• Clinical Research •

Efficacy of trabeculectomy combined with collagen implant and mitomycin C compared to with mitomycin C alone in glaucoma: a retrospective cohort study

Medhat A Bakr[1], Ussama Alnaqib[2], Saleh S. Algamdi[3], Hatim Najmi[4], Askar K. Alshaibani[4], Moataza M. Abdel Wahab[5], Mohammed Barnawi[6], Abdulaziz I. AlSomali[7], Khalid B. Alburayk[3]

[1]Ophthalmology Department (Glaucoma), Imam Abdulrahman Bin Faisal University, Dammam 34221, Saudi Arabia
[2]Glaucoma Department, Dhahran Eye Specialist Hospital, Dhahran 34257, Saudi Arabia
[3]Ophthalmology Department, Imam Abdulrahman Bin Faisal University, Dammam 34221, Saudi Arabia
[4]Dhahran Eye Specialist Hospital, Dhahran 34257, Saudi Arabia
[5]Family and Community Medicine Department, Imam Abdulrahman Bin Faisal University, Dammam 31441, Saudi Arabia
[6]Postgraduate Training Program for Preventive Medicine in Taif, Ministry of Health, Taif 21944, Saudi Arabia
[7]King Faisal University, Ahsaa 31982, Saudi Arabia
Correspondence to: Medhat A Bakr. Ophthalmology Department, Imam Abdulrahman Bin Faisal University, Dammam 34221, Saudi Arabia. medhat_6@hotmail.com
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Abstract

● **AIM:** To compare trabeculectomy with mitomycin C (MMC) alone to trabeculectomy with a combination of MMC and Ologen implant in glaucoma patients.

● **METHODS:** A retrospective cohort study including 94 eyes recruited in two groups [50 in the mitomycin C (MMC) group and 44 in the combined Ologen+MMC (OLO) group]. The medical charts of the patients were collected and analyzed at different time points: 1d, 10-30d, 3-5mo, 6-9mo, 1, 2, and 3y postoperatively. We assessed the intraocular pressure (IOP) reduction, cup-disc (CD) ratio, visual acuity (VA), bleb morphology, and complications.

● **RESULTS:** Both groups showed a significant reduction of the mean IOP from 28.8 to 10 mm Hg in 1 and 2y. However, no significant difference was noticed between both groups. We observed a stable visual acuity in 40% and 11.8%, improved in 20% and 41.2%, and worsened in 40% and 47.1% in the MMC and OLO groups, respectively. Complications were statistically significantly lower in the OLO group than in the MMC group. Bleb morphology showed statistically significant differences between the groups, with grade C blebs being more prevalent in the OLO group (43.2% in 1y) compared to the MMC group (16% in 1y) and flat blebs being more prevalent in the OLO group (43.2% in 2y) compare to MMC group (20% in 2y). Both MMC and OLO groups were effective in reducing IOP.

● **CONCLUSION:** The combined use of the Ologen implant and MMC may provide better outcomes in terms of preserving the optic nerve structure, reducing complications, and maintaining stable bleb morphology postoperatively.

● **KEYWORDS:** Ologen implant; mitomycin C; intraocular pressure; glaucoma; trabeculectomy

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INTRODUCTION

Intraocular pressure (IOP) is considered the most important risk factor for the development and progression of glaucoma. Irreversible blindness is caused by glaucoma which serves as the leading cause of blindness globally. It is also responsible for bilateral blindness after cataracts which ranked glaucoma as the second leading cause worldwide. Hence, therapies are mainly targeting IOP control to stop glaucoma progression, either by medical management or surgical intervention[1].

Trabeculectomy was first described in 1968 by Cairns[2] and modified by Watson[3] and Onol[4]. Risk factors for failure of trabeculectomy encompass uveitic or neovascular glaucoma, previous intraocular surgery, young age, and black race[5]. Trabeculectomy aims to decrease the IOP to prevent the progression of glaucomatous optic neuropathy; however, several complications can limit and prevent this aim. Bell *et al*[6] explored the recent effectiveness of mitomycin C (MMC)

adopted in performing trabeculectomy in IOP which has been a gold standard glaucoma surgery since the mid of 1960s. The author aimed to identify the difference trabeculectomy may cause for slightly intrusive glaucoma surgery devices along with the analysis of the range of doses and agents utilized during the process. The success rate was observed to be higher when utilizing 20 μg of MMC compared to 10 μg with the XEN microshunt. PreserFlo microshunt showed a higher rate of success with substantial MMC dosage, which results in adverse events and chances of surgery to happen again which is costly. The ideal MMC dose for PreserFlo has not yet been determined. In comparison, trabeculectomy with MMC is a more well-established procedure with strong evidence of success[6]. Thus, trabeculectomy with MMC appears to have a more consistent record of success compared to the PreserFlo microshunt, which still requires further evaluation and optimization regarding dosage and associated risks. The author further expresses higher chances of improvement if MMC is adopted for bleb-forming slightly intrusive glaucoma procedures[6].

