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Ologen implant versus mitomycin-C for trabeculectomy

A meta-analysis

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Abstract

Aim: To evaluate the efficacy and safety of trabeculectomy (Trab) with mitomycin-C (MMC) versus Trab with implant.

Methods: Studies published in different languages were retrieved by systematically searching Embase, PubMed, Cochrane library, China Biology Medicine disc, and Google Scholar from 1966 to April 2018, as well as manually examining the references of the original articles. The outcome measures of efficacy covered intraocular pressure, glaucoma medications reductions, and success rate. Safety evaluation was measured by relative ratio of complications.

Results: A total of 11 studies involving 443 participants were covered in this meta-analysis. The weighted mean difference (WMD) in the percentage of intraocular pressure (IOP) reduction (IOPR%) comparing Ologen group with MMC group was −3.69 (95% CI: −6.70 to −0.68) at 1 month, −2.69 (−5.17 to −0.21) at 3 months, −3.67 (−6.09 to −1.25) at 6 months, −3.24 (−6.08 to −0.41) at 12 months, 1.24 (−9.43 to 11.90) at 24 months, and 1.10 (−10.11 to 12.31) at 60 months, which showed that there was statistically significant difference at 1,3, 6, and 12 months after the surgery. A significantly higher incidence of postsurgery hypotony (0.64 (95% CI: 0.42 to 0.98)) and suture lysis (0.30 (95% CI: 0.10–0.93)) was observed in MMC group. However, there was no significant difference in the reduction in glaucoma medications, success rate, and incidence of other complications.

Trab with 0.2 mg/mL MMC presented higher rates of complete success compared with Trab with 0.4 mg/mL MMC (*P* = .01).

Conclusion: Trab with MMC was associated with a higher IOP-lowering efficacy and a higher incidence of postsurgery hypotony and suture lysis in contrast to that of Trab with Ologen.

Abbreviations: IOP = intraocular pressure, IOPR = IOP reduction, MMC = mitomycin C, Trab = Trabeculectomy.

Keywords: glaucoma, meta-analysis, mitomycin C, Ologen implant, trabeculectomy

1. Introduction

Glaucoma is a serious irreversible eye disorder. Elevated intraocular pressure is one of the most dangerous causes among a great many pathogenic factors concerning glaucoma.[1]

Trabeculectomy (Trab) was the most commonly adopted glaucoma filtration surgery.[2] It is well known that the hypotensive effect of this surgery has been limited to postoperative episcleral fibroblast proliferation and subconjunctival scar formation.[3] Thus, the use of Antiscarring medications in the process of the surgery is supposed to improve the success rates of Trab. However, antimetabolites, such as mitomycin C (MMC) and 5-fluorouracil, predispose some patients to a higher risk of postoperative side effects linked with filtering bleb, such as low intraocular pressure, macular edema, bleb leak, shallow anterior chamber, and endophthalmitis.[4,5]

Accordingly, there is an urgent need for creating biomedical devices to get rid of the risks of antimetabolites. Ologen collagen matrix, a degradable 3D collagen-glycosaminoglycan scaffold, is designed to promote and modulate the postoperative tissue regeneration with minimal fibroblast proliferation and scar formation. It influences the fibrosis process by guiding the patterns of fibroblast migration and normalizing the secreted extracellular matrix deposition. Its porous structure allows fibroblasts to grow within the matrix and impair extracellular matrix lay down so as to avoid scarring and wound shrinkage. Theoretically, this implant can help create a healthy and prominent bleb. Furthermore, Its porous structure, which serves as a reservoir, can create a buffer to reduce filtration, thereby avoiding postoperative low intraocular pressure.[6]

In comparison with the adjunctive therapy with MMC, the success of using Trab with Ologen implant varies with respect to the reported outcomes.[6–16] In a recently published meta-analysis, it was found that the outcomes were similar, but only 7 randomly controlled trials involving 227 eyes were included in this meta-analysis.[17] An updated meta-analysis is thus required because several new trials have been published since then. The

Cochrane Handbook recommends that systematic reviews should be updated in 2 years, because "systematic reviews that are not maintained may become out of date or misleading"[18]. In addition, these previous studies only probed into RCTs prescribing 0.2 mg/mL of MMC. Several recent studies have focused on 0.4 mg/mL MMC. Thus, a subgroup analysis was chosen based on the concentration of MMC in the current meta-analysis.

2. Materials and methods

2.1. Literature search and selection

A literature search was carried out which involved sources of EMBASE, PubMed, China Biology Medicine disc, the Cochrane library, and Google Scholar (from 1966 to April 2018) according to the following search terms: ("Mitomycin C" OR "MMC"), ("Ologen" OR "Collagen matrix" OR "OculusGen") and "Trabeculectomy". Also, the reference lists of the retrieved articles were examined and no imposed language restrictions were found.

All the studies have to fulfill the following criteria:

(1) prospective cohort studies;
(2) patients with glaucoma failed in the conservative therapy;
(3) comparison of the outcome of Trab with Ologen implant versus MMC;
(4) a minimum follow-up of 6 months;
(5) at least 1 of the outcomes of interest was included.

The following were excluded:

(1) studies involving other types of glaucoma surgery, such as non-penetrating glaucoma surgery;
(2) studies including pediatric cases or patients with repeated glaucoma surgery;
(3) Abstracts from conferences, editorials, duplicate publications, letters, reviews, and retrospective study.

Glaucoma was defined as the presence of optic disc excavation associated with a visual field defect on standard automated perimetry.

As the present meta-analysis was performed based on previously published studies, thus no ethical approval and patient consent are required.

