOP less than 21mmHg and at least 20% reduction in preoperative pressure, with reduction of at least 2 medications at 6th month follow-up time.

3- Failure: It was defined as an IOP more than 21mmHg at the last follow-up visit or the need for further glaucoma surgery to control the IOP at 6th month follow-up visit.

Statistical Analysis

The statistical analysis was done by SPSS software version 20.0. Chi-square test was used for qualitative data among groups. Mann-Whitney U test was used to compare quantitative data (means± SD) among groups. P-value <0.05 was considered statistically significant.

RESULTS

Thirty eyes of thirty patients fulfilled inclusion criteria and assigned to one of two study groups. Each study group included fifteen eyes of fifteen patients. Participants were 14 males and 16 females. Mean ages of patients assigned to MMC and BVZ were54.0±7.33 and52.7±6.9 years respectively. The difference in mean ages was statistically insignificant among treatment groups (p=0.740). Mean number of pre-operative anti-glaucoma medications used by MMC and BVZ treatment groups were 2.47±0.52 and 2.47±0.52 with no significant difference among treatment groups (p=1.00).

Table (1): Patient's demographic data

Variables	Group I (n= 15) No. (%)	Group II (n= 15) No. (%)	P-value
Age (years)			
Mean ± SD	54.0 ± 7.33	52.7 ± 6.9	0.74*
Range	42 - 65	35 – 60	
Gender			
Male	6(40%)	8(53.3%)	0.464#
Female	9(60%)	7(46.7%)	
Systemic co morbidity			
Diabetes Mellitus	1(6.7%)	4(26.7%)	0.289#
Hypertension	6(40%)	3(20%)	
Ischemic heart disease	0(0%)	1(6.7%)	
DM & HTN	1(6.7%)	1(6.7%)	
Blep morphology			
Flat vascular	3(20%)	3(20%)	0.644#
Flat avascular	1(6.7%)	2(13.3%)	
High vascular	5(33.3%)	7(46.7%)	
High avascular	6(26.7%)	3(20%)	
Success rate			
Complete	5(33.3%)	4(26.7%)	0.708#
Qualified	7(46.7%)	6(40%)	
Failure	3(20.3%)	5(33.3%)	
No. of anti-glaucoma medications			
Pre-operative			
0 drug	0(0%)	0(0%)	---
1 drug	0(0%)	0(0%)	---
2 drugs	8(53.33%)	8(53.33%)	1#
3 drugs	7(46.67%)	7(46.67%)	1#
Post-operative			
0 drug	5(33.33%)	4(26.67%)	0.690#
1 drug	6(40.0%)	4(26.67%)	0.438#
2 drugs	1(6.67%)	2(13.33%)	0.942#
3 drugs	3(20%)	5(33.33%)	0.408#

***:** Mann-Whitney U test. **#:** Chi-square test.

Mean baseline IOP measurements in MMC and BVZ treatment groups were 28.2±3 and 28.07±2.09 mmHg respectively, with no statistically significant difference (p=0.917). One day post-operatively, the IOP dropped significantly to 10.73±2.31 and 9.33±2.02 mmHgin MMC and BVZ groups respectively. No significant difference in IOP values from day one till month six among both groups (table **2**).

Table (2): Pre-operative IOP and post-operative follow up at one day, one week, one month, two months, three months and 6th month

Intra-ocular pressure	Group I (n= 15)	Group II (n= 15)	P-value[1]
Pre-operative			
Mean ± SD	28.20±3.0	28.07±2.09	0.891
After 1 day			
Mean ± SD	10.73±2.31	9.33±2.02	0.088
P-value[2]	<0.0001*	<0.0001*	---
After 1 week			
Mean ± SD	13.6±1.88	14.13±2.77	0.544
P-value[2]	<0.0001*	<0.0001*	---
After 1 month			
Mean ± SD	15.33±2.06	17.07±3.99	.144
P-value[2]	<0.0001*	<0.0001*	---
After 2 months			
Mean ± SD	16.13±3.58	18.47±4.26	0.114
P-value[2]	<0.0001*	<0.0001*	---
After 3 months			
Mean ± SD	16.47±3.4	18.8±4.33	0.112
P-value[2]	<0.0001*	<0.0001*	---
After 6 months			
Mean ± SD	16.87±4.12	19.33±4.84	0.145
P-value[2]	<0.0001*	<0.0001*	---

P 1: Comparison between Group I and Group II (Mann-Whitney U test). **P2:** Comparison between pre-operative IOP in Group I & Group II and IOP at different follow-up visits (Mann-Whitney U test).
***:** Statistical significant difference (P <0.05).