Sharpe *et al*[7] presented a comparative study for the implantation of ab interno XEN gelatin stent (Allergan, Dublin, Ireland) with MMC and primary trabeculectomy in patients using the MMC. From 2014 to 2019 minimum complication was observed for both groups; however, IOP complications were nearly equal to IOP reductions in MMC. It was noted that XEN came in handy in reducing IOP to a sustainable rate. Implantation of XEN gelatin stent successfully qualified in safety and efficacy as compared to trabeculectomy with MMC. A collagen matrix implant, known as the Ologen implant, has been introduced into the practice field of managing glaucoma to increase the success rate of trabeculectomy. It is a biodegradable and implantable dry porous material composed of collagen (>90%) and glycosaminoglycans (<10%). Ologen implants can guide fibroblasts, affect postoperative fibrotic processes, modulate scar formation, and separate the conjunctiva from the episcleral tissue; thus, preventing adhesion[8]. Multiple studies have compared MMC intrusion with other disease-alleviating drugs, with mixed results.

José *et al*[9] investigated the outcomes of primary trabeculectomy in patients using MMC compared to the effects of MMC combined with intracameral bevacizumab in the treatment of open angle glaucoma. The author concluded that intracameral bevacizumab during MMC-augmented primary trabeculectomy elevates the possibility of achieving low IOP outcomes. This approach may be beneficial when planning surgeries that aim to target pressures in the low teens. Chean *et al*[10] determine the long-lasting results of post-operation for deep sclerectomy-trabeculectomy (DST) for glaucoma treatment with MMC. A decrease in IOP medication was noticed with an average IOP reduction at every follow-up. Totally 85.7% of the eyes achieved absolute success at the final follow-up. Complications that were recorded consist of transient hyphaema, transient choroidal effusion, shallow anterior chamber, bleb leak, bleb revision, bleb needling, and surgery. The author concluded that the use of DST combined with MMC shows effective and lasting long-term results in glaucoma treatment, with no significant complications observed. Multiple studies have compared its use with that of MMC, with mixed results[11-13].

In this study, we aimed to compare the use of Ologen implants combined with MMC versus the use of MMC alone in glaucoma patients who underwent trabeculectomy.

PARTICIPANTS AND METHODS

Ethical Approval This study was approved by the Institutional Review Board (IRB) at Dhahran Eye Specialist Hospital (1081/2020). The need for consent was waived due to the retrospective nature of the study. However, the data were confidentially handled. All patients (or guardians in the case of congenital glaucoma) signed consent forms for the surgical interventions.

This retrospective cohort study was conducted at Dhahran Eye Specialist Hospital, Eastern Province, Saudi Arabia. In this study, we analyzed the medical charts of all patients with medically uncontrolled glaucoma who underwent trabeculectomy with MMC plus an Ologen implant (OLO group) between January 2016 and December 2021, and matched the number of those participants with patients who underwent trabeculectomy with MMC alone (MMC group); considering the age, type of glaucoma, and disease severity of disease at the same period of time for all participants.

Study participants included individuals with medically uncontrolled primary open angle glaucoma, secondary open angle glaucoma, primary angle-closure glaucoma (ACG), or primary congenital glaucoma. Patients with uveitic glaucoma, neovascular glaucoma, and previous glaucoma or vitreoretinal surgery were excluded from the study.

We collected the patients' demographics, comorbidities, type of glaucoma, number of glaucoma medications, visual acuity (VA), cup-disc (CD) ratio, pre-op IOP, and history of laser glaucoma therapy if present.

Postoperative data were collected at several time points, day 1, days 10-30, months 3-5, months 6-9, year 1, year 2, and year 3 postoperatively, this included IOP, CD ratio, number of medications, and bleb morphology. Bleb morphology was categorized into four grades: A, flat bleb; B, low focal, thin cystic, or vascularized bleb; C, high local, low diffuse, or formed bleb; and D, well-formed, high diffuse, or large paucivascularized bleb. Complications including bleb leakage, blebitis, hypotony maculopathy, choroidal effusion, and endophthalmitis, were assessed. Failure of surgery was defined

as either the development of high IOP despite complete medication or the need for additional glaucoma surgery to control IOP.

Data were manually collected from hospital records and double-checked by two authors for each participant retrospectively to ensure the accuracy and reliability of the records. This process involved ensuring that the information gathered, including demographic details, clinical histories, and treatment outcomes was consistent to minimize errors and enhance the validity of the study results.

Sample Size For a study power of 99% and at a confidence level of 95%, IOPs of 11.9±2.9 and 14.6±2.7 mm Hg were assumed. A minimum required sample size of 13 eyes for each group was calculated using the Stata/SE software version 11.0. However, the number of participants in the present study exceeded this value. We started the study with 50 eyes in the MMC group, 44 eyes in the OLO group (Ologen+MMC), followed by 39 and 30 eyes in the year-2 and 36 and 16 eyes, in the year-3 follow-up, respectively.

Data Management Improvement was considered in cases with decreased IOP, stable VA, and decreased number of medications required to control IOP. Success was analyzed at three different target levels: IOP≤21, ≤17, and ≤15 mm Hg, complete success was defined as the achievement of the target IOP without medications, and qualified success was defined as the achievement of the target IOP regardless of medications.

Surgical Techniques A single glaucoma surgeon performed all trabeculectomies using local or general anesthesia. The procedure involved placing an 8-0 polyglactin vicryl corneal traction suture and designing a fornix-based conjunctival flap under surgical asepsis. Sub-Tenon dissection and hemostasis were performed. A rectangular 4.0×4.0-mm half-thickness scleral flap was created in the superiotemporal area. Four sponges soaked in a 0.2 mg/mL MMC solution were applied for 2min under the superior and temporal bulbar conjunctiva in a diffuse area spanning 90 degrees. The area was then thoroughly irrigated with a balanced salt solution. Next, a 3.0×1.0-mm sclerectomy and a peripheral iridectomy were conducted. The scleral flap was repositioned and closed with a single interrupted 10-0 monofilament nylon suture. In the OLO group, an Ologen implant (6 mm diameter, 2 mm height) was positioned on the scleral flap without suture and the conjunctiva was closed using an interrupted 10-0 monofilament nylon suture. Postoperative care included applying topical moxifloxacin and 1% prednisolone acetate eye drops four times a day, with a gradual tapering of the steroid drops over the subsequent 8wk.

