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ORIGINAL PAPER

Comparison of the effect of mitomycin C and bevacizumab–methylcellulose mixture on combined phacoemulsification and non-penetrating deep sclerectomy surgery on the intraocular pressure (a clinical trial study)

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Abstract

Purpose Comparison of the effect of mitomycin C (MMC) versus bevacizumab–methylcellulose mixture (BMM) on combined phacoemulsification and non-penetrating deep sclerectomy surgery on the intraocular pressure in patients with open-angle glaucoma was made.

Methods The current study is a controlled, randomized, double-blind clinical trial. Thirty-eight patients were enrolled, with a total of 40 eyes, and underwent a combined phacoemulsification and non-penetrating deep sclerectomy surgery from 2016 to 2017. MMC with concentration of 0.2 mg/mL for 2 min was used for 20 eyes before separating the scleral flap, and 0.3 mL of BMM (bevacizumab 1.25 mg incorporated into 2% methylcellulose) was injected subconjunctivally following surgery. The success rate of surgery was categorized as complete, relative and failure. Fisher's exact, Mann–Whitney U and Chi-square tests were employed to data analysis. A p value < 0.05 was supposed significant.

Results Patients had the same distribution in terms of age, sex, type of glaucoma and type of cataract. Patients were followed up for a mean of 6 months. The mean intraocular pressure before surgery in the MMC group was 24.85 ± 2.83 mmHg with 3.2 ± 0.523 anti-glaucoma drugs, which reached 13.75 ± 3.552 mmHg with 0.15 ± 0.489 anti-glaucoma drugs at the latest visit. The average intraocular pressure before surgery in the BMM group was 24.45 ± 2.48 mmHg with 2.9 ± 0.641 anti-glaucoma drugs, which reached 15.40 ± 3.267 mmHg with 0.25 ± 0.55 anti-glaucoma drug at the last follow-up. The intraocular pressure was notably lower in the MMC group than BMM group 6 months after surgery. There was not a significant difference from the aspect of success rate and failure rate among the two groups at the 6-month follow-up ($p = 0.135$).

Discussion Based on the results of this study, MMC and bevacizumab–methylcellulose both seem to be effective in the success of combined phacoemulsification and non-penetrating deep sclerectomy surgery, but MMC decreases intraocular pressure in patients at 6 months post-surgery.

Keywords Non-penetrating deep sclerectomy · Mitomycin C · Bevacizumab–methylcellulose mixture · Intraocular pressure · Phacoemulsification

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Introduction

Glaucoma is one of a group of ocular diseases whose main feature is optic neuropathy, which ultimately causes visual impairment. Increased intraocular pressure is a primary and important risk factor for the disease, which can damage neurons and vascular tissues. Surgical treatments are used when IOP cannot be reduced to an acceptable level with medication [1]. Non-penetrating glaucoma surgery is a glaucoma surgery that is performed in three methods: viscocanalostomy, canaloplasty and deep sclerectomy. The purpose of these methods is to reduce IOP and prevent complications of standard trabeculectomy. All these methods have a deep sclerectomy that includes removing a secondary ciliary body along with removing the inner wall of Schlemm's canal [2–4].

Cataract is the principal reason of visual loss and diminished vision in the universe [1]. The prevalence of both cataract and glaucoma increases with age, and many glaucoma patients eventually suffer from cataract either naturally or due to the effects of glaucoma medications.

One of the factors in the failure of glaucoma surgery is the formation of scar tissue in conjunctiva, Tenon's capsule and middle episclera [5–7]. Healing of the wound is stimulated by the activity of fibroblasts and angiogenesis [8–10].

Many cytokines and inflammatory mediators such as transforming growth factor (TGF-ß) and fibroblast growth factor (FGF) stimulate proliferation of fibroblasts, which causes scarring. Antimetabolite such as MMC and fluorouracil 5 inhibits migration and proliferation of fibroblasts, and reduces the incidence of scarring at the surgical site. The use of these materials has not been proven to be satisfactory, and has led to complications such as leakage, blebitis, and hypotonia and endophthalmitis [11–15].

Angiogenesis performs a fundamental role in wound healing because the establishment of new vessels facilitates the emigration of fibroblasts and inflammatory cells into wound site. VEGF (vascular endothelial growth factor) is an effective factor for angiogenesis [16–19]. Anti-VEGFs, such as bevacizumab, inhibit angiogenesis and are a potent healing agent for wound healing.

Therefore, antimetabolites and anti-VEGFs are used in glaucoma surgery to prevent the formation of scar tissue and to increase the success of surgery. Thus, in this randomized controlled trial study, we investigated the efficacy of MMC versus bevacizumab–methylcellulose on surgical outcomes and complications in combined phacoemulsification and non-penetrating deep sclerectomy surgery.

Methods

The current study was double-blind randomized controlled approved by the Iran Clinical Trials Center in 2016.