2.2. Data extraction

First 2 investigators independently screened and extracted data from the literature based on the inclusion and exclusion criteria. Disagreement was encountered in discussing and soliciting the opinions of a third researcher. The information extracted from each study included authors, the year of publication, location, sample size, age, sex, follow-up period, intraocular pressure (IOP) measurements, the number of glaucomatous medications, and the number of patients with complete and qualified success. Patients who had reported to have suffered complications were also recorded.

2.3. Grading quality of evidence

Researchers evaluated the quality of the included studies based on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation, methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias),

Figure 1. Risk of bias summary.

which were classified into levels of very low, low, moderate, and high. Summary tables were constructed by means of the GRADE Profiler (Fig. 1).[19]

2.4. Outcome measures

The primary outcome was the IOP reduction (IOPR) reduction changing from preoperative to postoperative. When authors reported the mean and SD of IOP and IOPR, they were used directly. If not available, they were computed by the following means: The percentage reduction in intraocular pressure (IOPR %): $IOPR = IOP_{baseline} - IOP_{endpoint}$ and $SD_{IOPR} = (SD^2_{baseline} + SD^2_{endpoint} - SD_{baseline} \times SD_{endpoint})^{1/2}$. $IOPR\% = IOPR/IOP_{baseline}$ and $SD_{IOPR\%} = SD_{IOPR}/IOP_{baseline}$. The secondary outcome measure comparisons: complete success and qualified success rate, and the reduction in glaucoma medications. Complete success was defined as the target endpoint IOP (usually, 21 mm

Hg) without medications, while qualified success was defined as the target endpoint IOP with or without medications.

The other outcome from assessing safety included: Hyphema, Hypotony maculopathy, Hypotony, Bleb leakage, Encapsulated Bleb, Shallow anterior chamber, Choroidal detachment, Blebitis, Anterior chamber reaction, Suture lysis, and Needling.

2.5. Statistical analysis

This Meta-analysis was performed based on RevMan 5.3. For continuous data, mean differences (MDs) with 95% CIs, as well as a risk ratio (RR) with a 95% CI, was adopted as a summary measure for dichotomous data. Heterogeneity was quantified using the I^2 statistic, and $I^2 > 50\%$ indicated the presence of heterogeneity.[20] $P < .05$ was considered statistically significant, except where otherwise specified. Publication bias was evaluated by visually inspecting a funnel plot.

3. Results

3.1. Results of search

All studies are shown in Table 1. 11 fits in with all of the predefined inclusion and exclusion criteria (Table 1).

3.2. Characteristics and quality of trials

The characteristics of the eligible studies are summarized in Table 1. Clinical trials were carried out in Germany, Italy, Iran, UK, Egypt, China, and India. A total of 474 eyes were involved in this meta-analysis. The follow-up period ranged from 6 to 60 months. The mean baseline IOP ranged from 19.1 to 43.07 mmHg (Table 1).

3.3. Risk of bias assessment

Details of the risk of bias are shown in Figure 2.

3.4. Efficacy analysis
3.4.1. The percentage reduction in intraocular pressure (IOPR%).
Eleven studies were analyzed for the percentage reduction in IOP (IOPR%) at various follow-up time nodes. The difference in IOPR% was not statistically significant between the 2 compared groups with the exception of the 1st month.

Heterogeneity was evident for the outcome ($I^2 = 11\%$ for the 1st month, $I^2 = 41\%$ for the 3rd month, $I^2 = 60\%$ for the 6th month, $I^2 = 62\%$ for the 12th month, $I^2 = 62\%$ for the 12th month, $I^2 = 71\%$ for the 60th month), A random-effect model was adopted. After conducting a sensitivity analysis, we decided to present the pooled WMD separately with the inclusion or exclusion of one "outlier", The inclusion of this study significantly improved the between-study heterogeneity at various time nodes. The "outlier" study, conducted by Feiyuan and colleagues, presented a higher baseline IOP (>40 mmHg).[21] The results pooled from other 10 homogeneous studies showed that the Ologen implant was associated with a statistically lower percentage reduction in IOP compared with MMC in month 1, 3, 6, 12, respectively. The results of Feiyuan's study showed that Trab with Ologen implant had a statistically significant higher percentage reduction in IOP, compared with Trab plus MMC except the 1st month, with a WMD of 4.00 (-1.92, 9.92) in the 1st month, 9.60 (3.63, 15.57) in the 3rd month, 8.00 (1.90, 14.10) in the 6th month, 8.70 (2.74, 14.66) in the 12th month, and 13.20 (7.26, 19.14) in 5 years (Fig. 3).

The amount of IOP reduction from baseline was as follows: 17.13 (10.07) mmHg versus 18.06 (6.23) mmHg in the 1st month; 17.05 (7.44) mmHg versus 16.51 (5.53) mmHg in the 3rd month; 14.99 (7.50) mmHg versus 15.56 (3.78) mmHg in the 6th month; 16.10 (8.78) mmHg versus 15.73 (6.60) mmHg in the 12th month; 12.17 (3.3) mmHg versus 10.64 (2.49) mmHg in the 24th month; 27.70 (9.43) mmHg versus 17.37 (6.91) mmHg in 5 years. By excluding Feiyuan's study, the amount of IOP decreasing from the baseline was as follows: 14.45 (8.70) mmHg versus 16.32 (4.71) mmHg in the month; 14.53 (4.59) mmHg versus 14.91 (4.10) mmHg in the 3rd months; 12.66 (4.96) mmHg versus 14.08 (3.95) mmHg in the 6th months; 12.84 (6.14) mmHg versus 13.51 (5.04) mmHg in the 12th month; 12.17 (3.3) mmHg versus 10.64 (2.49) mmHg in the 24th month, 12.10 (5.20) mmHg versus 10.90 (4.51) mmHg in 5 years, The IOP reduction was numerically lower as for Ologen implant at all intervals with the exception of the 24th and the 60th month (Table 2).

