·Informatics Research·

Bare sclera resection followed by mitomycin C and/or autograft limbus conjunctiva in the surgery for pterygium: a Meta-analysis

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Abstract

• **AIM: To evaluate the recurrence and complications after bare sclera resection (BSR) combined with mitomycin C (MMC) treatment and/or autograft limbus conjunctiva (ALC) in the surgery for pterygium.**

• **METHODS: Meta-analysis was used to evaluate the differences in patient outcomes between BSR of pterygium with or without MMC and/or ALC. All included studies were randomized trials of patients with pterygium who received BSR followed by MMC and/or ALC in the surgery. The recurrence of pterygium and other complications resulting from different treatments were extracted for analysis.**

• **RESULTS: Thirteen studies met the inclusion criteria. The recurrence of pterygium with intraoperative (IO) MMC was higher than that with ALC (OR=2.38, 95% confidence interval 1.45-3.91, I^2=29%). Postoperative MMC resulted in an incidence of recurrence similar to that of ALC (OR= 0.66, 95% confidence interval 0.30-1.42, I^2=0%), and IO MMC treatment in combination with ALC produced similar patient outcomes to ALC alone (OR=0.41, 95% confidence interval 0.16-1.01, I^2=16%). Other complications such as punctate epitheliopathy, scleral thinning and ischemia, irritation and persistent epithelium defect, were more common in patients in the MMC group as compared to those treated with ALC.**

• **CONCLUSION: The recurrence of pterygium with BSR followed by ALC is lower than that of BSR followed by MMC, and the incidence of other complications is lower. While ALC is a more effective strategy for treating pterygium, the quality of the ALC transplant should be considered when the patient has a history of glaucoma.**

• **KEYWORDS:** pterygium; mitomycin C; conjunctiva; autograft
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INTRODUCTION

Pterygium, one of the most commonly diagnosed diseases in ophthalmology, is a fibrovascular growth arising from the conjunctiva of the eye that grows over the cornea. Vision is often significantly impaired when the growth extends to the center of the cornea obstructing the pupil, therefore, the proliferated tissue should be ablated as soon as possible. Although bare sclera resection bare sclera resection (BSR) is a relatively straightforward procedure, pterygium recurrence is between 24% and 89%[1]. There are multiple strategies to decrease the high rate of pterygium recurrence following BSR including conjunctival transposition [2] by amniotic membrane or stem cell transplantation, or by inhibiting regrowth using various treatments such as thiotepa [3], β radiation[3], or mitomycin C (MMC)[4].

MMC is an alkylating compound derived from Streptomyces caespitosus. Due to its cytotoxic effects in inducing apoptosis [5,6], MMC is widely used as a chemotherapeutic agent [7]. The blood supply to pterygium mainly comes from the surface conjunctiva [8], and the usage of MMC following resection can reduce the rate of recurrence[9], in part because it can suppress neovascularization. However, because the apoptotic effects of MMC can potentially lead to other complications such as scleral thinning and ischemia, this treatment strategy may not be ideal[9].

Another well-known and effective method to reduce the recurrence of pterygium is the transplantation of autograft limbus conjunctiva (ALC), which is taken from the identical or contralateral eye following the BSR. The conjunctiva will cover the wound, and block the regeneration of the fibrovascular tissue onto the cornea, thereby decreasing the rate of recurrence [10]. Many studies have reported that the usage of MMC and ALC following BSR can reduce

pterygium recurrence, however, these results have never been compared across multiple studies[11]. The Meta-analysis described in this study was performed to compare the recurrence rates and other complications between the two methods.

MATERIALS AND METHODS

Literature Search Studies that compared the two different methods to treat pterygium were searched without language restriction. The keywords used in the literature search were pterygium, mitomycin and conjunctiva. The databases searched for published articles included the Cochrane Central Register of Controlled Trials, Medline (1990 to present), and Embase (1990 to present). In addition, the databases of OpenSIGLE and NTIS were searched for unpublished articles. The final literature search occurred on October 3rd, 2013.