Based on the results of the pilot study, conducted on a scale of five samples per group, the IOP reduction rate after 6 months was evaluated as 35% for the group BMM, and as 50% for the group MMC. Given the values $\alpha = 0.05$, 80% power and the 15% difference in the IOP reduction rate, it was determined that the study required a minimum of 17 samples per group: This number was increased to 20 in order to enhance the validity of the study and to account for the possibility of sample size reduction. Random block sampling method and random allocation software were used to randomly select the patients into two groups. Participants were divided into two groups of 20, and then divided into two study groups based on blocking.

In the implementation stage, the surgeon was aware of the type of drug used but not aware of the choice of the relevant block and the allocation, and the evaluator (resident) was unaware of the type of drug used.

Patients with a diagnosis of open-angle glaucoma assigned to the glaucoma clinic of the Nikookari Hospital at Tabriz University of Medical Sciences and who otherwise met the inclusion criteria were enrolled in the current study. After explaining the research goals of the project, an informed consent form was given to the patients. Further explanation of the study was given to patients upon request, and patients were enrolled after signing the informed consent form. Patients underwent a combined phacoemulsification and non-penetrating deep sclerectomy surgery by one surgeon (A Mostafaei) between 2016 and 2017.

Inclusion criteria included patients with open-angle glaucoma who had advanced cup-to-disk ratio and progressive visual field defects and simultaneously needed cataract surgery, patients with glaucoma who needed a drug to control IOP but did not tolerate it well, or patients whose IOP was not well controlled

with maximal medication, and patients with glaucoma who needed multiple drugs to control IOP.

Exclusion criteria included patients who did not have acceptable systemic condition to receive bevacizumab, such as uncontrolled HTN, heart failure, arterial thromboembolic disease, and lack of proper access to patient for long-term follow-up, patients with congenital abnormalities of the anterior chamber angle, ocular infections, previous ocular surgery, uveitis, corneal diseases which can affect IOP or its measurement such as large pterygium or corneal scar, patients under 40 years of age, patients with diabetes, or patients with neovascular glaucoma. All patients were evaluated by a detailed visual examination before surgery, such as slit lamp biomicroscopy, BCVA (best spectacle-corrected visual acuity) by Snellen chart, measurement of intraocular pressure by Goldmann Applanation Tonometer, fundoscopy with a 90 D lens (evaluating cup/optic disk ratio), gonioscopy, lens opacity (classification system III), and the Humphrey 24-2 SITA Standard Perimeter (HFA 24-2) or (HFA 10-2) visual field evaluation depending on the cup/disk ratio; HFA 10-2 was used in patients with high cup/disk ratio, and finally, the number of drugs used was evaluated.

Surgical interventions

Non-penetrating glaucoma surgery is a glaucoma surgery performed by one of three methods: viscocanalostomy, canaloplasty and deep sclerectomy. In this study, patients underwent deep sclerectomy surgery. All patients were operated by one surgeon. Selected patients underwent general anesthesia. First, the bridle suture was used in the upper limbus using 0–6 silk for better exposure of the surgical site. A superior fornix-based conjunctival flap was dissected, followed by a 5 × 5 mm scleral flap, with an approximate thickness of 200 μm with the aid of 15° knife and 55° crescents. The scleral flap was dissected about 1–1.5 mm from the clear cornea. Twenty patients received MMC with concentration of 0.2 mg/mL for 2 min (SPAL Private Limited, Biotech Park, India) on sponge fragments placed on the edge of the scleral flap and then were washed using BSS. Phacoemulsification was then performed by a 3.5-mm clear corneal incision. The anterior chamber was filled with viscoelastic (sodium hyaluronate) (Bausch & Lomb, USA), and then, a continuous curvilinear capsulorhexis with a diameter of 5 mm was developed using capsulorhexis forceps. The phacoemulsification was done by the horizontal chop method, and the residual cortex was aspirated. After filling the capsular bag with sodium hyaluronate and folding of the intraocular lens (Alcon, Alcon Laboratories, USA) by injector, the implantation was attempted through a 3.5-mm corneal incision. The viscoelastic was removed, and the space of anterior chamber was formed with BSS. The corneal wound was closed using the stromal hydration technique. At the depth of the initial scleral flap, an internal scleral flap was created with a depth of 90% of the scleral thickness and dimensions of 4 × 4 mm. The internal flap was dissected anteriorly and excised. The roof of the Schlemm's canal was removed, and the two holes of the Schlemm's canal were dilated through a special 190-μm cannula with repeated and slow injection of sodium hyaluronate. The inner scleral flap was moved upward, and an indentation was created using the tip of a cotton swab on the roof of the canal and the Descemet's membrane. The Descemet's membrane was removed from the cornea, and a trabeculo-descemetic window was created. When the window was completed, the internal scleral flap was cut and the outer scleral flap was closed with nylon 10-0 sutures. Sodium hyaluronate was injected under the flap to temporarily fill the inside of the scleral area and prevent collapse and scarring after surgery. Finally, the conjunctiva was anchored by nylon 10-0 suture. Twenty patients received 0.3 mL of BMM (bevacizumab 1.25 mg incorporated into 2% methylcellulose) (F. Hoffmann-La Roche, Switzerland) as a subconjunctival injection at the flap site. Subconjunctival betamethasone and cefazolin were injected, and the eye was dressed.