The subgroup difference of the percentage reduction in intraocular pressure according to the concentrations of Mitomycin C (MMC) was not statistically significant ($P = .68$ in the 1st month, $P = .70$ in the 3rd month, $P = .56$ in the 6th month, $P = .05$ in the 12th month, $P = .47$ in the 24th month) (Table 3).

Table 1
Baseline characteristics of eligible randomized clinical trials.

study	location	No.Eyes*	Age (yr)*	Follow-up (m)*	Baseline IOP (mmHg) [mean (SD)] Implant	MMC	Intraoperative MMC mg/mL	time (min)
Zeiad H. Eldaly 1 2017	Egypt	10/10	54.7/53.3	6/6	27.43 (2.97)	27.56 (2.69)	0.2	NN
Zeiad H. Eldaly 2 2017	Egypt	10/10	54.7/51.9	6/6	27.43 (2.97)	28.40 (3.24)	0.4	NN
Fathi El-Sayyad 2017	Egypt	20/20	NN	12/12	34.70 (5.1)	35.50 (5.0)	0.4	2
Fei Yuan 2015	China	31/ 32	55.7/54.9	60/60	43.07 (6.23)	41.41 (5.11)	0.2	2
Tamer I. Salem 2015	Egypt	20/20	59.5/59.6	12/12	27.75 (3.01)	27.45 (2.23)	0.2	4
Senthil 2013	India	19/20	48/45	24/24	27.2 (10.5)	22.4 (6.6)	0.4	2
André Rosentreter 2014	Germany	15/15	67.9/65.0	12/12	28.0±9.4	23.9±5.0	0.2	3
Marey 2013	Egypt	30/30	50.2/49.1	12/12	29.9 (3.4)	31.5 (3.8)	0.2	2
Mitra 2012	UK	28/36	61.2/62.4	6/6	28.4 (8.4)	30.2 (8.4)	NN	NN
Cillino 2011	Italy	20/20	65.8/63.2	24/24	27.3 (6.0)	26.5 (5.2)	0.2	2
Nilforushan 2011	Iran	7/7	59/59	13/14	19.1 (3.8)	21.7 (4.1)	0.2	3
Rosentreter 2010	Germany	10/10	64.9/60.6	12/12	27.2 (10.5)	22.4 (6.6)	0.2	3

* Ologen implant group/MMC group; IOP = intraocular pressure, MMC = mitomycin C, NN = not note, OLO = Ologen implant.
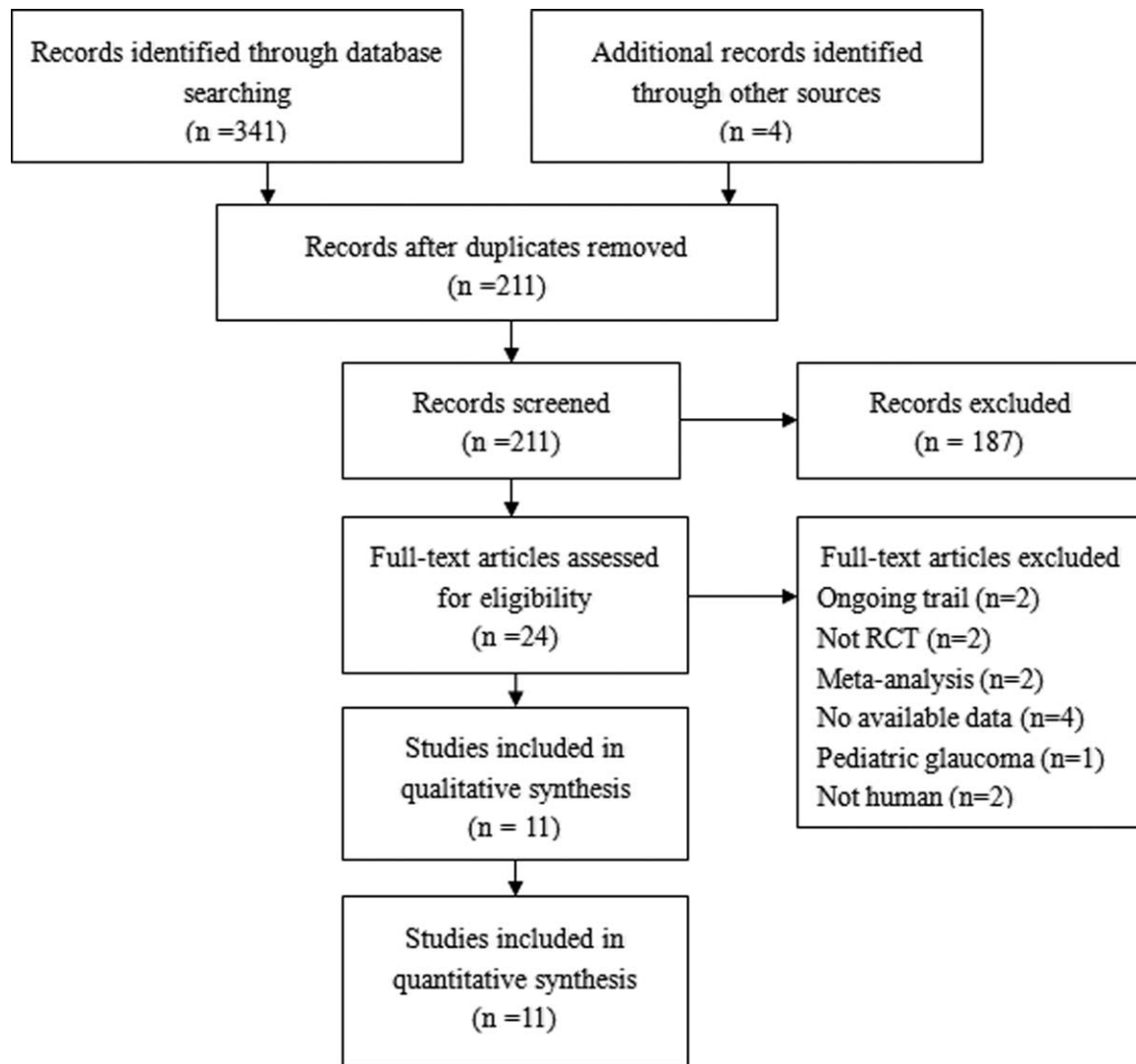
Figure 2. Flowchart of the trials included in the meta-analysis.