Article Criteria and Selection All included studies were randomized controlled trials comparing at least two groups that used MMC and ALC following BSR, and the recurrences of the two groups respectively. The studies involving pseudo-pterygium or including any therapy other than MMC or ALT were excluded.

Two reviewers independently examined all articles. Inclusion in the meta-analysis was determined by reviewing the titles and abstracts of the searched papers according to the aforementioned criteria, then further selecting for relevant studies by reading the entire article. Any discrepancies between reviewers were resolved by discussion. The selection of articles for inclusion in the study was relatively consistent between reviewers (κ=0.86).

Data Extraction The data were independently extracted by two reviewers. This included the country and language of the origin of the study; the parameters of the study design such as methods, doses and duration of treatments and postoperative care; patient information including gender, age, and disease state; the outcomes of the study including rate of recurrence as well as other associated complications involved in the included studies. Any discrepancies between reviewers were resolved by discussion. Both reviewers consistently extracted similar data from the relevant articles (κ=0.83).

Study Characteristics and Quantitative Data Analysis Due to the existence of more than two treatment groups in some included studies, only the comparison between MMC and ALC was extracted. First, the heterogeneity of pterygium recurrence was analyzed, and represented as I^2. If $I^2 < 50\%$, the heterogeneity of recurrence was considered acceptable, and the data was subsequently used for fixed-effect meta-analysis. If $I^2 > 50\%$, the heterogeneity was considered unacceptable, and studies were further divided into sub-groups according to heterogeneity resources. If no adequate resources could be identified, a random-effect meta-analysis was performed. Meta-regression and meta-trim were also performed to further assess the bias between studies. A P-value less than 0.05 was considered significant. An additional Meta-analysis was performed for data in relation to other complications resulting from pterygium treatment according to the methods described above. All analyses were carried out in Stata 11.

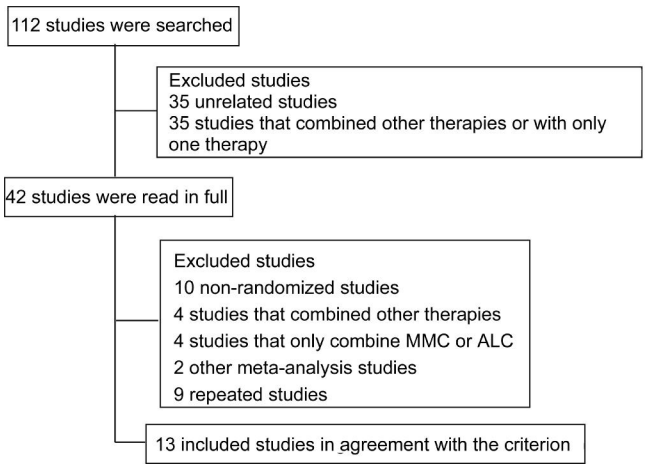

Figure 1 Criteria and selection of studies to be included in the Meta-analysis.

RESULTS

Trial Flow and Study Characteristics A total of 112 studies were identified in our original literature search using the aforementioned criteria, 103 of which were written in English, 5 in Chinese, 2 in French, 1 in German and 1 in Polish. Upon further selection, a total of 13 papers [12-24] were included after reading titles, abstracts and full papers. All included articles were written in English (Figure 1, Table 1).

Quality Assessment Assessment of the quality of the included articles was carried out according to the criteria of the Cochrane Library. All included studies were randomized controlled trials, however, only 3 of the 13 described the methods of randomization [15,18,22], and in one of the studies two eyes of some subjects were treated indicating no randomization [19]. Most included studies did not mention the process of allocation concealment. It was impossible to completely blind the study to operators and subjects. In some studies, nearly non-degradable nylon sutures were used [14,16,17,21,23]. Consequently, during the assessment of recurrence and other complications, treatment strategy was revealed to the doctors administering postoperative care (Table 2). Nonetheless, the overall quality of the 13 included studies was moderate to high, and thus the data were subsequently analyzed using GRADEpro software.