Statistical Analysis Statistical analyses were performed using SPSS software version 26 (Armonk, NY: IBM Corp). Statistical tests were two-tailed, with the significance level set at 5%.

Numerical data have been expressed as ranges, means±standard deviations, and medians, whereas categorical data are expressed as numbers and percentages. Shapiro-Wilk test was employed to assess the normality of the data. Numerical data were compared using an independent Student's *t*-test and the Mann-Whitney *U* test for parametric and non-parametric analyses, respectively. Categorical variables were analyzed using the *Z*-test of proportion and the Chi-squared test (Fisher's exact test for small, expected values).

Kaplan-Meier survival curves were used to assess the cumulative probability of success. Inter-group success probabilities were compared using the log-rank test.

As for both correlation and regression, significance was set at $P<0.05$. Pearson's correlation was performed to determine the relationship between continuous variables. A multiple linear regression analysis was conducted to assess the association between IOP and various independent variables.

RESULTS

This study included 94 eyes: 50 and 44 in the MMC and OLO groups, respectively. Patients' baseline characteristics are shown in Table 1. There were no statistically significant differences between the MMC and OLO groups in terms of the type of glaucoma, laterality, pre-operative laser treatment, pre-operative laser peripheral iridotomy (PI), whether the procedure was combined with phacoemulsification for cataract extraction, presurgical CD ratio, IOP, number of medications, or comorbidity. There were more women in the OLO group than in the MMC group. The average age was lower in the OLO group than in the MMC group, and preoperative VA was better in the OLO group than in the MMC group (Table 1).

Reduction in IOP The median IOP significantly decreased ($P<0.01$) from 28.8 to 5 mm Hg in 1 day, 6 mm Hg in 10-30d, 9 mm Hg in 3-9mo, and 10 mm Hg in 1 and 2y postoperatively. There were no statistically significant differences between the MMC and OLO groups regarding postoperative IOP from day 1 to year 2 (Figure 1) or in the percent change in IOP (Table 2).

We analyzed the outcome based on two categories: success and qualified success. The success rates at different study time points for the three target IOP levels in the two groups are presented in Table 3. For year 2, at ≤21 mm Hg target IOP, complete success was achieved in 63.2% and 73.3% of the eyes in the MMC and OLO groups, respectively, with no statistically significant difference. Qualified success was achieved in 97.4% and 100% of the eyes in the MMC and OLO groups, respectively ($P>0.05$).

The Kaplan-Meier cumulative survival curves relating either the ≤21, ≤17, or ≤15 mm Hg target IOPs did not show significant intergroup differences for complete (log-rank $P=0.782$, 0.644, and 0.810, respectively) or qualified success rates (log-rank $P=0.667$, 0.46, and 0.621, respectively; Figure 2).

Table 1 Preoperative characteristics of patients in both groups *n* (%)

Characteristics	MMC (*n*=50)	OLO (*n*=44)	Total (*n*=94)	*P*
Age (y)				0.042
Min-max	4d-79.88y	7d-78.70y	4d-79.88y	
Mean±SD	31.76±29.31	20.21±27.19	26.30±28.7	
Median	29.99	8.8mo	6.66	
Gender				0.002
Male	32 (64.0)	14 (31.8)	46 (48.9)	
Female	18 (36.0)	30 (68.2)	48 (51.1)	
Type of glaucoma				0.246
POAG	26 (52.0)	14 (31.8)	40 (42.6)	
ACG/narrow angle	2 (4.0)	3 (6.8)	5 (5.3)	
SOAG	2 (4.0)	2 (4.5)	4 (4.3)	
Primary congenital glaucoma	20 (40.0)	25 (56.8)	45 (47.9)	
Laterality				0.563
Right	25 (50.0)	24 (54.5)	49 (52.1)	
Left	25 (50.0)	20 (45.5)	45 (47.9)	
Preoperative MPCPC				0.896
No	48 (96.0)	42 (95.5)	90 (95.7)	
Yes	2 (4.0)	2 (4.5)	4 (4.3)	
Preoperative PI				0.990
No	42 (84.0)	37 (84.1)	79 (84.0)	
Yes	8 (16.0)	7 (15.9)	15 (16.0)	
Phacoemulsification				0.990
No	42 (84.0)	37 (84.1)	79 (84.0)	
Yes	8 (16.0)	7 (15.9)	15 (16.0)	
Comorbidity				0.413
Diabetes	2 (4.0)	4 (9.1)	6 (6.4)	
Hypertension	4 (8.0)	3 (6.8)	7 (7.4)	
Kidney	2 (4.0)	0	2 (2.1)	
Heart disease	1 (2.0)	0	1 (1.1)	
Diabetes & hypertension	5 (10.0)	3 (6.8)	8 (8.5)	
Hypertension & heart disease	0	1 (2.3)	1 (1.1)	
Pre-surgery visual acuity in infants				0.001
CSM	2 (4.0)	0	2 (2.1)	
F and F	4 (8.0)	17 (38.6)	21 (22.3)	
Pre-surgery visual acuity in adults				0.046
Min-max	0.005-0.8	0.005-1	0.005-1	
Mean±SD	0.25±0.176	0.44±0.318	0.32±0.255	
Median	0.26	0.36	0.32	
Pre-surgery CD ratio				0.337
Min-max	0.1-1	0.4-0.95	0.1-1	
Mean±SD	0.71±0.27	0.79±0.16	0.74±0.23	
Median	0.8	0.8	0.8	
Pre-surgery IOP				0.286
Min-max	16-45	10-54	10-54	
Mean±SD	30.0±7	28.7±9.1	29.4±8.1	
Median	29.5	28.0	28.8	
Pre-surgery medication				0.828
Min-max	0-5	0-5	0-5	
Mean±SD	3.3±1.3	3.4±1.1	3.3±1.2	
Median	4	3	3	