3.4.2. Complete success and qualified success rates. All of the 11 studies reported data for complete success rate and qualified success rate. The results showed that there was no statistically significant difference in the success rate between these 2 groups [pooled RR 0.91 (0.74, 1.13) for complete success rate; 1.02 (0.97, 1.07) for qualified success rate] (Table 4).

The subgroup difference incomplete success according to the concentration of Mitomycin C was statistically significant ($P = .01$). 0.2 mg/mL MMC provided a higher rate of complete success compared with 0.4 mg/mL MMC. The subgroup difference in qualified success according to the concentration of Mitomycin C was not statistically significant ($P = .16$) (Table 3).

3.4.3. The percentage reduction in the number of glaucoma medications. The pooled results suggested that the difference of the percentage reduction in the number of glaucoma medications between groups was not statistically significant except the 12th month (WMD = −6.80, 95% CI: −14.75 to 1.16, $P = .09$ in the 6th month; WMD = −25.16, 95% CI: −45.26 to −5.05, $P = .01$

in the 12th month; WMD = 5.33, 95% CI: −1.65 to 12.30, $P = .13$ in the 24th month).

The reduction in the number of glaucoma medications (95% CI) was respectively as follows: 2.56 (1.54–3.58) versus 2.88 (1.74–4.02) in the 6th month; and 2.63 (1.63–3.90) versus 2.74 (1.50–3.98) in the 12th month, 2.45 (0.91–3.99) versus 2.40 (0.92–3.88) in the 24th month (Table 2).

There was no significant heterogeneity in these analyses ($P > .1$).

3.4.4. Complications. The post-operative complications were similar in the 2 groups, except for hypotony and suture lysis, which were comparatively more in MMC group. The rates of the more frequently reported complications were as follows: Hyphema (pooled RR 1.65 (0.83–3.29), Hypotony maculopathy (pooled RR 0.50 (0.18–1.40)), hypotony (pooled RR 0.64 (0.42–0.98)), Bleb leakage (pooled RR 0.81 (0.41–1.63)), Encapsulated Bleb (pooled RR 1.68 (0.30–9.43)), Shallow anterior chamber (pooled RR 0.88 (0.50–1.53)), choroidal detachment (pooled RR 1.10 (0.56–2.15)), Blebitis (pooled RR 0.73 (0.21–2.47)), Anterior chamber reaction