Quantitative Data Analysis The relative recurrence of pterygium after BSR followed by intraoperative MMC or ALC is shown in Figure 2. Only data from patients with

Table 1 Data extracted from included studies

Study (country)	Disease	Intervention	Position of autograft	Follow-up (mo)	Number (F %)	Age (a)	Lost to follow-up	Suture
Akinci and Zilelioglu 2007 (Turkey)[12]	PP	IO 0.02%MMC×5min	Superior	⩾12	52 (53.85%)	44.03 (35-52)	NM	NM
		ALC			60 (48.33%)	43.08 (33-54)		8-0 polyglactin
Andrade *et al* 2004 (Venezuela)[13]	PP	IO 0.02%MMC×1min+ ALC	Superior	12 (9-20)	30 (ND)	40.3 (25-85)	NM	NM
		ALC			28 (ND)			
Biswas *et al* 2007 (India)[14]	PP	IO 0.02%MMC×2min	Superior temporal	6	30 (ND)	35.56 (25-60)	NM	10-0 nylon
		ALC			30 (ND)			10-0 nylon
Chen *et al* 1995 (USA)[15]	PP	PO 0.02%MMC (2/d×5d)		12.2±3.9	24 (58.33%)	43.0±12.5	NM	NM
		PL		9.3±2.5	17 (52.94%)	45.4±11.6		NM
		ALC	Superior	13.5±2.5	23 (52.17%)	48.4±13.7		8-0 polyglactin
Frucht-Pery *et al* 2006 (Israel)[16]	PP	IO 0.02%MMC×3min	Superior	31.5±3.4	30 (ND)	40.2±11.6	NM	all 10-0 nylon
		ALC		29.3±2.5	30 (ND)	43.4±12.2		
		PL		36.2±2.8	30 (ND)	44.6±11.3		
		IO 0.02%MMC×3min+ ALC		21.3±2.4	30 (ND)	41.8±11.8		
Keklikci *et al* 2007 (Turkey)[17]	PP	IO 0.02% MMC×2min	Superior temporal	23.44±7.24	32 (43.8%)	44.72±11.21	NM	10-0 nylon
		ALC		24.38±7.93	32 (53.1%)	39.84±11.69		10-0 nylon and 8-0 Vicryl with cornea tissue
		AM		23.63±7.30	30 (46.7%)	41.83±13.41		10-0 nylon and 8-0 Vicryl
Koranyi *et al* 2012 (Sweden)[18]	PP	IO 0.04%MMC×3min	Superior temporal	12-48	56 (41%)	48.3±15	NM	NM
		ALC			59 (39%)	48.6±16		7-0 vicryl
Mahar 1997 (Saudi Arabia)[19]	PP	PO 0.02%MMC (2/d×5d)	Superior temporal	14.41±1.65	32 (17.9%)	28.86±5.99	NM	NM
		ALC		15.27±1.48	27 (13.6%)	30.04±8.64		
Manning *et al* 1997 (USA)[20]	PP	PO 0.02%MMC (4/d×7d)	Superior temporal	6-28	19 (33.33%)	47.8	7, ND	NM
		ALC			18 (57.89%)	49.5		
Mutlu *et al* 1999 (Turkey)[21]	RP	IO 0.04%MMC×3min	Superior temporal	15.5±1.5	19 (26.32%)	47.1	NM	10-0 nylon, 8-0 polyglactin with cornea tissue
		IO 0.02%MMC×3min+ ALC			41 (39%)	34.27±11.3		
		ALC		16±1.9	40 (37.5%)	34.83±12.4		10-0 nylon and 8-0 polyglactin
Ari *et al* 2009 (Turkey)[22]	PP	IO 0.02%MMC×2min	Superior temporal	16.0±1.9	50 (48%)	48.0±12.3	7	10-0 polyglactin
		ALC		15.0±1.7	50 (46%)	49.0±12.6	6	10-0 nylon
Sharma *et al* 2000 (India)[23]	PP	IO 0.02%MMC×2.5min	Superior temporal	38 (13-58)	21 (28.57%)	21-40	NM	NM
		ALC		36 (14-54)	20 (35.00%)	41-60		10-0 nylon
Young *et al* 2004 (China)[24]	PP	IO 0.02%MMC×5min	Superior	16.17±3.47	63 (58.73%)	59.06±14.67	31 (32.98%)	NM
		ALC		16.73±4.01	52 (63.46%)	60.04±10.56	21 (28.77%)	8-0 polyglactin

PP: Primary pterygium; RP: Recurrent pterygium; IO: Intraoperative; PO: Post-operative; ALC: Autograft limbus conjunctiva; AM: Amnion; PL: Placebo; ND: No detail; NM: Not mentioned.