MMC: Mitomycin C; OLO: Ologen+MMC; MPCPC: Micropulse cyclophotocoagulation; PI: Peripheral iridectomy; CSM: Central steady maintained; F and F: Fixes and follows; CD: Cup/disc; IOP: Intraocular pressure; POAG: Primary open angle glaucoma; SOAG: Secondary open angle glaucoma.

Table 2 Postoperative changes in VA, CD ratio, IOP, and complications of patients in both groups *n* (%)

Items	MMC	OLO	Total	*P*
VA in 1y				0.091
Improved	6 (20.0)	7 (41.2)	13 (27.7)	
Same	12 (40.0)	2 (11.8)	14 (29.8)	
Deteriorated	12 (40.0)	8 (47.1)	20 (42.6)	
CD ratio in 1y				0.037
Decreased or stable CD ratio	27 (67.5)	25 (89.3)	52 (76.5)	
No improvement (increase)	13 (32.5)	3 (10.7)	16 (23.5)	
Range of increase in CD ratio	0.05-0.4	0.05-0.1		
Median change	0.1	0.05		
Percent reduction in IOP, mean±SD (median)				
Post-operative time				
1d	-79.1±11.8 (-82.1)	-76.1±18 (-80.6)	-81.5	0.546
10-30d	-73.4±13.0 (-76.7)	-74.2±14.1 (-77.7)	-77.3	0.546
3-5mo	-63.9±17.5 (-68.0)	-63.2±20.8 (-70.0)	-69.2	0.895
6-9mo	-64.6±16.4 (-66.4)	-65.9±18.9 (-71.4)	-70.0	0.614
1y	-64.0±16.7 (-66.7)	-57.2±22.9 (-60.0)	-65.8	0.285
2y	-62.2±18.3 (-67.6)	-63.5±17.3 (-68.6)	-67.6	0.827
3y	-55.5±26.7 (-65.6)	-60.4±19.0 (-63.8)	-65.3	0.797
Medications				
1y no medication	37 (82.2)	33 (78.6)	70 (80.5)	
Min-max (median)	1-4 (2.5)	1-3 (2)	1-4 (2)	0.65
2y no medication	32 (69.6)	35 (81.4)	67 (75.3)	
Min-max (median)	2-4 (3)	1-17 (2)	1-17 (3)	0.091
3y no medication	30 (65.2)	33 (82.5)	63 (73.3)	
Min-max (median)	2-4 (3)	1-8 (3)	1-8 (3)	0.074
Percent reduction in medication, (median=-100%), mean±SD				
1y	-87.5±30.5	-87.3±34.8	-87.4±32.5	0.895
2y	-70.9±43.8	-76.2±92	-73.6±72	0.098
3y	-66.9±47.9	-84.7±44.3	-75.6±46.8	0.061
Output				0.005
No complication	25 (50.0)	36 (81.8)	61 (64.9)	
Complication and	14 (28.0)	4 (9.1)	18 (19.1)	
Intervention failure of surgery	11 (22.0)	4 (9.1)	15 (16.0)	

MMC: Mitomycin C; OLO: Ologen+MMC; VA: Visual acuity; CD: Cup/disc; IOP: Intraocular pressure.

Visual Acuity in One Year We observed a stable VA in 40% and 11.8%, improved in 20% and 41.2%, and worsened in 40% and 47.1% in the MMC and OLO groups respectively. However, the difference between the groups was not statistically significant (Table 2).

Cup/Disc Ratio in One Year The decreased or stable CD ratio was higher in the OLO group (89.3%) than in the MMC group (67.5%; *P*=0.037; Table 2).

Reduction in the Number of Glaucoma Medications In years 1 and 2, the reduction rates in glaucoma medications were 80.5% and 75.3%, in the MMC and OLO groups respectively, with an average of two and three medications, respectively (average percent reduction, -87.4±32.5 and -73.6±72, respectively). No significant differences were observed between the MMC and OLO groups (Table 2).

Output and Complications Our data showed that 50% of the patients in the MMC group did not develop complications or need surgical intervention, compared with 81.8% in the OLO group, this which was a statistically significant difference. Complications (including failure of surgery) were significantly more common in the MMC group (50%) than in the OLO group (18.2%). A sub-analysis was specifically performed for the failure of surgery. In total, 22% of patients in the MMC group and 9.1% of patients in the OLO group had failed surgery.