After surgery, corticosteroid drops (betamethasone every 2 h) were started for patients, which were discontinued gradually over 2 months, and antibiotic drops (chloramphenicol every 6 h) were prescribed for 1 month. In the case of intraocular pressure of more than 21 mm Hg (by Goldmann Tonometer) during follow-up, anti-glaucoma eye drops were begun. Latanoprost was the first selective anti-glaucoma agent, and if the patient did not respond and the need for the second anti-glaucoma drug was seen, timolol 0.5% eye drops were used.

All patients were followed up with 1 day, 1 week, 2 weeks, 1 month, 3 months and 6 months post-operation. All patients were evaluated in terms of

visual acuity, intraocular pressure measurement (Goldmann Tonometer), slit lamp biomicroscopy and bleb morphology examination, fundoscopy with 90D lens, required drugs, ocular and systemic complications including increased blood pressure in patients at each visit. Subsequently, patients were subjected to Humphrey 24-2 SITA Standard perimetry (HFA 24-2) or HFA 10-2 primers after a 6-month follow-up.

Patients' blebs were evaluated after surgery using the Moorfields Bleb Grading System. In this system, bleb area, bleb height and bleb vascularity are examined. The bleb area is classified as a central demarcated area and a maximal area, each of which is graded from 1 to 5, depending on the Bleb area. Bleb Height is graded from 1 to 4 depending on the height of the Bleb. Bleb Vascularity is also graded from 1 to 5, each of which was evaluated and recorded in periodic examinations. The amount of leak from the Seidel test was evaluated by fluorescein paper and a slit lamp test.

The initial purpose of the current study was to evaluate the intraocular pressure and success rate of surgery within 6 months of follow-up. Complete success was described as IOP < 18 or at least 20% diminution in IOP from baseline without using an anti-glaucoma drug by the 6-month post-surgery follow-up. Relative success was described as IOP < 18 or at least 20% diminution in IOP from baseline with one anti-glaucoma drug at the 6-month follow-up after surgery and failure rate was described as IOP > 21 or not a 20% diminution in IOP from baseline at the 6-month follow-up after surgery, with either drug therapy or controlled IOP with more than one anti-glaucoma medication or IOP ≤ 5 in two consecutive visits 3 months after surgery or requiring further surgical treatment. Secondary outcomes of this study were to evaluate the patient's visual acuity and complications of MMC and BMM group, including thinning and conjunctival necrosis, bleeding, cell and flare in the anterior segment of the eye, etc. Any required therapeutic procedures during the 6-month follow-up were also reported.

Statistical analysis of data

Shapiro test was used to check the normalization of quantitative variables. An independent T test was applied to compare the mean of quantitative variables among the two groups, and in case of abnormality, the Mann–Whitney U test was used. Fisher's exact and Chi-square tests were applied to assess qualitative variables. In order to compare the variables that were measured before and 6 months after the intervention, a covariance analysis was used with regard to the previous values as auxiliary variables. The variance analysis of repeated measures was used to evaluate the effect of interventions over time. The results are reported as mean $\pm$ standard deviation for quantitative and frequency (percentages) for qualitative variables. A p value < 0.05 was supposed statistically significant.

Results

Forty patients were enrolled in the current study. Patients were randomly separated into two groups. At a 6-month follow-up, one patient in the MMC group and one in the group of BMM did not fully refer to postsurgical examinations and were excluded from the study. Two patients randomly underwent surgery in both eyes. Thus, 40 eyes in 38 patients were followed completely for 6 months. Twenty eyes were randomly selected and underwent a combined phacoemulsification and non-penetrating deep sclerectomy surgery with MMC, and 20 eyes underwent combined phacoemulsification and non-penetrating deep sclerectomy surgery along with subconjunctival bevacizumab–methylcellulose mixture. The primary specifications of patients are presented in Table 1. The initial characteristics of the patients, including age, sex, visual acuity, type of glaucoma, type of cataract and the amount of anti-glaucoma used in the two groups, were statistically similar in frequency distribution. The Consort flow diagram of this study is described in Fig. 1.

The intraocular pressure variations measured during the 6-month follow-up are shown in Fig. 2. The intraocular pressure of patients before surgery in the MMC group was 24.85 ± 2.83, which decreased to 13.75 ± 3.552 6 months after surgery. The intraocular pressure of patients before surgery in the BMM group was 24.45 ± 2.48, which decreased to 15.40 ± 3.267 6 months after surgery. The intraocular pressure reduction in both groups before surgery compared to 6 months after surgery was statistically significant ($p < 0.05$). Intraocular pressure reduction among two groups of MMC and BMM in 1 day