Table 2 Quality assessment of included studies

Studies	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome addressed	Free of selective reporting	Free of other bias
Akinci and Zilelioglu [12]	Unclear	Unclear	No	Yes	Yes	Yes
Andrade *et al*[13]	Unclear	Unclear	No	Unclear	Unclear	Yes
Biswas *et al*[14]	Unclear	Unclear	No	Yes	Yes	Unclear
Chen *et al*[15]	Yes	Yes	Unclear	Unclear	Yes	Yes
Frucht-Pery *et al*[16]	Unclear	Unclear	Unclear	No	Yes	Unclear
Keklikci *et al*[17]	Unclear	Unclear	No	Yes	Yes	Yes
Koranyi *et al*[18]	Yes	Unclear	Unclear	Unclear	Yes	Yes
Mahar[19]	Unclear	Unclear	No	Unclear	Yes	Yes
Manning *et al*[20]	Unclear	Unclear	Unclear	Yes	Yes	Yes
Mutlu *et al*[21]	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Ari *et al*[22]	Yes	Yes	Unclear	Yes	Yes	Yes
Sharma *et al*[23]	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Young *et al*[24]	Unclear	Unclear	Unclear	Yes	Yes	Yes

primary pterygium were included in the analysis. Pterygium recurrence in the MMC group was higher than that of the ALC group (OR=2.38, 95% confidence interval 1.45-3.91, I^2=29%).

The relative recurrence of pterygium after BSR followed by postoperative MMC or ALC is shown in Figure 3. Only data from patients with primary pterygium were included in the analysis. There was no significant difference in recurrence between the two groups (OR=0.66, 95% confidence interval 0.30-1.42, I^2=0%).

The relative recurrence of pterygium after BSR followed by postoperative MMC combined with ALC or ALC alone is shown in Figure 4. All patients presented with either primary or recurrent pterygium, and there was no further division into

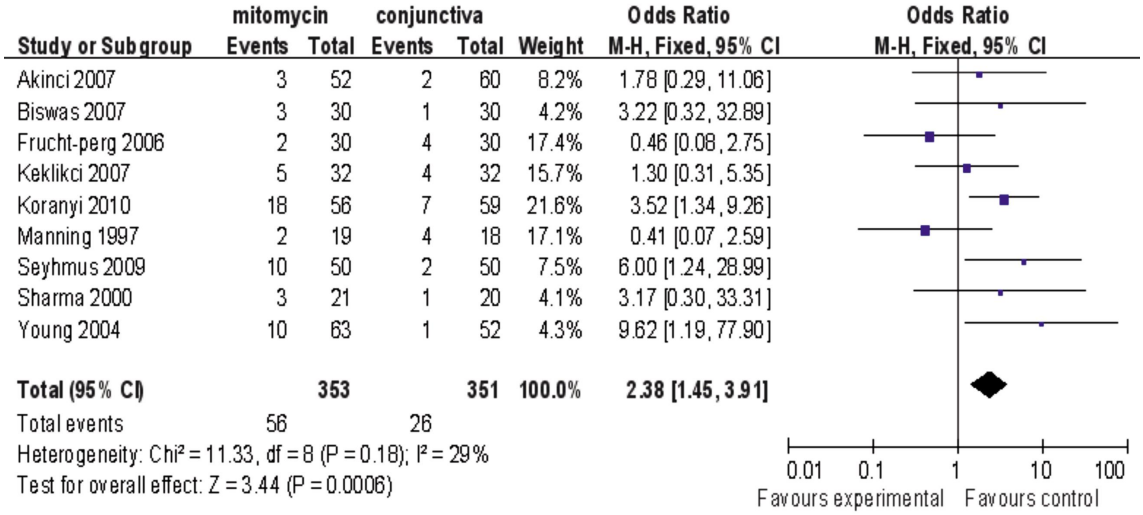

Figure 2 Comparison of pterygium recurrence after BSR followed by intraoperative MMC or ALC.