Bleb Morphology The postoperative types of blebs in the two groups along the study time points are presented in Table 4. In year 1, the incidence rate of grade C (high local, low diffuse, or formed) blebs was higher in the OLO group (43.2%) than in the MMC group (16%). In year 2, the incidence rate of grade A (flat) blebs was higher in the OLO group (43.2%) than in the MMC group (20%). The incidence rate of grade B (low focal,

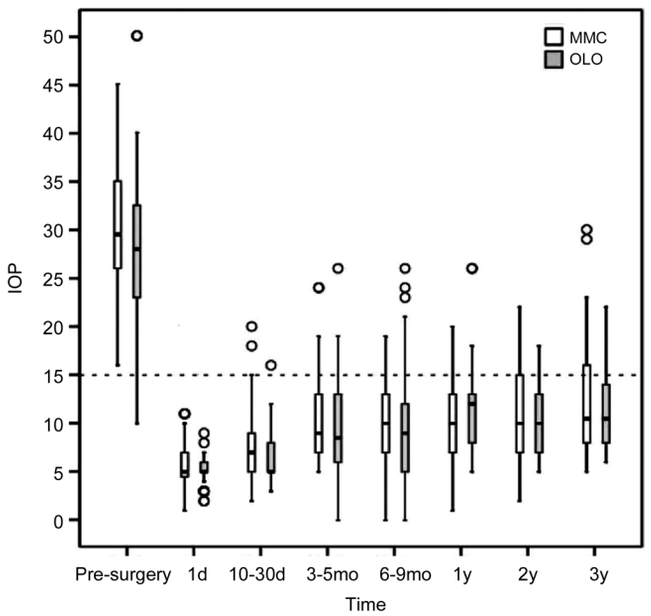

Figure 1 Box plot representation of IOP values over 36mo of follow-up: median values (dark lines), error standard (T-bars), and outliers (circles) IOP: Intraocular pressure; MMC group: Mitomycin C group; OLO group: Ologen+mitomycin C group. *P*>0.05 in all intervals.

thin cystic, or vascularized) blebs was higher in the MMC group (32%) than in the OLO group (6.8%). These differences were statistically significant.

Secondary Objectives (Secondary Outcome) The factors associated with statistically significant differences in the level of IOP at different time points of the study were assessed.

The IOP of eyes with pre-operative micropulse cyclophotocoagulation (CPC) was lower at 3-5mo and 2y (7 and 6 mm Hg, respectively) than that of eyes without pre-operative CPC (10.2 and 10.6 mm Hg, respectively; *P*=0.016 and 0.001, respectively). The eyes that underwent pre-operative PI had higher IOP (8.67 *vs* 5.49 mm Hg) at day 1, whereas pre-operative PI had lower IOP (8.2 *vs* 10.76 mm Hg) at 2y (*P*=0.001 and 0.012, respectively). The eyes that underwent trabeculectomy with phacoemulsification had higher IOPs compared to those without phacoemulsification, IOP was on day 1 (8.4 *vs* 5.5 mm Hg) and days 10-30 (10.2 *vs* 6.7 mm Hg; *P*=0.006 and 0.003) respectively. Patients with diabetes mellitus (DM) showed higher IOP at 10-30d (10.3 *vs* 6.8 mm Hg) and 3-5mo (12.8 *vs* 9.6 mm Hg). Furthermore, those who had hypertension had higher IOP at 1 day (8.2 *vs* 5.5 mm Hg) and 10-30d (10.8 *vs* 6.6 mm Hg). Patients with heart disease showed higher IOP at 1 day (11.5 *vs* 5.9 mm Hg), 10-30d (18 *vs* 7.1 mm Hg), and 6-9mo (22 *vs* 9.5 mm Hg). Moreover, ACG/narrow-angle glaucoma had the highest IOP (12.4 mm Hg) among all types on 1 day and 10-30d postoperatively. The differences were considered statistically significant. Age at surgery had an intermediate direct correlation with IOP on day 1 (*r*=0.329, *P*=0.001) and days 10-30 (*r*=0.455, *P*=0.0001) postoperatively.

