

Original Article



Efficacy of Bevacizumab and a Bevacizumab-Methylcellulose Mixture on Intraocular Pressure After Deep Sclerectomy: A Double-Blind, Randomized Controlled Clinical Trial

Ali Mostafaei^{1,2*}, Nazli Taheri², Neda Moghaddam², Hanieh Salehi-Pourmehr¹

¹Research Center for Evidence-Based Medicine, Iranian EBM Centre: A JBI Centre of Excellence, Tabriz University of Medical Sciences, Tabriz, Iran

²Ophthalmology Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Article info

Article History:

Received: May 16, 2024

Revised: February 18, 2025

Accepted: April 12, 2025

ePublished: May 13, 2026

Keywords:

Non-penetrating deep sclerectomy, Mitomycin C, Bevacizumab, Bevacizumab-methylcellulose combination, Intraocular pressure

Abstract

Introduction: This study aimed to compare the effectiveness of bevacizumab administered alone versus combined with methylcellulose in reducing intraocular pressure during a six-month period following deep sclerectomy.

Methods: This comparative investigation, serving as an extension of a prospective randomized controlled trial, enrolled 30 eyes from 30 individuals diagnosed with open-angle glaucoma (15 eyes assigned to each treatment arm). Among participants, 33.3% presented with secondary open-angle glaucoma (pseudoexfoliation syndrome), while 66.7% had primary open-angle glaucoma requiring deep sclerectomy. Postoperatively, Group A received subconjunctival bevacizumab injections, whereas Group B received subconjunctival injections of a bevacizumab-methylcellulose mixture. Primary outcome measures included surgical success rates and bleb morphology assessment.

Results: Among eligible participants, 66.7% were male and 33.3% were female. Visual acuity measurements demonstrated no significant intergroup differences before or after surgery. Although Group B exhibited greater IOP reduction compared to Group A, statistically significant differences between groups emerged only at postoperative day one and at the six-month follow-up assessment. Success rates (complete or relative success) at six months showed no statistically significant variation between groups ($*P > 0.05$), nor did mean preoperative and postoperative values with standard deviations differ significantly. Vascularity scores decreased markedly in Group B at one-month, three-month, and six-month evaluations relative to Group A.

Conclusion: Utilizing a sustained-release delivery system that extends bevacizumab bioavailability appears to enhance surgical outcomes compared to conventional isolated bevacizumab ocular injections.

Trial Registration: IRCT2016121831450N1

Introduction

Global economic losses attributable to visual impairment approach US \$411 billion annually, imposing a substantial financial strain worldwide.¹ An estimated 4.4 million individuals (12% of blindness cases) experience vision loss due to glaucoma, ranking second only to cataract-related blindness, which accounts for 48% of cases.² Primary open-angle glaucoma (POAG) affects approximately 57.5 million people globally. Risk factors for glaucoma development include advanced age (over 60 years), family history of the disease, corticosteroid use, Diabetes Mellitus (DM), high myopia, hypertension, central corneal thickness below 500 micrometers, and ocular trauma. . In accord with statistics, projections indicate that 111.8 million individuals will have glaucoma by 2040.³ Enhancing

diagnostic capabilities and therapeutic strategies remains essential for minimizing glaucoma-associated disability. In recent years, non-penetrating deep sclerectomy has been increasingly adopted as a surgical intervention for POAG, offering fewer complications compared to conventional trabeculectomy.^{4,5} The primary mechanism underlying surgical failure involves fibrosis development in subconjunctival tissues and fibroblast accumulation at operative sites.⁵ Numerous investigations have explored the adjunctive use of mitomycin C and 5-fluorouracil.^{4,6} However, complications associated with these antifibrotic agents have prompted investigation of alternative pharmacological approaches to minimize adverse effects.² Anti-vascular endothelial growth factor agents, including bevacizumab and methylcellulose combinations, have been

*Corresponding Author: Ali Mostafaei, Email: alimostafaie@yahoo.com

Study Highlights

What is current knowledge?

- Bevacizumab is used as an adjunct in glaucoma surgery
- It reduces intraocular pressure by preventing scarring
- Standard injection uses bevacizumab alone

What is new here?