Table 1 Primary characteristics of the patients in MMC and BMM groups

	MMC group	BMM group	*p* value
Number	19	19	
Age	73.65 ± 7.849	70.70 ± 8.405	0.258†
Male/female	15/5	14/6	0.723*
Right/left	7.13	12t.8	0.113*
BCVA (logMAR)	1.01 ± 0.366	0.975 ± 0.316	0.392”
IOP (mmHg)	24.85 ± 2.834	24.45 ± 2.481	0.638†
Number of anti-glaucoma drugs	3.2 ± 0.523	2.9 ± 0.641	0.192”
Glaucoma type			
Exfoliation	15	12	0.311*
Primary open angle	5	8	0.311*
C/D ratio	0.88 ± 0.104	0.795 ± 0.139	0.026†

logMAR logarithm of minimal angle of resolution, *BCVA* best- spectacle - corrected visual acuity, *IOP* intraocular pressure, *C/D* cup/disk ratio, *MMC* mitomycin C, *BMM* bevacizumab–methylcellulose mixture

*Pearson Chi-square test

†Independent *T* test

”Mann–Whitney *U* test

($p = 0.545$), 1 week ($p = 0.542$), 2 weeks ($p = 0.507$), 1 month ($p = 0.055$) and 3 months ($p = 0.596$ in the BMM group and $p = 0.597$ in the MMC group) was not statistically different after surgery. However, the difference was statistically significant 6 months after surgery ($p = 0.135$), and the IOP reduction in the MMC group was more than the BMM group during the 6-month follow-up (mean 13.75 ± 3.552 mmHg vs. 15.40 ± 3.267 mmHg, respectively). The numerical value of the intraocular pressure of patients by group and time of follow-up of patients are shown in Table 2.

According to Table 2, the mean IOP at 6 months was statistically significantly lower (independent *T* test) ($p = 0.135$).

The average number of anti-glaucoma medications used in both the MMC and BMM groups was reduced from 3.2 ± 0.523 and 2.9 ± 0.641 before surgery to 0.15 ± 0.489 and 0.25 ± 0.55, respectively, 6 months after surgery, which was statistically significant ($p < 0.05$). There was no significant difference between the two groups in terms of the number of anti-glaucoma drugs used before surgery ($p = 0.192$) and 6 months after surgery ($p = 0.620$). Finally, 3 eyes (15%) from the MMC group and 4 eyes (20%) from the BMM group needed anti-glaucoma medications for intraocular pressure control. There was not any notable discrepancy between the two groups in terms of the number of anti-glaucoma drugs administered at any time ($p < 0.05$).

The mean visual acuity of patients before the surgery in the MMC and BMM groups was 1.01 ± 0.366 and 0.975 ± 0.316 Log MAR, respectively, which reached 0.461 ± 0.406 and 0.346 ± 0.299 Log MAR, respectively, 6 months after surgery (Fig. 3).

There was not any significant difference between the visual acuity of the patients among the two groups at any time ($p > 0.05$).

Seventeen of 20 eyes (85%) in the MMC group and 16 of 20 eyes (80%) in the BMM group were completely successful at the 6-month follow-up. One of 20 eyes (5%) in the MMC group and two of 20 eyes (10%) in the BMM group were relatively successful at the 6-month follow-up. Two of 20 eyes (5%) in the MMC group and two of 20 eyes (5%) in the BMM group failed to succeed at the 6-month follow-up. There was not any significant discrepancy in terms of success and failure between the two groups at the 6-month evaluation ($p = 0.362$).

The percentages of eyes with complete and relative success and failure were categorized by the group, as shown in Fig. 4.