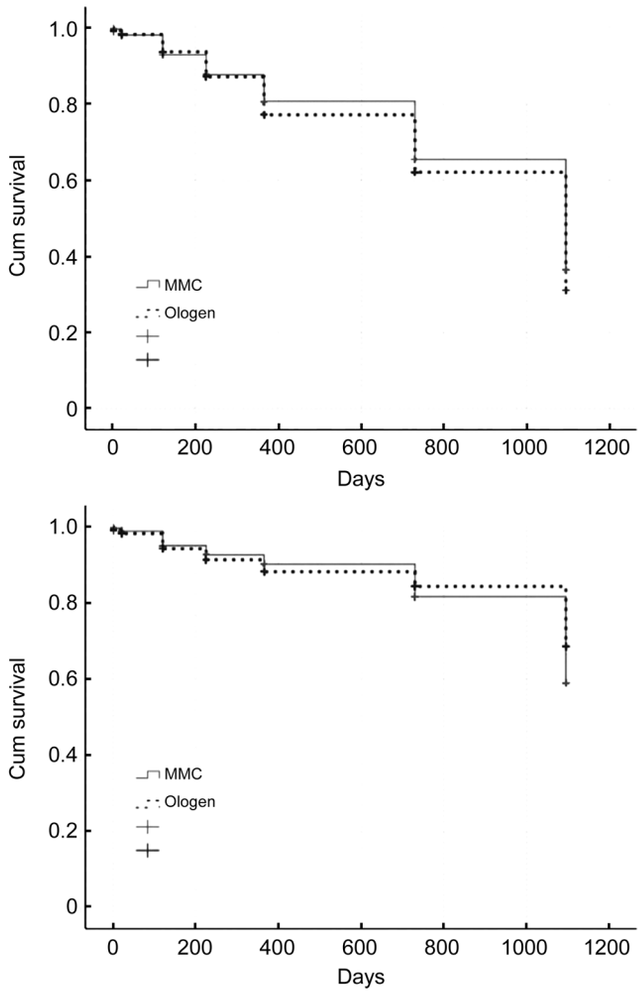

Figure 2 Kaplan-Meier cumulative probability curve of complete success (without medications) at ≤15 mm Hg target IOP in the MMC (solid line) *vs* OLO groups (dotted line; log-rank test Chi-squared=0.351, *P*=0.554) and of qualified success (with or without medications) at ≤15 mm Hg target IOP in the MMC (solid line) *vs* OLO groups (dotted line; log-rank test Chi-squared=0.033, *P*=0.856) IOP: Intraocular pressure; MMC group: Mitomycin C group; OLO group: Ologen+mitomycin C group.

Performing multiple linear regression with IOP at different points of time as the dependent variable, the only significant factors were ACG/narrow-angle glaucoma at day 1 (*B*=5.761) and days 10-30 (*B*=4.701), hypertension at days 10-30 (*B*=2.950), and pre-op CPC at 2y (*B*=-5.009).

DISCUSSION

We observed a statistically significant difference in the CD ratio between the OLO and MMC groups. The OLO group showed a higher percentage of eyes with a decreased or stable CD ratio compared with the MMC group. This finding suggests that the combined use of OLO and MMC may have a more favorable effect on preserving the optic nerve structure compared with MMC alone. Numerous studies have explored the relative effectiveness of Ologen implant alone versus MMC in trabeculectomy. However, to the best of our knowledge only

Table 3 Success rates (%) until the 3-year follow-up study endpoint in the MMC and OLO groups at three target IOP levels

IOP (mm Hg)		MMC		OLO		*P*
		n	%	*n*	%	
Day 1						
≤21	Complete	49	100.0%	43	97.7%	>0.05
	Qualified	49	100.0%	43	97.7%	>0.05
≤17	Complete	45	97.8%	28	93.3%	>0.05
	Qualified	47	97.9%	42	95.5%	>0.05
≤15	Complete	48	98.0%	42	95.5%	>0.05
	Qualified	47	97.9%	42	95.5%	>0.05
10-30d						
≤21	Complete	46	95.8%	41	97.6%	>0.05
	Qualified	48	100.0%	41	97.6%	>0.05
≤17	Complete	44	91.7%	41	97.6%	>0.05
	Qualified	46	95.8%	41	97.6%	>0.05
≤15	Complete	44	91.7%	40	95.2%	>0.05
	Qualified	46	95.8%	40	95.2%	>0.05
3-5mo						
≤21	Complete	42	85.7%	40	95.2%	>0.05
	Qualified	47	95.9%	41	97.6%	>0.05
≤17	Complete	39	79.6%	39	92.9%	>0.05
	Qualified	42	85.7%	40	95.2%	>0.05
≤15	Complete	38	77.6%	34	81.0%	>0.05
	Qualified	41	83.7%	35	83.3%	>0.05
6-9mo						
≤21	Complete	40	87.0%	34	81.0%	>0.05
	Qualified	46	100.0%	40	93.0%	>0.05
≤17	Complete	39	84.8%	33	78.6%	>0.05
	Qualified	44	95.7%	39	90.7%	>0.05
≤15	Complete	37	80.4%	33	78.6%	>0.05
	Qualified	42	91.3%	39	90.7%	>0.05
1y						
≤21	Complete	31	79.5%	32	78.0%	>0.05
	Qualified	39	100.0%	39	95.1%	>0.05
≤17	Complete	30	76.9%	31	75.6%	>0.05
	Qualified	38	97.4%	38	92.7%	>0.05
≤15	Complete	30	76.9%	31	75.6%	>0.05
	Qualified	36	92.3%	38	92.7%	>0.05
≤21	Complete	24	63.2%	22	73.3%	>0.05
	Qualified	37	97.4%	30	100.0%	>0.05
≤17	Complete	24	63.2%	22	73.3%	>0.05
	Qualified	33	86.8%	29	96.7%	>0.05
≤15	Complete	24	63.2%	21	70.0%	>0.05
	Qualified	31	81.6%	28	93.3%	>0.05
≤21	Complete	20	55.6%	9	56.3%	>0.05
	Qualified	33	91.7%	15	93.8%	<0.05
≤17	Complete	20	55.6%	8	50.0%	>0.05
	Qualified	29	80.6%	13	81.3%	<0.05
≤15	Complete	20	55.6%	8	50.0%	>0.05
	Qualified	26	72.2%	13	81.3%	>0.05

IOP: Intraocular pressure; MMC: Mitomycin C; OLO: Ologen and mitomycin C.