- Bevacizumab was combined with methylcellulose for sustained release
- The combination showed greater IOP reduction at day one and six months
- It also produced lower bleb vascularity scores at 1, 3, and 6 months
- Overall six-month surgical success rates did not differ between groups

described in previous researches.⁷⁻¹⁰ Given that Vascular Endothelial Growth Factor (VEGF) is upregulated in the aqueous humor of glaucomatous eyes and stimulates fibroblast proliferation, contributing to postsurgical scarring, bevacizumab administration reduces fibroblast accumulation in vitro and enhances surgical outcomes.⁹⁻¹³ Following trabeculectomy in glaucoma patients, bevacizumab appears to diminish scarring complications and slow glaucomatous progression. Considering bevacizumab's relatively short half-life, researchers have proposed various strategies to address this limitation, including combination with nanomaterials such as Thermosensitive PEG-PCL-PEG (PECE) Hydrogel, which enables sustained medication release, maintains effective local concentrations, and facilitates Intraocular Pressure (IOP) regulation.² Another approach combines bevacizumab with methylcellulose, a semisynthetic cellulose derivative possessing osmotic and nonabsorbent properties,¹⁴ thereby potentially improving surgical success through extended bevacizumab bioavailability via slow-release delivery systems. Experimental glaucoma surgery utilizing bevacizumab-containing implants has demonstrated both feasibility and promise.² Nevertheless, a systematic review of surgical intervention safety and efficacy in this population yielded inconclusive findings regarding deep sclerectomy, underscoring the need for additional investigation.¹⁵ Considering these promising perspectives, the present study compared bevacizumab monotherapy with a bevacizumab-methylcellulose combination following deep sclerectomy, evaluating differences in hypotensive efficacy, complication profiles based on glaucoma hemifield testing, and bleb characteristics according to the Moorfields Bleb Grading System over a six-month follow-up period.

Materials and methods

Study design and participants

This double-blind, randomized controlled clinical trial

adhered to the Declaration of Helsinki and was approved by the regional Ethics Committee. The study protocol was registered under code IRCT2016121831450N1. Trial reporting followed Consolidated Standards of Reporting Trials (CONSORT) guidelines.¹⁶ (Supplementary file 1).

Eligibility criteria for participants

Thirty patients diagnosed with open-angle glaucoma requiring surgical intervention at Nikookari Eye Hospital, Tabriz, Iran, were enrolled in our study. POAG diagnosis required IOP exceeding 21 mmHg despite medical therapy, glaucomatous optic disc changes, or visual field defects.

Exclusion criteria comprised previous ocular surgery history, other glaucoma types, pregnancy or breastfeeding, documented bevacizumab adverse effects, age below 40 years, ocular infections, uveitis, and congenital anterior chamber or angle abnormalities. All patients provided written informed consent.

Randomization and intervention

Enrolled patients underwent random assignment to two study groups (15 participants each), based on previous study findings.¹⁷ A computer-generated randomization system employing 1:1 allocation, with block sizes of four and six, determined assignment order. An independent third party, uninvolved in recruitment or data collection generated the allocation sequence to maintain blinding and ensure allocation concealment. Although the surgeon knew the intervention types, they remained unaware of patient block or allocation status. The evaluating resident physician remained blinded to the intervention type throughout the follow-up assessments.

Surgical interventions

All patients underwent standardized deep sclerectomy performed by a single anterior segment surgeon (A.M.). Selected patients received general anesthesia. A 6-0 silk bridle suture was placed at the superior limbus to optimize surgical field exposure. Following superior fornix-based conjunctival flap dissection, a 5×5 mm scleral flap approximately 200 microns thick was created using 15° and 55° crescent knives. The scleral flap was dissected approximately 1-1.5 mm into the clear cornea. At the initial scleral flap depth, an internal scleral flap measuring 4×4 mm was fashioned at 90% scleral thickness. The internal flap underwent anterior dissection and excision, exposing Descemet's membrane and creating a trabeculo-Descemet window. Following window completion, capsulorhexis forceps were used to unroof Schlemm's canal, the internal scleral flap was excised, and the external scleral flap was closed with 10-0 nylon sutures. Sodium hyaluronate injection beneath the flap temporarily filled the intrascleral space, preventing postoperative collapse and scarring. Conjunctival closure employed 10-0 nylon sutures.

Finally, a subconjunctival bevacizumab injection (1.25 mg/0.1 mL; F. Hoffmann-La Roche, Switzerland) was

administered at the flap site. For Group B, 0.3 mL of BMM (bevacizumab 1.25 mg incorporated into 0.5 cc of 2% methylcellulose) was delivered subconjunctivally using a 2cc syringe.