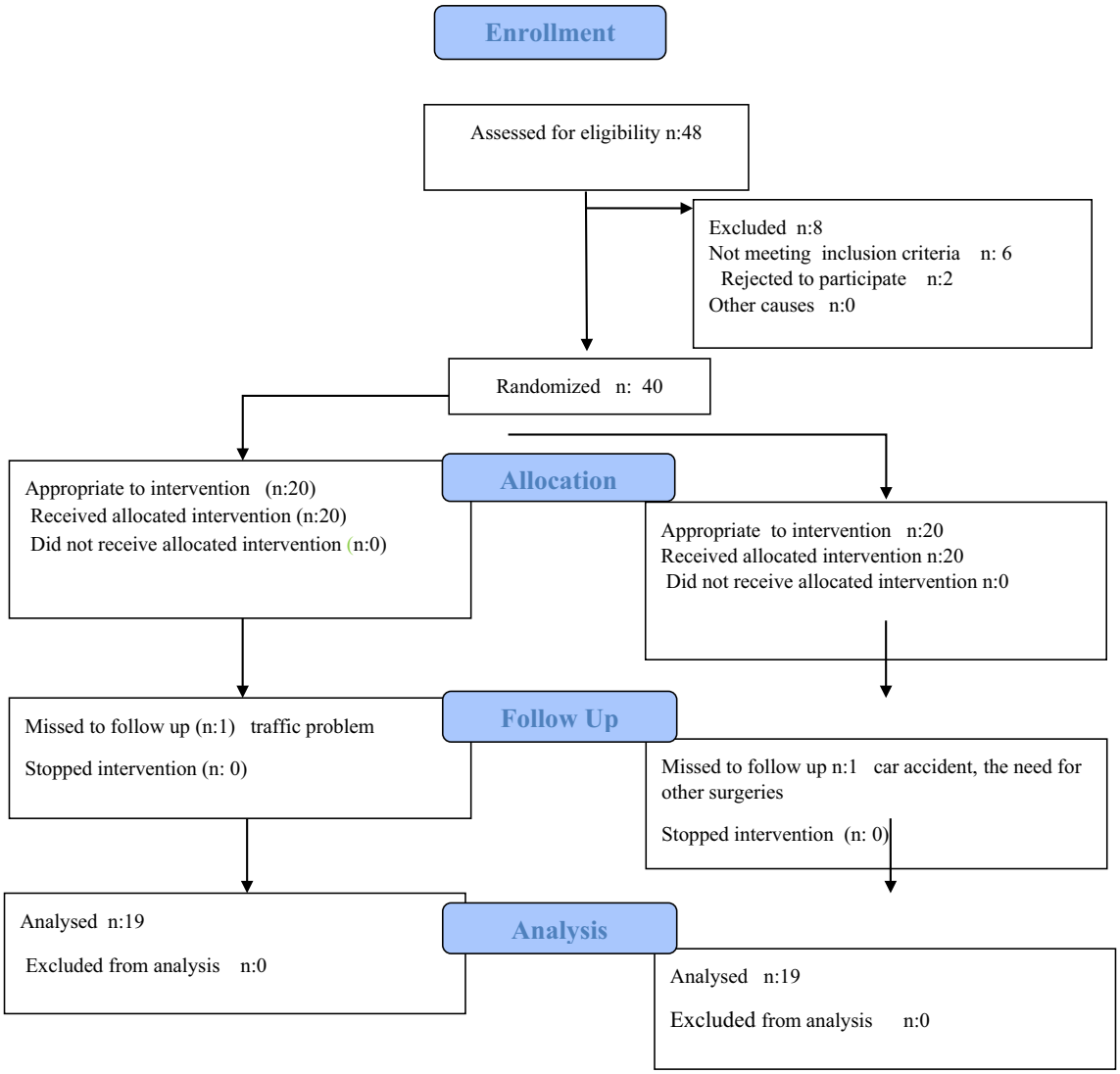

Fig. 1 Consort flow diagram of the study protocol

There was not any significant difference between the two treatment groups and the complete or relative success and failure at the 6-month follow-up ($p > 0.05$).

In most patients, the cataract was the nuclear sclerotic type (3 +), with 13 patients (59.1%) in the group of BMM and 9 patients (40.9%) in the group of MMC. The distribution of cataract was not prominently different among the 2 groups ($p = 0.536$). Performing perimetry for 17 eyes in the BMM group and 13 eyes in the MMC group was possible. Two eyes in the BMM group and five eyes in MMC group did not have enough visibility to perform perimetry due to severe lens opacity, and 1 eye in the BMM group and two eyes in the MMC group did not have acceptable perimetry due to low cooperation from the patients.

The mean MD before surgery in the MMC and BMM groups was -9.37 ± 4.09 and -7.92 ± 4.47, respectively, which reached -5.68 ± 3.73 and -4.66 ± 3.35, respectively, within 6 months after surgery which was statistically significant in each group ($p = 0.001$). There was no significant difference between the two groups in the mean MD 6 months after surgery ($p = 0.871$).

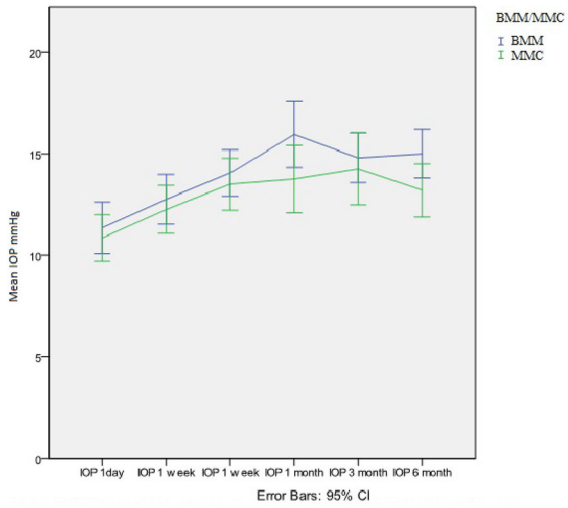

Fig. 2 IOP variations in two groups of MMC and BMM at different times 6 months after surgery. *IOP* intraocular pressure, *MMC* mitomycin C, *BMM* bevacizumab–methylcellulose mixture

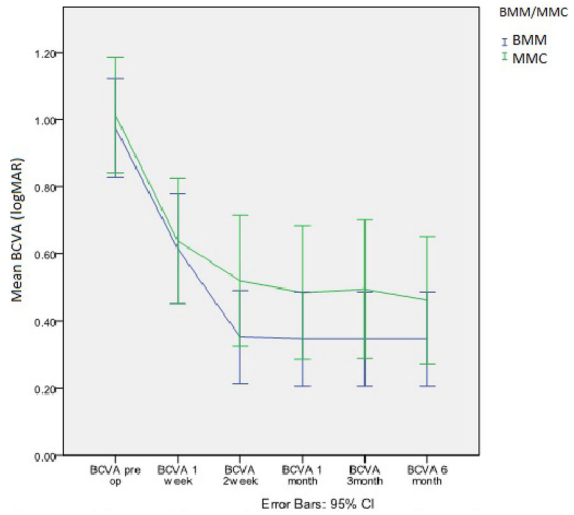

Fig. 3 BCVA comparison of patients at different times before and after surgery. *BCVA* best spectacle - corrected visual acuity, *logMAR* logarithm of minimal angle of resolution, *MMC* mitomycin C, *BMM* bevacizumab–methylcellulose mixture