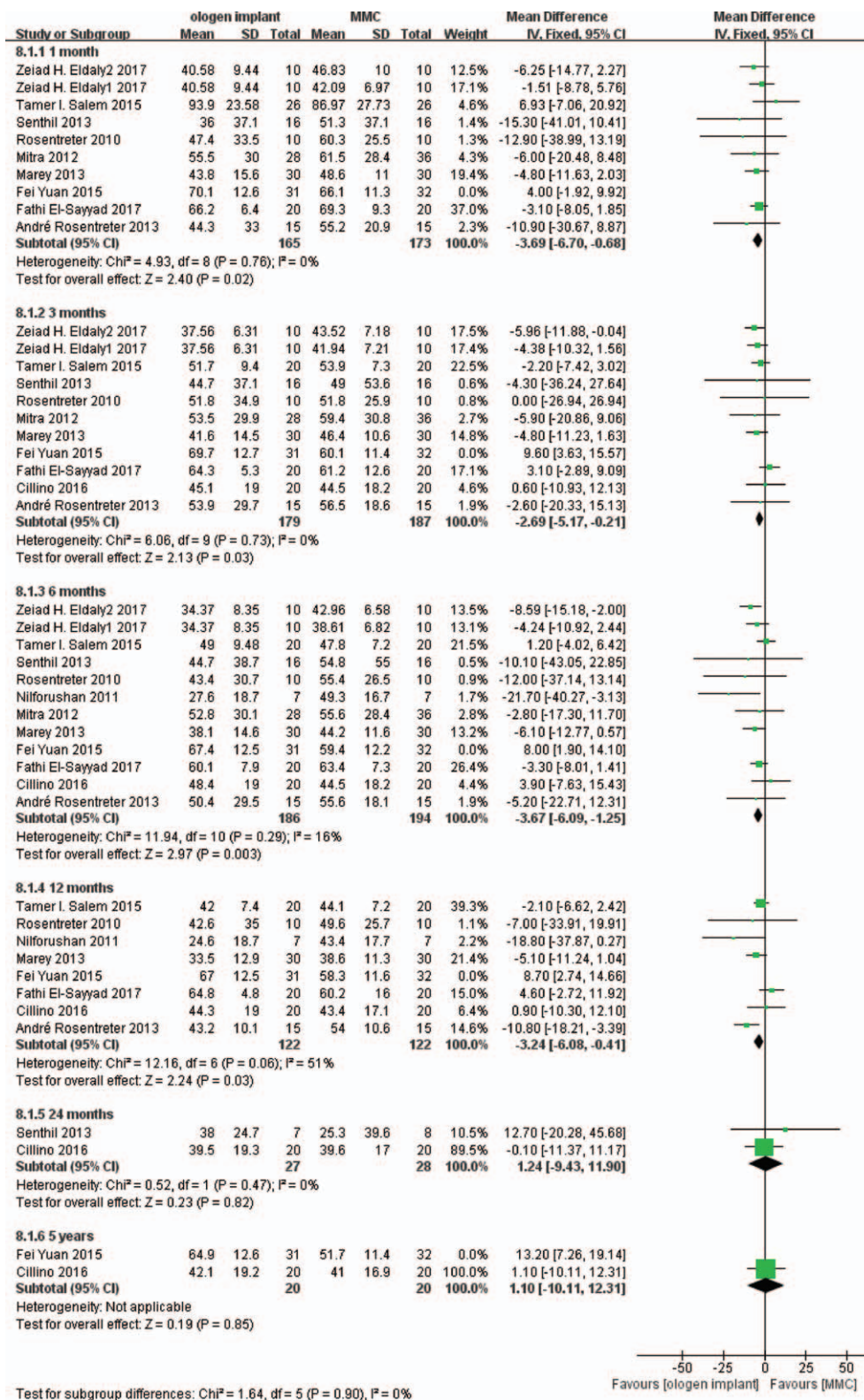| Study or Subgroup	ologen implant			MMC			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
8.1.1 1 month									
Zeiad H. Eldaly2 2017	40.58	9.44	10	46.83	10	10	12.5%	-6.25 [-14.77, 2.27]	
Zeiad H. Eldaly1 2017	40.58	9.44	10	42.09	6.97	10	17.1%	-1.51 [-8.78, 5.76]	
Tamer I. Salem 2015	93.9	23.58	26	86.97	27.73	26	4.6%	6.93 [-7.06, 20.92]	
Senthil 2013	36	37.1	16	51.3	37.1	16	1.4%	-15.30 [-41.01, 10.41]	
Rosentreter 2010	47.4	33.5	10	60.3	25.5	10	1.3%	-12.90 [-38.99, 13.19]	
Mitra 2012	55.5	30	28	61.5	28.4	36	4.3%	-6.00 [-20.48, 8.48]	
Marey 2013	43.8	15.6	30	48.6	11	30	19.4%	-4.80 [-11.63, 2.03]	
Fei Yuan 2015	70.1	12.6	31	66.1	11.3	32	0.0%	4.00 [-1.92, 9.92]	
Fathi El-Sayyad 2017	66.2	6.4	20	69.3	9.3	20	37.0%	-3.10 [-8.05, 1.85]	
André Rosentreter 2013	44.3	33	15	55.2	20.9	15	2.3%	-10.90 [-30.67, 8.87]	
Subtotal (95% CI)			165			173	100.0%	-3.69 [-6.70, -0.68]	
Heterogeneity: Chi² = 4.93, df = 8 (P = 0.76); I² = 0%									
Test for overall effect: Z = 2.40 (P = 0.02)									
8.1.2 3 months									
Zeiad H. Eldaly2 2017	37.56	6.31	10	43.52	7.18	10	17.5%	-5.96 [-11.88, -0.04]	
Zeiad H. Eldaly1 2017	37.56	6.31	10	41.94	7.21	10	17.4%	-4.38 [-10.32, 1.56]	
Tamer I. Salem 2015	51.7	9.4	20	53.9	7.3	20	22.5%	-2.20 [-7.42, 3.02]	
Senthil 2013	44.7	37.1	16	49	53.6	16	0.6%	-4.30 [-36.24, 27.64]	
Rosentreter 2010	51.8	34.9	10	51.8	25.9	10	0.8%	0.00 [-26.94, 26.94]	
Mitra 2012	53.5	29.9	28	59.4	30.8	36	2.7%	-5.90 [-20.86, 9.06]	
Marey 2013	41.6	14.5	30	46.4	10.6	30	14.8%	-4.80 [-11.23, 1.63]	
Fei Yuan 2015	69.7	12.7	31	60.1	11.4	32	0.0%	9.60 [3.63, 15.57]	
Fathi El-Sayyad 2017	64.3	5.3	20	61.2	12.6	20	17.1%	3.10 [-2.89, 9.09]	
Cillino 2016	45.1	19	20	44.5	18.2	20	4.6%	0.60 [-10.93, 12.13]	
André Rosentreter 2013	53.9	29.7	15	56.5	18.6	15	1.9%	-2.60 [-20.33, 15.13]	
Subtotal (95% CI)			179			187	100.0%	-2.69 [-5.17, -0.21]	
Heterogeneity: Chi² = 6.06, df = 9 (P = 0.73); I² = 0%									
Test for overall effect: Z = 2.13 (P = 0.03)									
8.1.3 6 months									
Zeiad H. Eldaly2 2017	34.37	8.35	10	42.96	6.58	10	13.5%	-8.59 [-15.18, -2.00]	
Zeiad H. Eldaly1 2017	34.37	8.35	10	38.61	6.82	10	13.1%	-4.24 [-10.92, 2.44]	
Tamer I. Salem 2015	49	9.48	20	47.8	7.2	20	21.5%	1.20 [-4.02, 6.42]	
Senthil 2013	44.7	38.7	16	54.8	55	16	0.5%	-10.10 [-43.05, 22.85]	
Rosentreter 2010	43.4	30.7	10	55.4	26.5	10	0.9%	-12.00 [-37.14, 13.14]	
Nilforushan 2011	27.6	18.7	7	49.3	16.7	7	1.7%	-21.70 [-40.27, -3.13]	
Mitra 2012	52.8	30.1	28	55.6	28.4	36	2.8%	-2.80 [-17.30, 11.70]	
Marey 2013	38.1	14.6	30	44.2	11.6	30	13.2%	-6.10 [-12.77, 0.57]	
Fei Yuan 2015	67.4	12.5	31	59.4	12.2	32	0.0%	8.00 [1.90, 14.10]	
Fathi El-Sayyad 2017	60.1	7.9	20	63.4	7.3	20	26.4%	-3.30 [-8.01, 1.41]	
Cillino 2016	48.4	19	20	44.5	18.2	20	4.4%	3.90 [-7.63, 15.43]	
André Rosentreter 2013	50.4	29.5	15	55.6	18.1	15	1.9%	-5.20 [-22.71, 12.31]	
Subtotal (95% CI)			186			194	100.0%	-3.67 [-6.09, -1.25]	
Heterogeneity: Chi² = 11.94, df = 10 (P = 0.29); I² = 16%									
Test for overall effect: Z = 2.97 (P = 0.003)									
8.1.4 12 months									
Tamer I. Salem 2015	42	7.4	20	44.1	7.2	20	39.3%	-2.10 [-6.62, 2.42]	
Rosentreter 2010	42.6	35	10	49.6	25.7	10	1.1%	-7.00 [-33.91, 19.91]	
Nilforushan 2011	24.6	18.7	7	43.4	17.7	7	2.2%	-18.80 [-37.87, 0.27]	
Marey 2013	33.5	12.9	30	38.6	11.3	30	21.4%	-5.10 [-11.24, 1.04]	
Fei Yuan 2015	67	12.5	31	58.3	11.6	32	0.0%	8.70 [2.74, 14.66]	
Fathi El-Sayyad 2017	64.8	4.8	20	60.2	16	20	15.0%	4.60 [-2.72, 11.92]	
Cillino 2016	44.3	19	20	43.4	17.1	20	6.4%	0.90 [-10.30, 12.10]	
André Rosentreter 2013	43.2	10.1	15	54	10.6	15	14.6%	-10.80 [-18.21, -3.39]	
Subtotal (95% CI)			122			122	100.0%	-3.24 [-6.08, -0.41]	
Heterogeneity: Chi² = 12.16, df = 6 (P = 0.06); I² = 51%									
Test for overall effect: Z = 2.24 (P = 0.03)									
8.1.5 24 months									
Senthil 2013	38	24.7	7	25.3	39.6	8	10.5%	12.70 [-20.28, 45.68]	
Cillino 2016	39.5	19.3	20	39.6	17	20	89.5%	-0.10 [-11.37, 11.17]	
Subtotal (95% CI)			27			28	100.0%	1.24 [-9.43, 11.90]	
Heterogeneity: Chi² = 0.52, df = 1 (P = 0.47); I² = 0%									
Test for overall effect: Z = 0.23 (P = 0.82)									
8.1.6 5 years									
Fei Yuan 2015	64.9	12.6	31	51.7	11.4	32	0.0%	13.20 [7.26, 19.14]	
Cillino 2016	42.1	19.2	20	41	16.9	20	100.0%	1.10 [-10.11, 12.31]	
Subtotal (95% CI)			20			20	100.0%	1.10 [-10.11, 12.31]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.19 (P = 0.85)									