Medical intervention

Postoperative treatment included corticosteroid drops (betamethasone administered every two hours) tapered gradually over two months, antibiotic drops (chloramphenicol administered every six hours) for one month, and pilocarpine 2% eye drops administered every six hours for two months. When IOP exceeded 21 mmHg (measured by Goldmann tonometry), anti-glaucoma eye drops were initiated during follow-up. Latanoprost served as the first-line selective anti-glaucoma therapy; nonresponsive patients received timolol 0.5% eye drops.

Follow up

All patients underwent regular six-month postoperative follow-up at postoperative day one, weeks one, two, and four, and months three and six. A blinded resident physician performed all follow-up examinations.

Outcome Assessment

Comprehensive visual examinations conducted preoperatively and postoperatively included slit-lamp bio-microscopy, bleb morphology assessment (height, vascularity, extension), best spectacle-corrected visual acuity measurement using Snellen chart, Goldmann applanation tonometry for IOP, 90 D lens fundoscopy (cup-to-disc ratio), gonioscopy, and Humphrey 24-2 SITA standard perimetry or HFA 10-2 perimetry for patients with residual central fields only. Required medications, ocular complications, and systemic adverse events, including blood pressure elevation, were documented.

Success criteria were categorized as complete success, relative success, or failure. Complete success required IOP < 18 mmHg or $\geq 20\%$ reduction from baseline without anti-glaucoma medication at six-month follow-up. Relative success required IOP < 18 mmHg or $\geq 20\%$ reduction from baseline with one anti-glaucoma agent at six-month follow-up. Failure criteria included IOP > 21 mmHg or failure to achieve $\geq 20\%$ reduction from baseline at two consecutive visits three months postoperatively, despite medication, controlled IOP requiring more than one anti-glaucoma agent, IOP ≤ 5 mmHg at two consecutive visits three months postoperatively, or need for additional surgical intervention. All patients underwent Humphrey 24-2 (SITA standard) or HFA 10-2 perimetry at six-month follow-up.

Statistical Analysis

Statistical analyses were employed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Data normality was assessed using the Kolmogorov-Smirnov testing. Quantitative comparisons utilized independent-sample t-tests; qualitative analyses employed chi-square tests. Mann-Whitney U and Wilcoxon signed-rank

tests were used to compare quantitative data between and within groups for nonparametric distributions. Descriptive statistics presented categorical variables as frequencies and percentages, normally distributed quantitative data as means \pm standard deviations, and non-normally distributed data as medians with ranges. Statistical significance was defined as $P < 0.05$.

Results

Participant Flow and Baseline Characteristics

Screening identified 38 potentially eligible patients; eight of which were excluded (six were unable to meet the criteria, and two declined participation). The remaining 30 patients underwent random assignment to the study groups (15 per group). [Figure 1](#) presents the CONSORT flow diagram.

Among the 30 open-angle glaucoma cases, 33.3% had secondary Open Angle Glaucoma (OAG) and 66.7% had POAG. Males constituted 66.7% of the participants. [Table 1](#) displays baseline patient characteristics. Results demonstrated statistically similar baseline distributions for age, sex, visual acuity, glaucoma type, and number of anti-glaucoma medications across groups ($P > 0.05$).

Visual Acuity Outcomes

Preoperative mean visual acuity in Groups A and B was 0.42 ± 0.84 and 0.31 ± 0.42 Logarithm of the Minimum Angle of Resolution Logarithm of the Minimum Angle of Resolution (LogMAR), respectively, changing to 0.35 ± 0.67 and 0.37 ± 0.50 LogMAR at the six-month follow-up.

Intraocular Pressure Reduction

Both groups demonstrated statistically significant IOP reduction from preoperative values to the six-month follow-up ($P < 0.05$). In the bevacizumab group, mean preoperative IOP decreased from 26.73 ± 5.54 mmHg to 19.46 ± 6.90 mmHg at six months. The BMM group showed a reduction from 24.93 ± 4.33 mmHg preoperatively to 13.84 ± 6.04 mmHg at six months. [Table 2](#) presents mean IOP values for both groups throughout the follow-up period.