Table 2 Degree of IOP in patients at different times of follow-up

IOP	MMC/BMM	Mean ± SD	*p value
Pre-op	BMM	24.45 ± 2.481	0.638
	MMC	24.85 ± 2.834	
1 day	BMM	11.35 ± 2.720	.545
	MMC	10.85 ± 2.455	
1 week	BMM	12.75 ± 2.613	.542
	MMC	12.25 ± 2.531	
2 week	BMM	14.05 ± 2.438	.507
	MMC	13.50 ± 2.743	
1 month	BMM	15.95 ± 3.471	.055
	MMC	13.75 ± 3.552	
3 month	BMM	14.80 ± 2.608	.596
	MMC	14.25 ± 3.796	
6 month	BMM	15.40 ± 3.267	0.135
	MMC	13.75 ± 3.552	

MMC mitomycin C, *BMM* bevacizumab–methylcellulose mixture

*Independent *T* test

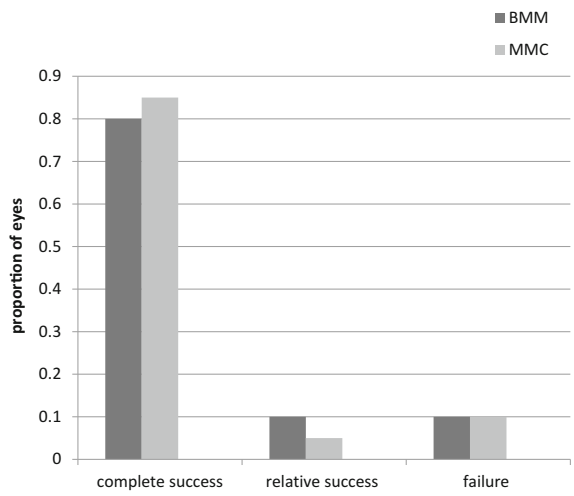

Fig. 4 Percentage of eyes with complete and relative success and failure by the group in 6-month follow-up

The PSD mean of the patients in the MMC and BMM groups was 5.64 ± 2.23 and 4.22 ± 2.82, respectively, which reached 4.70 ± 1.81 and 4.026 ± 2.57, respectively, 6 months after surgery, which was significant in the MMC group (p = 0.009), but there was no significant difference in the BMM group (p = 0.072). The PSD between the two groups did not differ significantly in the 6th month (p = 0.157).

There was no significant difference between the type of cataract with MD and PSD reduction 6 months after surgery ($p > 0.05$).

In terms of bleb morphology, based on the Moorfields Bleb Grading System, the rate of vascularity was significantly decreased in the MMC group after

1 month ($p = 0.053$), 3 months ($p = 0.03$) and 6 months ($p = 0.025$) compared to the BMM group. Bleb height was significantly higher in the BMM group 1 day after surgery ($p = 0.005$), but no statistically notable difference was observed between the two groups within 1 month or at 3 months or 6 months after surgery ($p > 0.05$). There was no significant difference in bleb extension among the two groups at the 6-month follow-up ($p = 1$). In general, however, patients in the MMC group encompassed more diffuse blebs than BMM group. The bleb morphology grading is given in Table 3.

Figure 5 shows the degree of vascularity, Fig. 6 shows the bleb extension by division of the group at different post-operation times, and Fig. 7 shows the bleb height by division of the group at different postsurgical times.

In terms of postoperative complications, one eye in the MMC group had an early leakage in the bleb site after surgery, which was treated with a bandage soft contact lens (Bausch and Lomb) and tissue adhesive within 1 week after surgery and did not require re-suturing. One case of conjunctival necrosis was observed near bleb in the MMC group, but intraocular pressure was normal, and the patient was followed up carefully. A case of hypotonic maculopathy was observed in the BMM group. No symptomatic complication was observed in any of the patients. Endophthalmitis was not observed in any of the patients. A case of cystic bleb with a maximum length of less than 3 mm was observed in the BMM group at the last examination at 6 months, and there was no need for an anti-glaucoma medication. Other postsurgical complications are listed in Table 4.