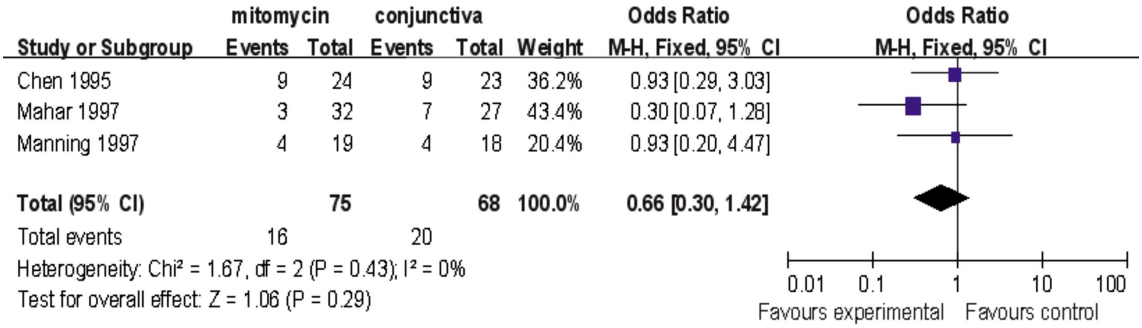

Figure 3 Comparison of pterygium recurrence after BSR followed by postoperative MMC or ALC.

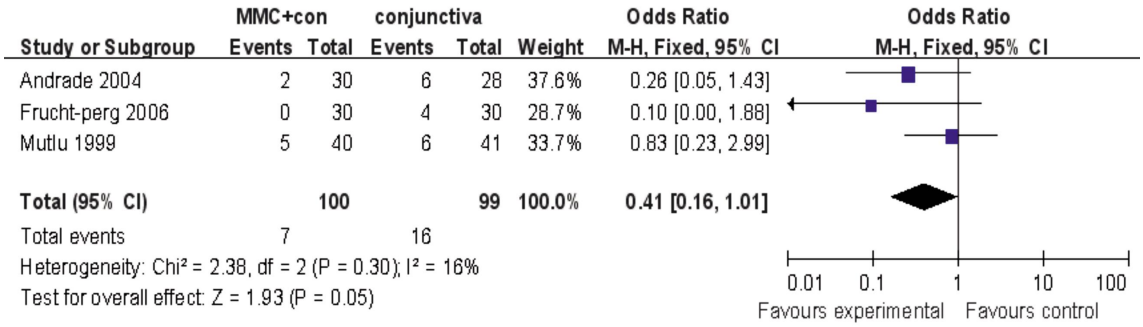

Figure 4 Comparison of pterygium recurrence after BSR followed by postoperative MMC combined with ALC or ALC alone.

subgroups, as only 3 studies were included. The two treatment groups shared the same incidence of recurrence (OR=0.41, 95% confidence interval 0.16-1.01, I^2=16%).

Analyses of Sensitivity and Publication Bias The meta-trim analysis carried out using these studies involved the comparison of pterygium recurrence between BSR followed by intraoperative MMC and ALC, and did not show a significant change upon removal of any included study. There was no significant difference between included studies though the meta-regression, and the bias factor was -0.617±1.468 (t=0.42, P=0.687) (Figure 5). Therefore, the heterogeneity and bias were considered acceptable.