Group B (BMM) generally exhibited greater IOP reduction than Group A (bevacizumab), with six-month means of 13.86 ± 6.04 mmHg versus 19.46 ± 6.90 mmHg, respectively. Independent t-test analysis revealed significant intergroup differences only at postoperative day one and at the six-month follow-up ($P = 0.02$ for both). [Figure 2](#) illustrates IOP variations across the six-month follow-up period.

Medication Requirements

No significant intergroup differences emerged regarding anti-glaucoma medication requirements preoperatively ($P = 0.211$) or at the six-month follow-up ($P = 0.538$). Three eyes (20%) in the bevacizumab group and three eyes (20%) in the BMM group required anti-glaucoma medications for IOP control. The number of prescribed

CONSORT 2010 Flow Diagram

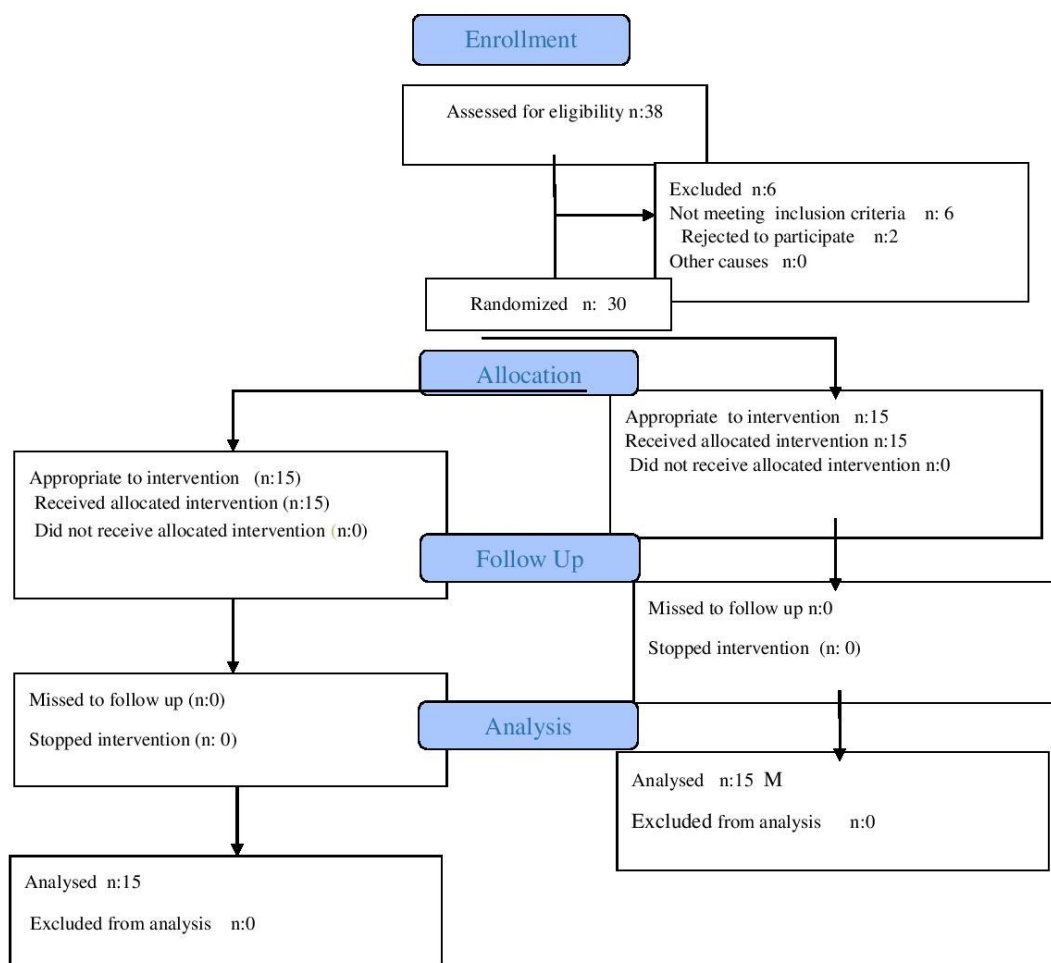


Figure 1. The CONSORT flow diagram of the study protocol

Table 1. Primary characteristics of patients in two group

	Bevacizumab group	BMM group	P value
Age	72.23 ± 9.39	70.32 ± 8.44	0.23 [‡]
Sex	10 male/5 female	10 male/5 female	1.0 [*]
Number of antiglaucoma agents	3.1 ± 0.42	3.2 ± 0.51	0.43 [*]
Glaucoma type	10 POAG/ 5 PEX glaucoma	10 POAG/ 5 PEX glaucoma	1.0 [*]
Mean preoperative IOP	26.73 ± 5.54	24.93 ± 4.33	0.3 [‡]

POAG: primary open-angle glaucoma /PEX glaucoma: pseudo-exfoliative glaucoma/ BMM: bevacizumab-methylcellulose mixture/ IOP: intraocular pressure

* Chi-square test

[‡] Independent T-test

^{*} Mann–Whitney U test

anti-glaucoma agents showed no significant intergroup variation ($P > 0.05$).