Mean changes of intraocular pressure:

Mean IOP reduction from pre-operative level was 11.33±5.95 and 8.74±6.88mmHg in MMC and BVZ treatment groups respectively at 6th month with no statistical significant difference between both groups (table **3**).

Table (3): Mean changes of intraocular pressure

Intra-ocular pressure	Group I (n= 15)	Group II (n= 15)	P-value[1]
Pre-operative			
Mean ± SD	28.20±3.0	28.07±2.09	0.892*
After 6 months			
Mean ± SD	6.87±4.12	9.33±4.84	0.145*
P-value[2]	<0.0001*	<0.0001*	---

***:** Mann-Whitney U test.

Bleb morphological features according to IBGS[6]:

Flat and vascular bleb was observed in three eyes in each group (20%), whereas one eye had flat and avascular bleb in group I (6.7%) versus two eyes in group II (13, 3). Five eyes were with height and vascular bleb in group I (33.3%) versus seven eyes in group II. Six eyes with high and avascular bleb were observed in group I **(**26.7%), while three eyes were observed in group II (20%).

Table (4): Height and vascularity of the bleb in both groups

Blep morphology:	Group I (n= 15)		Group II (n= 15)		P-value
	No.	%	No.	%	
Flat vascular	3	20	3	20	0.644
Flat avascular	1	6.7	2	13.3	
High vascular	5	33.3	7	46.7	
High avascular	6	26.7	3	20	

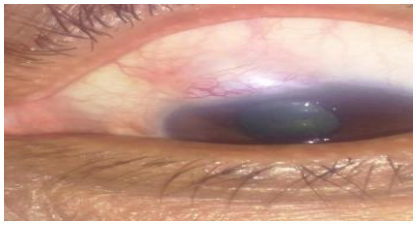

Figure (1): Medium bleb height moderate vascularity, in MMC group in case no.5

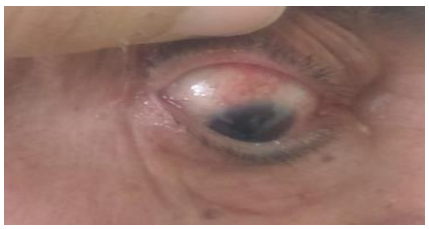

Figure (2): Low bleb height, moderate vascularity in BVZ group in a case no.11

The post-operative complications were 3 cases of shallow anterior chamber (peripheral iridocorneal touch with negative Siedel test), they were more frequent in MMC group than BVZ group (two cases in MMC and one case in BVZ) all of them were treated by tight bandage for 2 days. AC reactions were more frequent in BVZ group than MMC group (2 and 1 respectively), they all resolved completely by frequent topical steroids. Cataract was more frequently progressive in MMC group than BVZ group (3 and 2 respectively) all of them developed between 8 and 16 weeks, and two of them were visually significant (one case in MMC group and one case in BVZ group) and underwent uneventful phacoemulsification with posterior chamber intraocular lens (IOL) at the 4th month.

Encapsulated cystic bleb was frequently occurred in BVZ than MMC group (two cases versus one case respectively), all of them developed between

the 12 and 18 week post-operative, one of them (in MMC group) associated with qualified success in which IOP was 17 mmHg on 2 medications and two of them associated with failure one in MMC group and one in BVZ with IOP 30 mmHg and 28 mmHg respectively on two medications.

DISCUSSION

VEGF, which is an endothelial cell specific mitogen and an angiogenic inducer, was found to be an important stimulus for wound healing[7]. Bevacizumab is a non-selective anti- VEGF[8] may have utility in glaucoma filtering surgery, owing to its inhibitory effect on vascular and fibroblast proliferation, resulting in decreased scarring[9,10]. MMC reduces fibroblast proliferation in the subconjunctival space and in Tenon's capsule and thereby inhibits scar formation[11].

In the current prospective study, all groups demonstrated a significant reduction in the mean IOP at 6th month follow up visit. Though, MMC 0.2mg/ml group yielded higher IOP reduction at 6th month follow-up visit than BVZ 1.25mg/0.05ml, there was no statistical significant difference in the mean IOP among both groups at any follow-up visits. As predictor for final IOP after augmented trabeculectomy, baseline IOP was associated with final IOP at 6th month.

In the study conducted by **Kaushik *et al*.**[12], eighty eyes of eighty patients with uncontrolled primary open angel glaucoma (POAG) or intolerant to anti-glaucoma medications allocated for trabeculectomy with either MMC (0.2mg/ml)or BVZ (1.25mg/0.05ml). They reported that mean IOP at one year follow up was 13.84±0.73 mmHg in MMC groupand13.68±0.79mmHg in BVZ group with no statistically significant difference between both groups, as concluded in our study.