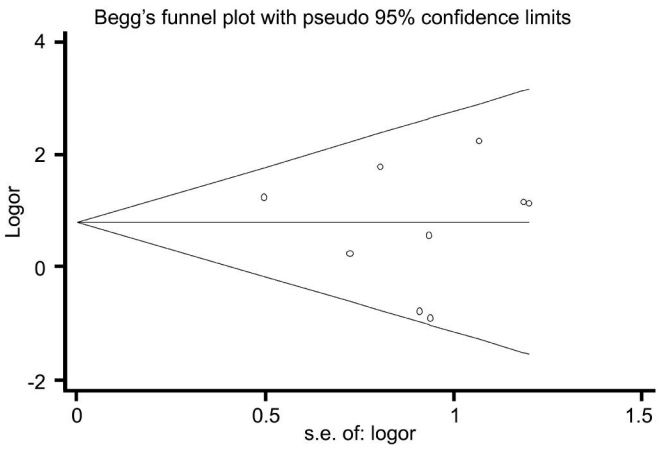

Figure 5 Tunnel plot of all studies involving primary pterygium.

Comparison of Other Complications Resulting from Different Interventions The incidence of other complications resulting from BSR followed by MMC or ALC are shown in Table 3. Due to low incidence of some

Table 3 Comparison of other complications resulting from BSR followed by MMC or ALC

Complications	Number (%)		OR		I^2	P
	MMC	ALC	Mean	95% confidential interval		
Graft edema[15,21,22]	-	113(38.05)	-	-	-	
Graft failure[15,18,21,22]	-	172(1.74)	-	-	-	
Granuloma[14,15,21-24]	228(1.75)	216(2.79)	0.75	0.27-2.05	2	0.58
Haematoma[12,16,21]	123(1.63)	131(4.58)	0.45	0.11-1.77	0	0.25
Punctate epitheliopathy[15,21]	64(28.13)	64(0)	25.05	3.43-183.10	23	0.002
Conjunctiva cyst[12,15,22,24]	189(4.23)	185(1.62)	2.55	0.72-9.05	0	0.15
Symblepharon[12,15,18,22,24]	229(2.62)	231(1.73)	1.38	0.45-4.22	0	0.57
Scleral thinning, ischemia[14,18,22,24]	183(5.46)	178(1.12)	5.46	1.31-22.88	0	0.02
Irritation[12,15]	76(34.21)	83(7.23)	7.03	2.71-18.26	0	＜0.0001
Persistent epithelium defect[12,15,18,23]	137(27.74)	149(2.01)	13.46	4.93-36.74	0	＜0.0001
Dellen[15,22,24]	137(1.50)	125(0.80)	1.31	0.25-6.77	0	0.75

complications (even as low as 0) the results of Meta-analyses should potentially be reevaluated. Nonetheless, it was shown that the incidences of punctate epitheliopathy, scleral thinning and ischemia, as well as irritation and persistent epithelial defects were higher in the MMC treatment group as compared to the ALC group.

DISCUSSION

The surgical approaches to pterygium management include BSR, amniotic membrane graft, tissue glue, the employment of MMC, and the transplantation of ALC. Due to the lower rate of pterygium recurrence and the relative convenience of the procedures, the most commonly used treatment regimen is BSR followed by MMC and/or ALC[25].

The two strategies following BSR have advantages and disadvantages. ALC following BSR will reconstruct the normal eye surface on the limbus. Furthermore, the conjunctiva, consisting of the cornea limbus, can theoretically provide resident stem cells on the wound that will ultimately make the microenvironment more favorable for recovery. However, whether or not the cornea tissue can truly provide local stem cells has been an issue of debate. It is shown in Figure 3 that the use of the conjunctiva with transparent cornea tissue was reported only in the Keklikci *et al*'s[17] study, in which the OR was 1.30 (95% confidential interval was 0.31-5.35), and whose weight in the comparison was 15.7%. The meta-trim was carried out to test the effect of Keclici's study on the final result. After excluding the study from the comparison, the OR of recurrence changed from 2.38 (95% confidential interval was 1.45-3.91, I^2=29%) to 2.59 (95% confidential interval was 1.52-4.40, I^2=34%). Even though the heterogeneity slightly increased, it was considered acceptable. Moreover, removing the transparent cornea tissue and stem cells from the superior limbus will create a new wound without stem cells. This effect on the new wound site should not be ignored. Related to this, extra caution should be taken when removing the superior conjunctiva of patients with a history of glaucoma. Scar tissue formation and potentially more serious complications could arise at the superior wound, which will negatively impact the treatment options for future glaucoma. As such, the inferior conjunctiva autograft should be considered in potential glaucoma patients.