Table 4 Postoperative types of bleb in patients of both groups *n* (%)

Post-operative bleb	MMC (*n*=50)	Ologen (*n*=44)	Total (*n*=94)	*P*
Day 1				0.364
A	4 (8.0)	1 (2.3)	5 (5.3)	
B	2 (4.0)	0	2 (2.1)	
C	33 (66.0)	28 (63.6)	61 (64.9)	
D	10 (20.0)	14 (31.8)	24 (25.5)	
NR	1 (2.0)	1 (2.3)	2 (2.1)	
10-30d				0.244
A	2 (4.0)	1 (2.3)	3 (3.2)	
B	3 (6.0)	0	3 (3.2)	
C	28 (56.0)	22 (50.0)	50 (53.2)	
D	17 (34.0)	19 (43.2)	36 (38.3)	
NR	0	2 (4.5)	2 (2.1)	
3-5mo				0.241
A	1 (2.0)	2 (4.5)	3 (3.2)	
B	9 (18.0)	2 (4.5)	11 (11.7)	
C	24 (48.0)	20 (45.5)	44 (46.8)	
D	14 (28.0)	17 (38.6)	31 (33.0)	
NR	2 (4.0)	3 (6.8)	5 (5.3)	
6-9mo				0.328
A	3 (6.0)	5 (11.4)	8 (8.5)	
B	8 (16.0)	3 (6.8)	11 (11.7)	
C	14 (28.0)	19 (43.2)	33 (35.1)	
D	21 (42.0)	14 (31.8)	35 (37.2)	
NR	4 (8.0)	3 (6.8)	7 (7.4)	
1y				0.006
A	4 (8.0)	5 (11.4)	9 (9.6)	
B	15 (30.0)	7 (15.9)	22 (23.4)	
C	8 (16.0)	19 (43.2)	27 (28.7)	
D	17 (34.0)	13 (29.5)	30 (31.9)	
NR	6 (12.0)	0	6 (6.4)	
2y				0.001
A	10 (20.0)	19 (43.2)	29 (30.9)	
B	16 (32.0)	3 (6.8)	19 (20.2)	
C	5 (10.0)	13 (29.5)	18 (19.1)	
D	13 (26.0)	7 (15.9)	20 (21.3)	
NR	6 (12.0)	2 (4.5)	8 (8.5)	
3y				0.001
A	12 (24.0)	25 (56.8)	37 (39.4)	
B	17 (34.0)	2 (4.5)	19 (20.2)	
C	2 (4.0)	5 (11.4)	7 (7.4)	
D	12 (24.0)	8 (18.2)	20 (21.3)	
NR	7 (14.0)	4 (9.1)	11 (11.7)	

A: Flat bleb; B: Low focal/thin cystic/vascularized bleb; C: High local/low diffuse/formed; D: Well-formed bleb/high diffuse/large paucivascularized bleb; NR: Not reported; MMC group: Mitomycin C group; OLO group: Ologen+mitomycin C group.

one study also assessed and compared trabeculectomy with MMC alone to trabeculectomy with MMC+Ologen implant[14]. Previously, the use of Ologen alone has been associated with a decrease in the CD ratio. Hamdi[15] investigated the efficacy and safety of Ologen in the treatment of congenital glaucoma. Their findings indicated that ologen treatment reduced the CD ratio from 0.7 to 0.5 at the 6-month follow-up. However, Elhefney *et al*[16] did not observe any statistically significant difference in the CD ratio before and after treatment in patients with glaucoma who received ologen treatment. In this study, a significantly higher percentage of decreased or stable CD ratio was observed in the OLO group than in the MMC group. We attribute this decrease in the CD ratio to the fact that a reasonable number of participants were diagnosed with congenital glaucoma with their optic discs having an elastic nature due to high elastic fiber content that may have reversed cupping that occurred from glaucomatous damage.

The primary objective of glaucoma treatment is to reduce the IOP to prevent or slow the progression of optic nerve damage. This study found a significant reduction in IOP across all time points, from baseline to 2y, in both the OLO and MMC groups. However, there was no statistically significant difference in IOP reduction between the two groups. Sen *et al*[14] reported a significant reduction in IOP at all postoperative visits in both groups compared with baseline (P<0.001). The mean IOP was comparable between the two groups for up to 6mo. However, at 12mo, the mean IOP was significantly lower in the MMC group (11.33±3.18 mm Hg) compared with the OLO group (14.35±3.34 mm Hg, P=0.0126)[14]. Previous studies have reported results similar to ours. Sarker *et al*[17] reported that at the 12-month follow-up, the mean IOP levels postoperatively were 12.8±1.6 mm Hg and 13.4±2.2 mm Hg in the OLO and the MMC groups respectively. Similarly, Mohamed *et al*[18] demonstrated that the mean pre-operative IOPs were 29±3.16 mm Hg in MMC and 29.8±3.08 mm Hg in the MMC and OLO groups, respectively, which reduced significantly at the 12-month follow-up (57.9% and 56.3%, respectively). Also, Kumar *et al*[19] reported that the IOPs reduced from 26.4±11.3 to 11.6±2.7 mm Hg in the OLO group and from 26.3±15.7 to 4.3±6.4 mm Hg in the MMC group without any statistically significant difference at 2y follow up period.

VA is not necessarily associated with the surgical success of trabeculectomy for controlling glaucoma because several factors may contribute to the decrease in VA post-trabeculectomy. One of the most important factors is the formation of cataracts because trabeculectomy accelerates cataract formation[20]. The OLO group had better baseline VA compared with the MMC group. Differences in the baseline VA between the groups can be a potential confounding factor. Better VA at baseline may indicate less advanced disease, which can affect the treatment response and outcomes. Adjusting for baseline VA or performing analyses stratified by VA levels can help determine the true effect of glaucoma control treatment. In the present study, the VA of almost 30% of the eyes remained the same and was higher in the MMC group than in the OLO group; however, the difference between the groups was not statistically significant. Similar to our results, in Sen *et al*[14] study at 12mo, the best-corrected VA were 0.903±0.89 and 0.84±0.53 in the MMC and OLO

groups, respectively. However, the change was not statistically significant (P=0.43 and 0.97), respectively. No significant change was noted in the pre-operative values (P=0.668)[14]. Cillino *et al*[21] also demonstrated that the VA remained stable postoperatively in both groups. The VA was comparable between the groups (P=0.949). These findings were also supported by those of Qin *et al*[22], who found no significant difference in VA between baseline and last follow-up for patients of MMC trabeculectomy (P=0.14). Qin *et al*[22] also demonstrated that the IOP was significantly reduced in patients receiving MMC treatment from 32.9±12.0 to 16.4±5.7 mm Hg (P<0.0001).