Test for subgroup differences: Chi² = 1.64, df = 5 (P = 0.90), I² = 0%

Favours [ologen implant]   Favours [MMC]

Figure 3. The percentage reduction in intraocular pressure comparing trabeculectomy with Ologen implant and MMC at various time points (without Fei Yuan's study). CI indicates confidence interval. MMC = mitomycin C.

(pooled RR 1.09 (0.61–1.93)), suture lysis (pooled RR 0.30 (0.10–1.93)), needling (pooled RR 0.11 (0.01–1.94)) (TALBE 4).

The subgroup difference of the complications based on the concentration of Mitomycin C was not statistically significant (*P* >.05) (TALBE 3).

Table 2

Pooled estimates for intraocular pressure and glaucoma medication reduction from baseline for Ologen implant versus MMC.

Index	Follow-up (mo)	No. studies	The pooled mean of reduction from baseline (95% CI)	
			Implant	MMC
IOP, mmHg	1	10	17.13 (10.07)	18.06 (6.23)
	3	9	17.05 (7.44)	16.51 (5.53)
	6	12	14.99 (7.50)	15.56 (3.78)
	12	9	16.10 (8.78)	15.73 (6.60)
	24	2	12.17 (3.3)	10.64 (2.49)
	60	2	27.70 (9.43)	17.37 (6.91)
IOP (mmHg) (Exclude Feiyuan' study)	1	9	14.45 (8.70)	16.32 (4.71)
	3	8	14.53 (4.59)	14.91 (4.10)
	6	11	12.66 (4.96)	14.08 (3.95)
	12	8	12.84 (6.14)	13.51 (5.04)
	24	2	12.17 (3.3)	10.64 (2.49)
	60	1	12.10 (5.2)	10.90 (4.51)
No. medications	6	4	2.56 (1.02)	2.88 (1.14)
	12	3	2.63 (1.27)	2.74 (1.24)
	24	2	2.45 (1.54)	2.40 (1.48)

3.5. Sensitivity analysis and publication bias

To evaluate the robustness of the results, each study in the meta-analysis was excluded in turn to test the influence of individual studies on the pooled estimates of IOPR% respectively in the 1st month, 3rd month, 6th month, 12th month, 24th month, and 60th month. The results indicated that the estimates before and after the deletion of Feiyuan's study were different, so we decided to delete this study. The results showed that the estimates before and after the deletion of any other single study were generally similar, which suggested high stability in the meta-analysis results (data not shown). A funnel plot analysis indicated that the complete success rates were distributed symmetrically, showing no evidence of publication bias (Fig. 4).

4. Conclusion

4.1. Main findings

The findings of this updated meta-analysis were as follows:

(1) Trab with Ologen and Trab with MMC were both associated with IOP-lowering efficacy, and the effect of MMC on lowering IOP was greater than that of Ologen for the 1st, 3rd, 6th, and 12th month.
(2) The complete success rates and quality success rates of MMC group were similar to those of Ologen group.
(3) Trab with MMC was connected with a significantly lower percentage reduction in the number of Glaucoma Medications compared with Trab plus MMC for the 12th month.