Surgical Success Rates

At the six-month follow-up, complete success criteria were met by 12 of 15 eyes (80%) in the bevacizumab group and 13 of 15 eyes (87%) in the BMM group. Relative success was achieved by 2 of 15 eyes (13.3%) in the bevacizumab group and 1 of 15 eyes (6.6%) in the BMM group. Treatment failure occurred in 1 of 15 eyes (6.6%) in each group. No significant intergroup differences emerged for complete success, relative success, or failure

at the six-month follow-up ($P > 0.05$) (Figure 3).

Visual Field Assessment

Goldmann perimetry performed preoperatively and at the six-month follow-up revealed no significant within-group or between-group differences (Table 3).

Bleb Morphology Assessment

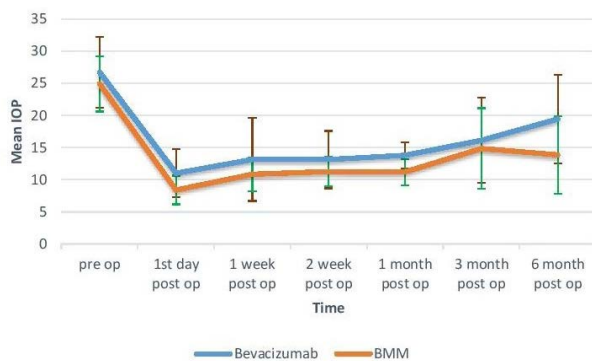
According to the Moorfields Bleb Grading System, vascularity scores decreased significantly in the BMM group at one month ($P = 0.043$), three months ($P = 0.021$), and six months ($P = 0.033$) compared to the bevacizumab

Table 2. The values of IOP by the time of follow up

IOP	Group	Mean ± SD	P value*
Pre-op	Bevacizumab	26.73 ± 5.54	0.3
	BMM	24.93 ± 4.33	
1 st -day post-op	Bevacizumab	11.00 ± 3.76	0.02
	BMM	8.40 ± 2.22	
One week post-op	Bevacizumab	13.14 ± 6.44	0.2
	BMM	10.86 ± 2.64	
2-week post-op	Bevacizumab	13.13 ± 4.45	0.1
	BMM	11.26 ± 2.28	
1-month post-op	Bevacizumab	13.80 ± 4.67	0.06
	BMM	11.20 ± 2.04	
3-month post-op	Bevacizumab	16.14 ± 6.64	0.6
	BMM	14.86 ± 6.27	
6-month post-op	Bevacizumab	19.46 ± 6.90	0.02*
	BMM	13.86 ± 6.04	

BMM: Bevacizumab-methylcellulose mixture

*Independent t-test

**Figure 2.** IOP variations before and after surgery over six months in bevacizumab and BMM groups. IOP: intraocular pressure/ BMM: Bevacizumab-methylcellulose mixture

group. Bleb height was significantly greater in the bevacizumab group at postoperative day one ($P=0.004$), but no statistically significant intergroup differences persisted at one, three, or six months ($P>0.05$). Bleb extension showed no significant intergroup difference at the six-month follow-up ($P=0.959$), although Group A demonstrated more diffuse bleb morphology than Group B. Table 4 and Figures 4-7 present detailed bleb morphology grading.

Complications

No systemic complications occurred in any patient. Ocular complications in the bevacizumab group included a shallow anterior chamber requiring resuturing in one patient and transient hyphema resolving with topical medication and observation in one patient. Endophthalmitis was not observed in either group. One encapsulated bleb measuring less than 3 mm was noted in the BMM group at the six-month follow-up, requiring no anti-glaucoma medication. Table 5 lists additional postoperative complications.