Furthermore, a decrease in glaucoma medications was observed in the present study following the implementation of both OLO and MMC groups. However, no statistically significant differences were observed between both groups. These findings were consistent with those reported by Kumar *et al*[19]. The mean number of medications in their study decreased from 3.2±0.9 to 0±0 in the OLO group, whereas it decreased from 3.2±0.9 to 0.1±0.3 in the MMC group with no statistically significant difference. Conversely, Sen *et al*[14] reported a significant decrease in the mean number of antiglaucoma medications from 3.64±0.67 to 0.52±1.08 and 3.2±0.92 to 0.40±0.81, at 12mo in the MMC and OLO groups, respectively (P=0.004 and P=0.001, respectively). Qin *et al*[22] also demonstrated reduction of IOP-lowering medications was significantly decreased from 3.0±0.9 to 0.9±1.0 (P<0.0001) in patients with the MMC group.

This study demonstrated significant differences in the types of bleb observed between the two groups at various time points. The OLO group had a higher percentage of high local, low diffuse, and formed blebs compared with the MMC group at 1y, whereas compared with the MMC group, flat blebs were more prevalent in the OLO group at 2y, which showed favorable bleb morphology in the OLO group in the early postoperative period; however, the average bleb morphology lasted longer in the MMC group than in the OLO group. Similarly, in a study by Dada *et al*[23], eyes with both MMC and OLO had diffuse, elevated, and well-formed blebs at each postoperative follow-up visit during the postoperative period[23]. Conversely, Sen *et al*[14] found that both groups had comparable bleb morphological features at each follow-up visit. They found no significant differences in bleb morphology between the MMC and OLO groups at the 1-, 3-, 6-, and 12-month follow-up periods[14]. On the other hand, Paul *et al*[24] concluded that the Ologen implant resulted in superior bleb morphology, leading to improved bleb health and safety.

Sen *et al*[14] reported shallow anterior chamber, hypotony, Tenon cyst, bleb sweating, and repeat trabeculectomy as complications. However, no significant difference was observed between the MMC and OLO groups in terms of complication rates (P=0.52)[14]. Kumar *et al*[19] also reported bleb leakage, hyphemia, and choroidal detachment as early treatment complications; however, these were also insignificant in both groups (P=0.786). These findings do not align with the present results, which showed that almost half 50% and 81.8% of the participants in the MMC and OLO groups did not develop any complications which was; statistically significant. Mohamed *et al*[18] demonstrated that the MMC group had a higher complication rate than the OLO group. Their findings showed complications in the form of thin polycystic blebs (60%), blebitis (10%), and shallow anterior chambers in two eyes (20%)[19].

When interpreting the findings of the present study, it is important to acknowledge the strengths and limitations. The strengths of this study include its relatively large sample size, long follow-up duration, comparative design, and detailed data collection for various parameters.

The limitations of this study include the lack of randomization, potential confounding factors, and the absence of specific details regarding complications. This study utilized a retrospective design, which can be prone to various biases and limitations, such as selection bias, incomplete data, and inability to establish causality. Although efforts were made to match baseline characteristics between the groups, there may still have been confounding factors that were unaccounted for that could have influenced treatment outcomes.

Given the retrospective nature of this study and the lack of randomization, the significant differences in age (P=0.042) and gender (P=0.002) between the MMC and OLO groups may have influenced the study's outcomes. The MMC group had a higher mean age (31.76y) compared to the OLO group (20.21y), and there were more males in the MMC group (64%) compared to the OLO group (31.8%). These demographic differences could affect factors such as disease progression, response to surgery, and overall recovery.

Even though the study benefits from a large sample size, it is important to acknowledge that potential confounding factors may still influence the results. Although we controlled for several key variables using multiple linear regression, the use of propensity score matching (PSM) could further minimize bias and improve the robustness of the findings.

Although we exceeded the minimum required sample size, the follow-up data were missing for several patients in the 3rd year, and we only had the data of 52 eyes, 36 (72%) in the MMC group and 16 (36%) in the OLO group, which might have limited the generalizability of the results for this time interval (3rd year). Factors such as surgeon experience and variations in surgical technique could affect the results; however, all surgeries were performed by only one surgeon, eliminating this bias.

This present study demonstrates that both methods, the combined use of OLO with MMC and MMC alone, have comparable efficacy in reducing IOP and achieving target IOP levels. However, the OLO group showed a more favorable CD ratio and preserved better bleb morphology in the first year than the MMC group. The complication rates were higher in the MMC group compared with the combined OLO group. Hence, the combined use of the ologen implant and MMC may provide better outcomes in terms of preserving optic nerve structure, reducing complications, and maintaining stable bleb morphology postoperatively.

However, future studies with randomized designs, longer follow-up durations, and detailed assessments of complications are warranted to validate these findings and provide further insights into the optimal treatment approach for glaucoma.

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Data Availability: The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon request.

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