MMC is the other commonly used pterygium treatment method analyzed in this study. As a kind of alkylating agent, MMC can selectively inhibit the synthesis of RNA and DNA, consequently arresting the cell cycle. BSR followed by MMC can decrease the recurrence of pterygium because MMC prevents neovascularization and the proliferation of surrounding fibroblasts at the site of resection. The technical proficiency required for MMC is much lower compared to ALC, and the time needed to perform this procedure is also shorter. One study [18] demonstrated that in comparing the surgery time between the two groups, ALC required on average 26 (18-32)min, and MMC only 13 (6-22)min. Furthermore, as there is no need to remove the superior conjunctiva, the site is preserved for an operation in the event of glaucoma.

The results of this Meta-analysis suggest that the recurrence of primary pterygium after BSR followed by intraoperative MMC is significantly higher than that of BSR followed by ALC. However, there is no significant difference between BSR followed by post-operative MMC or ALC. There is also no significant difference between BSR with intraoperative MMC combined with ALC and BSR with ALC alone. The meta-analysis comparing BSR followed by post-operative MMC or ALC did not show a significant difference, which is likely due to the fact that MMC was used one week after the operation, during the period in which the inflammatory response is the most intense. As a result, post-operative MMC treatment can decrease the incidence of recurrence as compared with intraoperative MMC. Another meta-analysis of the comparison between intraoperative MMC combined

with ALC versus ALC alone showed that the difference was on the limit. Because only 3 studies were included in each comparison and because the recurrence in one study was 0, the results need to be examined further.

Incidences of other complications, such as punctate epitheliopathy, scleral thinning and ischemia, as well as irritation and persistent epithelial defects, were higher in the MMC group than the ALC group. While some of these complications are transient, such as irritation and punctate epitheliopathy, other more serious complications, including scleral thinning, ischemia and persistent epithelial defects, require more attention. For example, severe scleral ischemia can potentially lead to secondary infection, scleral staphyloma, and even perforation of the eye, which ultimately increases the risk of total loss of sight. At the same time, persistent epithelial defects will also weaken the resistance to infection. MMC can be used to inhibit the proliferation of inflammatory cells and thus diminish the immune response, thereby increasing the risk of infection. The relative incidences of other complications were low, and for some of the associated complications, even equal to zero [22,24]. For example, in two of the included studies, the incidences of scleral thinning and ischemia were 0, which could negatively affect the accuracy of the meta-analysis. Therefore, further study needs to be done to address this issue.

While this Meta-analysis thoroughly examines the differences in treatment strategies for pterygium, there were several limitations of this study. For example, most of the included studies involved primary pterygium. It is important to note that recurrent pterygium manifests very differently and demonstrates different characteristics than primary pterygium. Therefore, further study should be done to understand which treatment regimen will be more suitable for pterygium that repeatedly grows back. Furthermore, very few studies discussed the methods of randomization in detail. Due to the study design and nature of the operations, treatment strategies could not be fully concealed to the doctors involved. As such, some included studies performed a single concealment to blind the evaluating physician; however in some instances, the treatment strategy was evident to the physicians providing follow-up care due to the presence of residual sutures. While the heterogeneities of these comparisons were all in the acceptable tolerance interval allowing for the execution of subsequent meta-analyses, the results should be carefully considered.

In conclusion, the recurrence and associated complications of primary pterygium upon BSR followed by ALC are less than those in the BSR followed by MMC group, suggesting that this is the optimum treatment strategy for this disorder. ALC is sufficient to lower the incidence of recurrence without the need for further transparent cornea tissue transplantation or intense follow-up care. Conversely, MMC, while not as efficient as ALC, is another suitable treatment option that is an excellent alternative for patients with a history of glaucoma.

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