Discussion

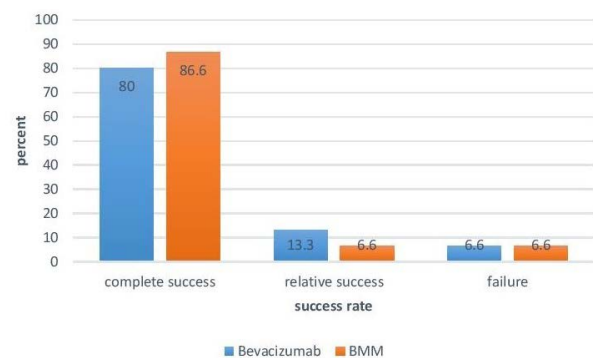
This investigation compared bevacizumab alone

Table 3. Comparison of GHT criteria between two group

	Group	Mean ± SD	P value*
Before	Bevacizumab	-20.94 ± 1.70(MD)	0.90
	BMM	-20.87 ± 1.81	
Six months after	Bevacizumab	-20.81 ± 1.22(MD)	0.93
	BMM	-20.77 ± 1.6	
Before	Bevacizumab	8.07 ± 0.65(PSD)	0.99
	BMM	8.07 ± 0.76	
Six months after	Bevacizumab	8.12 ± 0.53(PSD)	0.83
	BMM	8.20 ± 0.47	

GHT: glaucoma hemifield test, BMM: Bevacizumab-methylcellulose mixture, MD: mean, PSD: pattern standard deviation

*Independent t-test

**Figure 3.** The success rate of surgery at the six-month follow-up between groups. BMM: Bevacizumab-methylcellulose mixture

versus a bevacizumab-methylcellulose combination for IOP management following non-penetrating deep sclerectomy. Both groups demonstrated reduced anti-glaucoma medication requirements postoperatively, with no significant intergroup differences, preoperatively or postoperatively. Vascularity scores decreased significantly in the BMM group at one, three, and six months relative to the bevacizumab group. Bleb extension and height showed no significant intergroup differences at the six-month follow-up, nor did success rates (complete success, relative success, or failure) differ significantly between groups ($P>0.05$). Regarding postoperative complications, no systemic adverse events or endophthalmitis cases occurred. Subconjunctival tissue fibrosis and fibroblast accumulation at surgical sites represent primary mechanisms of bleb failure in glaucoma surgery.¹⁴ Neovascularization, fibroblast migration, and proliferation contribute to wound healing processes.^{15,18} Previous investigations have employed mitomycin C and 5-FU as adjunctive therapies.^{4,6} Complications associated with these antifibrotic agents, including hypotony and bleb leakage,² have stimulated interest in the alternative pharmacological approaches to minimize adverse effects while managing surgical failure.^{4,13} Anti-VEGF agents, including bevacizumab and methylcellulose combinations, have been explored for this purpose.^{4,7-10} Bevacizumab appears to reduce fibroblast proliferation and migration while inhibiting neovascularization, thereby diminishing scar formation and enhancing surgical outcomes.^{10,11}

Given bevacizumab's limited half-life, combination

Table 4. Bleb morphology grading based on Moorfields Bleb Grading System at six-month follow-up

	Bevacizumab	BMM	P value*
Height	1.66 ± 0.48	1.71 ± 0.46	0.176
Extension a	2.13 ± 0.35	2.07 ± 0.26	0.916
Extension b	2.93 ± 0.59	2.92 ± 0.26	0.959
Vascularity	2.21 ± 0.80	1.98 ± 0.35	0.033

Extension a: The central demarcated area of the bleb /Extension b: The maximal size of the bleb

BMM: Bevacizumab-methylcellulose mixture

*Independent t-test

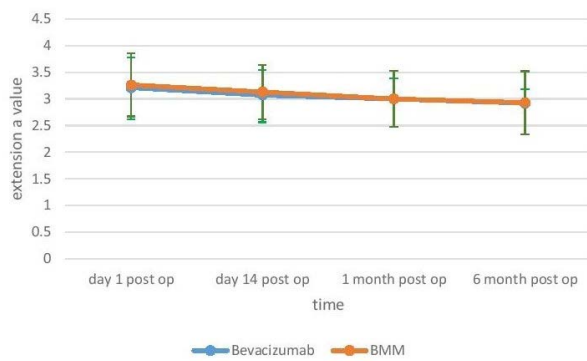


Figure 4. Bleb extension in both groups at different post-surgical times. BMM: Bevacizumab-methylcellulose mixture