In contrary to our study, a prospective, randomized, comparative study was performed by **Nilforushan *et al*.**[13] studied a subconjunctival BVZ (2.5mg/0.1ml) versus MMC (0.2mg/ml) adjunctive to trabeculectomyon thirty six eyes of thirty four patients, aged above eighteen years old with uncontrolled glaucoma (primary open angle glaucoma and pseudoexfoliation glaucoma) for six months follow-up. They found that; although subconjunctival BVZ was effective in lowering the IOP profile, MMC group displayed statistically significant better IOP control than BVZ group (base line IOP in MMC and BVZ was 23.3±4.9mmHg and 21.9±7.9mmHg respectively compared to 9.6±2.7mmHg and 13.6±3.2mmHg at 6th month). This difference from our results can be explained by different study population i.e. cases with pseudoexfoliation included in their study while in our study only cases with primary open angle glaucoma were included.

CONCLUSION

The post-operative IOP reduction showed no statistically significant difference in both group at all post-operative visits. Comparable success rates were achieved in the two groups. There was an obvious reduction in the utilization of anti-glaucoma medications after trabeculectomy augmented by either BVZ or MMC. The rate of complications among treatment groups was similar, reflecting the safety of utilization of both adjuvants under strict surgical precautions. From these results, we concluded that the BVZ may be a safe and effective alternative to MMC for increasing the success rate of trabeculectomy surgery.

REFERENCES

1. **Cairns JE (1968):** Trabeculectomy-Preliminary report of a new method. Am J Ophthalmol., 66:673–679.
2. **Suzuki R, Dickens CJ, Iwach AG *et al* (2002):** Long-term follow-up of initially successful trabeculectomy with 5-fluorouracil injections. Ophthalmology, 109: 1921–1924.
3. **How A, Chua JLL, Charlton A *et al.* (2010):** Combined treatment with bevacizumab and 5-fluorouracil attenuates the postoperative scarring response after experimental glaucoma filtration. Invest Ophthalmol Vis Sci., 51:928–932
4. **Marey HM and Ellakwa AF (2011):** Intravitreal bevacizumab with or without mitomycin C trabeculectomy in the treatment of neovascular glaucoma. Clin Ophthalmol., 5:841–845.
5. **Alkawas AA, Shahien EA and Hussein AM (2010):** Management of neovascular glaucoma with panretinal photocoagulation, intravitreal bevacizumab, and subsequent trabeculectomy with mitomycin C. J Glaucoma, 19:622–626.
6. **Cantor LB, Mantravadi A, Dunn DW *et al.* (2003):** Morphologic classification of filtering blebs after glaucoma filtration surgery: The Indiana bleb appearance. J Glaucoma, 12(3):266-71.
7. **Li J, Zhang YP and Kirsner RS (2003):** Angiogenesis in wound repair: angiogenic growth factors and the extracellular matrix. Microsc Res Tech., 60(1):107–114.
8. **Jurkowska-Dudzińska J, Kosior-Jarecka E and Żarnowski T (2012):** Comparison of the use of 5-FU and bevacizumab in primary trabeculectomy: results at one year. Clin Experimental Ophthalmology, 40(4):e135-142.
9. **Hurwitz H, Fehrenbacher L, Novotny W *et al.* (2004):** Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med., 350:2335–2342.
10. **Li Z, Van Bergen T, Van de Veire S *et al.* (2009):** Inhibition of vascular endothelial growth factor reduces scar formation after glaucoma filtration surgery. Invest Ophthalmol Vis Sci., 50:5217–5225.
11. **Kitazawa Y, Suemori-Matsushita H, Yamamoto T *et al.* (1993):** Low-dose and high-dose mitomycin trabeculectomy as an initial surgery in primary open-angle glaucoma. Ophthalmology, 1 00(11):1624-1628.
12. **Kaushik J, Kumar J, Parihar S, Jain VK *et al.* (2017):** Efficacy of bevacizumab compared to mitomycin-C modulated trabeculectomy in primary open angle glaucoma: A one-year prospective randomized controlled study. Current Eye Research, 42(2):217-224.
13. **Nilforushan N, Yadgari M, Kish SK *et al.* (2012):** Subconjunctival bevacizumab versus mitomycin C adjunctive to trabeculectomy. Am J Ophthalmol., 153(2): 352–357.e1.