Table 3

The subgroup analysis of IOPR%, Success rate and complications according to the concentrations of mitomycin C.

	MMC concentrations				P value for subgroup difference
	0.2 mg/mL		0.4 mg/mL		
IOPR%					
	WMD (95% CI)	I^2	WMD (95% CI)	I^2	
1m	−2.89 (−7.38, 1.61)	0	−4.20 (−8.42, 0.02)	0	.68
3m	−3.21 (−6.35, −0.06)	0	−1.59 (−9.10, 5.92)	55	.70
6m	−3.39 (-7.92.1.14)	35	−5.16 (−8.97, −1.35)	0	.56
12m	−3.86 (−7.44, −0.28)	0	4.60 (−2.72, 11.92)	−	.05
24m	−0.10 (−11.37, 11.17)	−	12.70 (−20.28, 45.68)	−	.47
Success rate					
	RR (95% CI)		RR (95% CI)		
Complete success	0.73 (0.62, 0.87)	50	1.15 (0.86, 1.54)	37	.01
Qualified success	1.00 (0.94, 1.07)	0	1.13 (0.96, 1.32)	11	.16
Complications					
	RR (95% CI)		RR (95% CI)		
Hypotony	0.69 (0.44, 1.10)	0	0.44 (0.16, 1.24)	23	.43
AC reaction	1.58 (0.64, 3.87)	44	1.27 (0.62, 2.59)	0	.71
Bleb leak	0.93 (0.45, 1.92)	7	0.21 (0.01, 4.11)	−	.34
Shallow AC	0.89 (0.35, 2.28)	0	0.87 (0.29, 2.65)	0	.98
Blebitis	0.57 (0.13, 2.54)	0	0.33 (0.01, 7.72)	−	.09
Choroidal detachment	0.76 (0.29, 1.98)	0	1.40 (0.36, 5.46)	−	.47

CI = confidence interval, IOPR% = The percentage reduction in intraocular pressure, RR = risk ratio, WMD = Weighted Mean Difference.

Table 4

The Rate of Success and Adverse Events Comparing Trabeculectomy With Ologen Implant and Trabeculectomy With MMC.

	Studies (n)	Pooled Rate [n/N (%)]		RR (95% CI)	I^2 (%)	P
		Implant	MMC			
Success rates						
Complete success	11	138/217	156/226	0.91 (0.74,1.13)	59	.39
Qualified success	11	201/217	198/226	1.02 (0.97,1.07)	1	.51
Complications						
Bleb leak	8	12/135	15/137	0.81 (0.41,1.63)	5	.56
Hyphema	9	18/165	11/167	1.65 (0.83,3.29)	9	.16
Shallow AC	9	17/162	20/171	0.88 (0.50,1.53)	0	.65
Hypotony	10	25/183	40/193	0.64 (0.42,0.98)	0	.04
Encapsulated Bleb	2	3/38	2/46	1.68 (0.30,9.43)	0	.56
Blebitis	3	3/109	5/118	0.73 (0.21,2.47)	0	.61
Hypotony maculopathy	1	4/20	8/20	0.50 (0.18,1.40)	–	.19
choroidal detachment	5	9/95	10/97	1.10 (0.56,2.15)	0	.78
AC reaction	5	18/100	17/102	1.09 (0.61,1.93)	0	.78
Suture lysis	1	3/20	10/20	0.30 (0.10,0.93)	–	.04
Needling	1	0/20	4/20	0.11 (0.01,1.94)	–	.13

MMC = mitomycin C.

(4) Postoperative complications were similar in both groups except for hypotony and suture lysis, which were more common in MMC group.

(5) Trab with 0.2 mg/mL MMC provided higher rates of complete success compared with Trab with 0.4 mg/mL MMC.

4.2. Comparison with other meta-analyses

Two main meta-analyses in this regard have been published.[17,21] but the differences between the meta-analysis in our study and the previous ones should be identified. First, the previous meta-analyses involved no more than 7 trials and 237 patients. By contrast, our meta-analysis involved 11 trials and 474 patients, which is also the latest and the most comprehensive one, generally concurring and further reinforcing earlier results of the previous meta-analyses. Second, it was found that when the preoperative IOP was more than 40 mmHg in Feiyuan' study, the Ologen group showed a significantly lower reduction in IOP and higher success rates compared with those of the MMC group, indicating that maybe the preoperative IOP had a potential influence on the 2

Figure 4. Funnel plots of comparing the complete success rate of trabeculectomy with Ologen implant and MMC (The funnel plot of meta-analysis of RR is symmetry). MMC = mitomycin C.

groups' outcome and additionally, Trab with Ologen was a better choice for the higher intraocular pressure glaucoma. Thirdly, it is noticeable that we have also conducted a subgroup analysis based on the concentration of MMC. Last but not least, our conclusion is slightly different from that of the previous meta-analyses.

4.3. Implications for clinical practice

As we all know, the main influencing factor of long-term success rates of Trab was postoperative scarring according to several histological studies. Since antimetabolites appeared, like MMC, which can reduce fibroblast proliferation in the subconjunctival space, the chance of scar formation has declined greatly.[22] It has been widely used to increase the success rates of Trab.[23]

However, the use of MMC in Trab has caused a great many complications (e.g., cataract formation, avascular filtering blebs, conjunctival thinning, blebitis, and endophthalmitis).[24,25] As a consequence, there is an urgent need to search for less-toxic agents and implants to inhibit cicatrization without adverse effects. Recently, Ologen has been used as a subconjunctival spacer during the primary. However, the results of the earlier studies were somewhat contradictory.