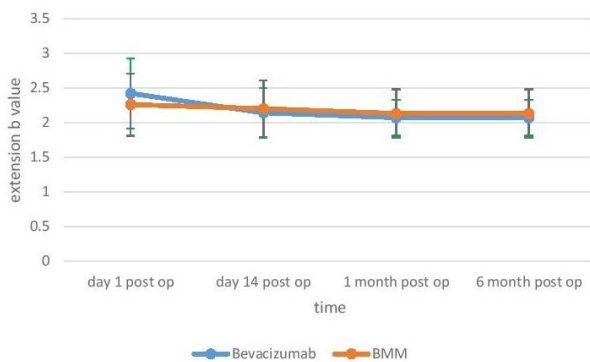


Figure 5. Bleb Extension b in both groups at different post-surgical times. BMM: Bevacizumab-methylcellulose mixture

with methylcellulose as a delivery system represents one strategy to address this limitation.¹⁴ Shouman et al.¹⁹ evaluated 2% methylcellulose application during trabeculectomy with subsequent histologic examination in an experimental animal model, concluding that methylcellulose may possess anti-healing properties that reduce IOP following trabeculectomy. However, they emphasized the need for additional research given potential interspecies differences in tissue response, while acknowledging methylcellulose’s promising profile.

Paula et al.⁹ (2013) investigated bevacizumab-loaded polyurethane implants as a novel drug delivery system for anti-VEGF antibody administration in a rabbit glaucoma filtration surgery model. In vitro bevacizumab release was quantified using size-exclusion high-performance liquid chromatography, while in vivo effects were examined through bleb characteristics, collagen deposition, and

Table 5. Postoperative complications of patients by group

	Bevacizumab	BMM
Shallow AC	1 (6.6%)	0 (0%)
Transient hyphema	1 (6.6%)	0 (0%)
Transient bleb Leak	0 (0%)	0 (0%)
Late bleb leak	0 (0%)	0 (0%)
Hypotony maculopathy	0 (0%)	0 (0%)
Endophthalmitis	0 (0%)	0 (0%)
Cystic bleb	0 (0%)	1 (6.6%)

BMM: Bevacizumab-methylcellulose mixture

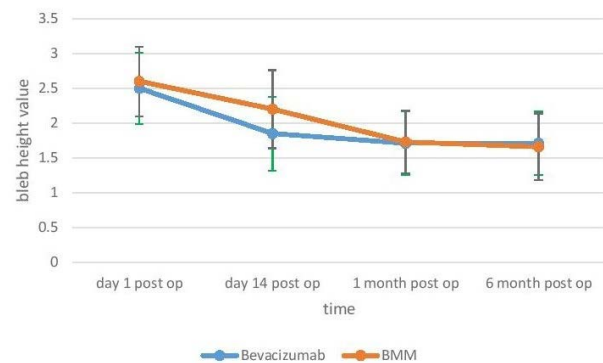


Figure 6. Bleb height in both groups at different post-surgical times. BMM: Bevacizumab-methylcellulose mixture

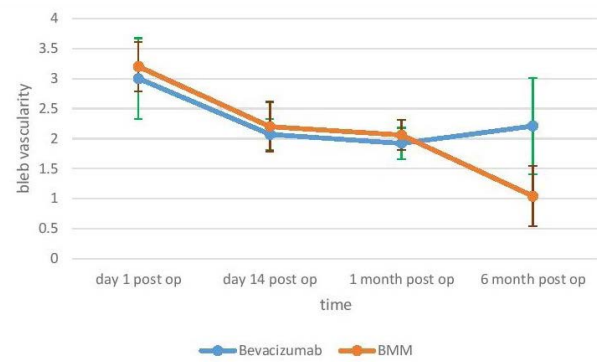


Figure 7. Bleb vascularity in both groups at different post-surgical times. BMM: Bevacizumab-methylcellulose mixture

immunohistological VEGF expression analysis. High-Performed Liquid Chromatography (HPLC) demonstrated that only 10% of implant-contained bevacizumab had been released by postoperative day five. Although in vivo studies revealed no adverse effects and reduced VEGF-expressing fibroblasts, no significant differences in bleb area scores or collagen deposition intensity emerged between Polyurethane Implant (PUI) PUI and Bevacizumab-loaded Polyurethane Implant (BPUI) groups. This research confirmed that BPUI bevacizumab release occurred only transiently—likely from film surfaces—yet the implants were well-tolerated in rabbit eyes.