Table 3 Bleb morphology grading based on Moorfields Bleb Grading System at 6-month follow-up

	MMC	BMM	*p value
Height	1.50 ± 0.827	1.80 ± 0.410	0.154
Extension			
a	2.65 ± 0.587	2.10 ± 0.553	0.086
b	3.10 ± 0.447	2.95 ± 0.366	1
Vascularity	1.90 ± 0.308	2.15 ± 0.366	0.025

Extension a the central demarcated area of the bleb, *Extension b* the maximal area of the bleb, *MMC* mitomycin C, *BMM* bevacizumab–methylcellulose mixture

*Independent *T* test

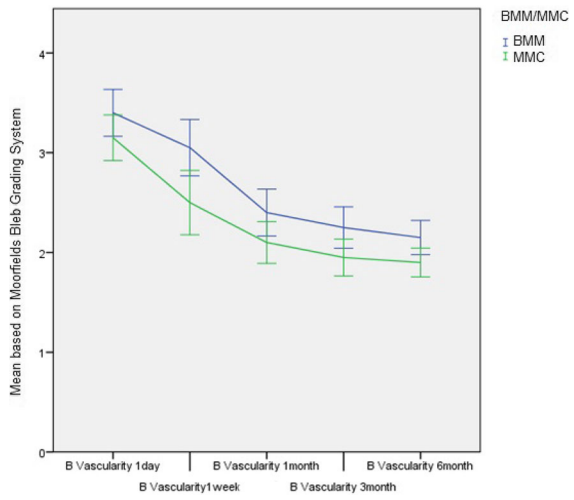

Fig. 5 Degree of vascularity by group. *MMC* mitomycin C, *BMM* bevacizumab–methylcellulose mixture

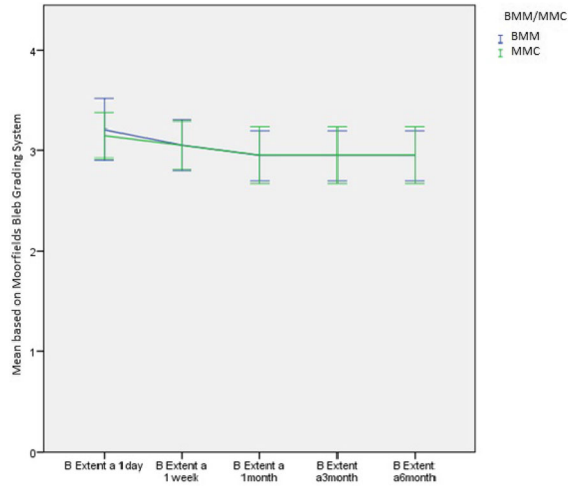

Fig. 6 Bleb extension a by group. *MMC* mitomycin C, *BMM* bevacizumab–methylcellulose mixture

Discussion

In this clinical trial, the effects of MMC and BMM were compared in combined phacoemulsification and non-penetrating deep sclerectomy surgery. The main reason of failure in glaucoma surgery is the creation of scar in the bleb site. Neovascularization, migration and proliferation of fibroblasts contribute to wound healing [20–22]. Anti-VEGFs reduce the migration of fibroblasts by inhibiting neovascularization. Anti-

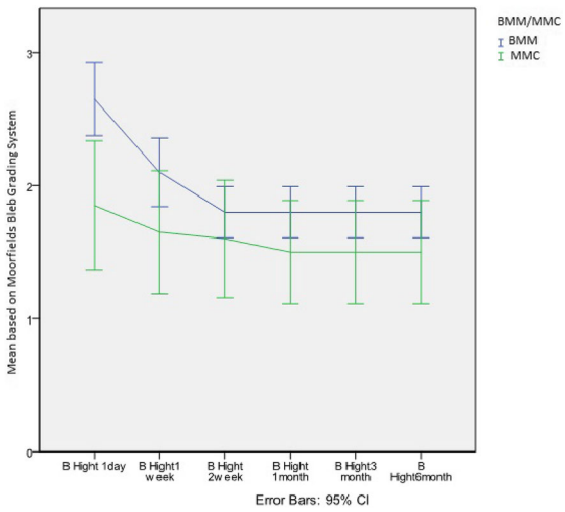

Fig. 7 Bleb height by group. *MMC* mitomycin C, *BMM* bevacizumab–methylcellulose mixture

VEGFs are effective in treating neovascularization of the anterior segment of the eye, including neovascular glaucoma [23–25]. Empirical evidence also suggests that these factors can have an inhibitory effect on Tenon's capsule fibroblasts [26]. Antimetabolites such as MMC and fluorouracil (5-FU) are used to regulate wound healing in glaucoma surgery. Increasing the success rate of surgery against the side effects of antibiotics such as bleb leakage, hypotonia, endophthalmitis, etc., should be considered [27, 28].