The present meta-analysis showed that Ologen implant was less effective compared with MMC in achieving low IOP levels except for the 24th and the 60th month, and no significant difference in the complete and qualified success rates was discovered. A possible explanation for such differences may be as follows. First, the pooled data of IOP reductions were based on only 2 papers involving 27 participants for the 24th month, and 1 paper involving 20 participants for the 60th month. Therefore, the results may be inaccurate at these 2 follow-up time nodes. Thus, further long-term studies with a larger sample size are required. Secondly, the learning curve is also an important factor, because Trab with Ologen implant is considered to be a relatively new technique compared with MMC. Similarly, the outcomes can change for the better over time, as surgeons are becoming more comfortable with the usage of Ologen.[26] The other reasons leading to these somewhat less effective lower IOP control in the Ologen implant are:

1. the Ologen implant only functions as a wound modulator but does not have any antifibrotic properties to counter the scarring response.
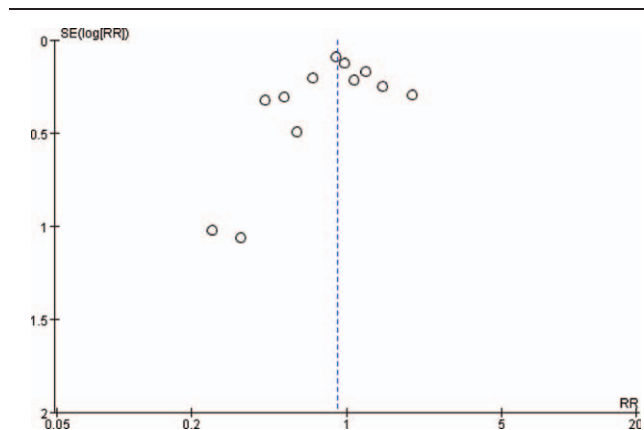
2. Ologen implant may cause secondary tissue reaction around the matrix scaffold in subconjunctival space.

In this updated meta-analysis, a significantly lower incidence of postsurgery hypotony was observed with Ologen[9]. Ologen is known to provide a scaffolding to randomize the fibroblast proliferation with a modulated wound healing. It can mechanically maintain the potential subconjunctival space and prevent the adhesion between the episcleral surface and the conjunctiva. Besides, it maintains the physiologic barriers through regeneration, even during partial degradation, thus allowing for diffuse functional bleb, which is also likely to normalize the dynamic aqueous balance and create a sound conjunctival system, so as to help maintain a low IOP while preventing hypotony.

Laser suture lysis was performed on 3 eyes in Ologen group and 10 eyes in MMC group. This is one of the advantages of the Ologen implant, as the scleral sutures can be placed not tightly, and placing the Ologen implant on the posterior edge of the flap may cause press against the flap. The implant influences the aqueous flow by maintaining the pressure on the top of the sclera flap and by acting as a reservoir, because the aqueous flow is absorbed through its pores, consequently preventing hypotony and simultaneously avoiding the need of removing the sutures.[27]

Feiyuan's study suggested that there was a statistically significant difference in the percentage reduction in intraocular pressure between the 2 groups in the 3rd month, the 6th month, the 1st year, the 3rd year, and the 5th year.[9] The 2 groups also differed significantly in the rates of complete success and overall success. At the end of the 5th year, complete success was observed in 61.29% of the eyes in Ologen group compared with 31.25% of the eyes in MMC group ($P = .017$). The overall success rate was 83.87% and 59.38%, respectively ($P = .031$). According to their study, it was found that the Ologen group had a significantly lower IOP and a higher success rate compared with that of the MMC group. Maybe it was associated with a higher baseline IOP (>40mmHg), and what's more, Trab with Ologen implant was likely to have a better effect on a higher baseline intraocular pressure glaucoma. It can be seen that further large-scale and well-designed randomized controlled trials are in urgent need.

The test for subgroup differences indicated that the dose of MMC influenced its efficacy of complete success. Trab with 0.2 mg/mL MMC helped to produce higher rates of complete success compared with those with 0.4 mg/mL MMC, but eyes treated with 0.2 mg/mL MMC were shown to have a comparable outcome with 0.4 mg/mL MMC-treated eyes in terms of IOP control, qualified success and complications. A possible explanation for such differences may be as follows. First, only 3 papers use 0.4 mg/ml MMC, which may have a significant impact on the results, Second, the effect of MMC is related to not only the concentration but also the time of usage, differences in the exposed time of MMC in each article will also affect the conclusion. However, in this meta-analysis, Trab with 0.4 mg/mL MMC does not seem to have more significant advantages over those of Trab with 0.2 mg/mL MMC.

5. Limitations

There are still some limitations in our meta-analysis. The analyses of the success rate and complications were based on data pooled from trials of different durations for lack of data reported in all phases of the follow-up. Thus, it was a compromising proposal to choose the data from the follow-up endpoint. In addition, the included studies were diverse in terms of design, population,

types of glaucoma, postoperative management, and outcomes investigated. Shortcomings of meta-analyses also include the covert and acknowledged duplication of data. In order to avoid this, our study only covered the most recent series of the same patient group.

This meta-analysis was carried out using robust methods. To avoid publication bias, apart from an electronic search, we also carried out a manual search for the references based on all the previous systematic review and reference lists of every primary article. Quality assessment was carried out independently by 2 researchers using questions derived from the well-used GRADE (Grading of Recommendations Assessment, Development, and Evaluation, methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias). The high heterogeneity was also observed among studies, which will influence the analysis, interpretation, and conclusions of this study. To minimize the effect of the heterogeneity, we used a random effect model. and deleted an "outlier" study, conducted by Feiyuan and colleagues, presented a higher baseline IOP (>40mmHg), then the heterogeneity disappeared at each postoperative time except for the 12th month. Furthermore, a subgroup analysis was also conducted based on the concentration of MMC to minimize the bias of this meta-analysis.

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