In a pilot study, Paula et al.²⁰ examined BMM for enhancing bevacizumab bioavailability as an adjunctive therapy to non-penetrating deep sclerectomy, demonstrating BMM’s safety and practicality as a

bevacizumab delivery system during early postoperative periods following deep sclerectomy. Their findings suggested that bevacizumab-methylcellulose combinations may maintain a therapeutic presence at surgical sites longer than simple subconjunctival antibody injections. Study limitations included the absence of a control group, limited sample size, and a brief follow-up duration. Anand et al.⁸ conducted a retrospective case-control investigation comparing mitomycin C (MMC) effects with subconjunctival bevacizumab injection in primary deep sclerectomy, finding comparable efficacy between subconjunctival bevacizumab and MMC augmentation with deep sclerectomy without additional adverse effects. Mostafaei et al.¹⁷ subsequently evaluated mitomycin C versus BMM effects on IOP following combined phacoemulsification and non-penetrating deep sclerectomy in open-angle glaucoma patients through a randomized double-blind controlled trial. While both MMC and BMM demonstrated efficacy in combined surgical success, MMC provided superior IOP control. Han Q et al.²¹ evaluated a sustained-release system incorporating bevacizumab-loaded PEG-PCL-PEG hydrogel for intracameral injection, demonstrating enhanced therapeutic efficacy in glaucoma filtration surgery. Their investigation of postoperative scarring and bleb survival following intracameral bevacizumab injection combined with PECE hydrogel drug release showed that the bevacizumab-loaded PECE hydrogel group achieved the lowest postoperative IOP values and significantly more persistent blebs, establishing superior efficacy compared with isolated bevacizumab injections.

IOP Reduction Analysis

Our primary focus involved demonstrating overall IOP reduction from baseline to six months, which reached statistical significance in both groups ($P < 0.05$). Multiple factors potentially contributed to this trend. Natural healing processes and trabecular meshwork remodeling following surgery²² may improve outflow facility as postoperative inflammation subsides, contributing to additional IOP reduction. Ongoing effects of postoperative medications, changes in medication regimens, or variations in patient adherence²³ may also influence IOP. Additionally, inherent IOP measurement variability and potential diurnal fluctuations warrant consideration.²⁴

Clinical Implication

This study establishes that BMM administration during non-penetrating deep sclerectomy may enhance surgical success rates without significant complications compared to bevacizumab monotherapy. BMM demonstrates superior efficacy in IOP reduction following deep sclerectomy and can be safely recommended for clinical application in deep sclerectomy procedures.

Limitations and Future Directions

Study limitations include a relatively short follow-up duration and a modest sample size. Future large-scale

randomized controlled trials should investigate alternative anti-VEGF agents and innovative bevacizumab delivery systems in glaucoma surgery.

Conclusion

Sustained-release delivery systems that extend bevacizumab bioavailability appear to improve surgical outcomes compared to conventional isolated bevacizumab ocular injections. Subsequent investigations should explore additional anti-VEGF agents and novel delivery platforms for bevacizumab administration in glaucoma surgery.

Acknowledgments

We would like to thank the Research Department and the Vice-chancellor of Tabriz University of Medical Sciences for financial support and ethical approval

Authors' Contribution

Conceptualization: Ali Mostafaei
 Data curation: Ali Mostafaei, Nazli Taheri, Neda Moghaddam
 Formal analysis: Hanieh Salehi-Pourmehr
 Funding acquisition: Ali Mostafaei
 Investigation: Ali Mostafaei
 Methodology: Ali Mostafaei, Nazli Taheri, Neda Moghaddam
 Project administration: Ali Mostafaei
 Resources: Ali Mostafaei, Nazli Taheri, Neda Moghaddam
 Software: Hanieh Salehi-Pourmehr
 Supervision: Ali Mostafaei
 Validation: Ali Mostafaei
 Visualization: Ali Mostafaei
 Writing—original draft: Nazli Taheri, Neda Moghaddam, Hanieh Salehi-Pourmehr
 Writing—review & editing: Ali Mostafaei

Competing Interests

The authors declare no conflict of interest.

Ethical Approval

The regional ethics committee of Tabriz University of Medical Sciences approved this study (IR.TBZMED.REC.1935.996).

Funding

Tabriz University of Medical Sciences supported this study.

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