Table 4 Postoperative complications of patients by group

	BMM	MMC
Shallow AC	2 (10%)	1 (5%)
Transient hyphema	1 (5%)	2 (10%)
Transient bleb leak	0 (0%)	1 (5%)
Late bleb leak	0 (0%)	0 (0%)
Hypotony maculopathy	1 (5%)	0 (0%)
Endophthalmitis	0 (0%)	0 (0%)
Fibrin reaction	3 (15%)	2 (10%)
Phimosis	1 (5%)	0 (0%)
Opacification of the posterior capsule	2 (10%)	1 (5%)
Intervention after surgery		
Suturolysis	0 (0%)	0 (0%)
Nd:YAG laser anterior or posterior	3 (15%)	1 (5%)
Fibrin glue	0 (0%)	1 (5%)

MMC mitomycin C, *BMM* bevacizumab–methylcellulose mixture

Anand et al. conducted a retrospective case–control study with the aim of comparing the effect of mitomycin (MMC) with bevacizumab subconjunctival injection in primary deep sclerectomy. In this study, patients underwent primary DS from 2008 to 2010. Seventy-five eyes of 73 patients were the subject of surgery. Thirty-two eyes received subconjunctival MMC with concentration of 0.2 mg/ml for 2 min before scleral flap incision, and 43 eyes received subconjunctival bevacizumab with concentration of 2.5 mg in 0.1 ml at the end of operation. This study found that subconjunctival bevacizumab injection has the same effect as an MMC injection with deep sclerectomy without any additional side effects. There was no statistically significant difference between the mean IOP in the two groups over 2 years [4]. Another study by Panahibazaz et al. (2015) aimed at comparing MMC with bevacizumab on the success rate of phacotrabeculectomy. Forty-nine patients (74 eyes in total) were randomly divided into two groups. In the first group, MMC (0.25 mg/ml for 3 min) on sponge was placed in the surgical site and in the second group, bevacizumab (1.25 mg in 0.5 ml) injected in the vicinity of bleb at the end of surgery. The results demonstrated that MMC was more efficacious than bevacizumab controlling IOP after phacotrabeculectomy. However, there was no significant discrepancy in side effects and bleb characteristics between the two groups [1].

In another study carried out by Akkan and Cilsim [5] on comparing the effectiveness of primary trabeculectomy with bevacizumab to MMC, 42 patients with primary open-angle glaucoma were enrolled. Twenty-one patients received subconjunctival bevacizumab injections (2.5 mg in 0.1 ml), and 21 patients received topical MMC with concentration of 0.2 mg/ml for 3 min during the surgery. Patients were evaluated for 1 year, and bevacizumab, along with trabeculectomy, was shown to be a safe and effective method to diminish IOP, but MMC could better control IOP [5].

Sengupta et al. [2] conducted a clinical trial study aimed at evaluating the effect of bevacizumab in comparison with MMC in preventing bleb failure in patients undergoing phacotrabeculectomy surgery in India. In this study, 38 patients with significant and simultaneous cataract with primary open-angle glaucoma or chronic angle closure glaucoma were randomly divided into three groups. Group one (n = 13)

received MMC 0.3 mg/ml for 3 min on the sponge at the scleral bleb site, the second group ($n = 13$) received one subconjunctival bevacizumab injection (1.25 ml in 0.05 ml) before surgery, one subconjunctival bevacizumab injection at the bleb site (at the end of surgery) and one injection a week after surgery, and the third group ($n = 12$) received bevacizumab on the sponge with concentration of 1.25 mg /0.05 ml for 3 min at the scleral area during surgery. The patients were followed up at 6 months. This study demonstrated that bevacizumab, as a subconjunctival injection, could increase the rate of success and decrease the rate of scarring after phacotrabeculectomy [2]. In another study, Nilforushan et al. [6] compared the results of trabeculectomy augmented with subconjunctival bevacizumab versus trabeculectomy with MMC. Thirty-four patients (a total of 36 eyes) with uncontrolled glaucoma were enrolled. Eighteen eyes underwent trabeculectomy with subconjunctival bevacizumab injection (2.5 mg/0.1 ml), and 18 eyes underwent trabeculectomy with MMC (0.02% for 3 min). This study did not reveal significant difference in IOP after surgery between the two groups. Subconjunctival bevacizumab with trabeculectomy is an effective approach in controlling IOP, but its effect is less than MMC [6].

Another study by Ali Mostafaei et al. [29] at this center (Nikoukari Hospital) aimed at examining the effect of trabeculectomy with bevacizumab. Thirty-seven patients (37 eyes in total) with medically not controlled open-angle glaucoma were enrolled in the study. Seventeen eyes underwent subconjunctival bevacizumab injection (0.2 mg) during trabeculectomy, and 20 eyes were treated with normal saline injection as a control group. This study showed that bevacizumab was not more efficacious than placebo in controlling IOP at a 3-month follow-up [29].

In the current study, intraocular pressure was considerably reduced in both groups 6 months after operation. The difference in intraocular pressure reduction between the two groups was significant 6 months after surgery: In the MMC group, intraocular pressure was lower. The visual acuity of patients improved in both groups within 6 months after surgery. The number of anti-glaucoma drugs decreased in both groups after surgery. Symptomatic complications were not observed in any of the patients. In terms of ocular complications, conjunctival thinning in the site of the bleb was more pronounced in the MMC group and not any case of endophthalmitis was observed in the two groups of patients.

The small number of patients in the present study is one of the limitations of this study, and the relatively short follow-up of patients can also be noted. It is recommended that in subsequent studies, more patients be studied over a longer period of time.

This study showed that MMC and bevacizumab in combined phacoemulsification and non-penetrating deep sclerectomy surgery can increase the success rate of surgery and reduce intraocular pressure, and the intraocular pressure is better controlled in the MMC group.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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