

Effectiveness of amniotic membrane transplantation combined with mitomycin C in the treatment of pterygium: a meta-analysis

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Abstract

• **AIM:** To evaluate the recurrence rate and safety of amniotic membrane transplantation (AMT) augmented with mitomycin C (MMC) compared with amniotic membrane transplantation alone during the pterygium excision.

• **METHODS:** We took a meta-analysis on this program. Pertinent studies were selected through extensive searches of the Cochrane Library, MEDLINE, EMBASE, CBMdisc, CNKI. Pooled estimates were carried out in RevMan software V4.2.

• **RESULTS:** Six trials reported postoperative recurrence rate of pterygium, included 882 eyes, three trials reported the complications. The results of meta-analysis showed that recurrence rate of AMT plus MMC group was 5.41%, AMT alone group was 16.89%, relative risk (RR) was 0.32, 95%CI ranged from 0.19 to 0.56, Z was 4.06, $P < 0.001$. Two trials reported early complication as punctate keratitis, the incidence rate of AMT plus MMC group and AMT alone group were 17.14% and 0.00%, RR was 12.11, 95%CI ranged from 1.62 to 90.76.

• **CONCLUSION:** Amniotic membrane transplantation with MMC is associated with lower recurrence rate compared with amniotic membrane transplantation alone in pterygium excision, whether accompanied a higher risk with adverse events need more investigation.

• **KEYWORDS:** pterygium; meta-analysis; amniotic membrane; mitomycin C

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INTRODUCTION

Pterygium is a common disorder of ocular surface, the incidence rate ranged from 0.7% to 31%^[1-3]. It could cause not only cosmetic problems but also astigmatism and vision loss. Early treatment just removed pterygium head from

the anterior corneal surface by simply excision, or may be the "bare sclera" technique^[4]. As the realization of high recurrence rate which may result from dysfunction of limbal stem cell and abnormal proliferation of fibroblast. Some grafts were transposed onto the area previously occupied by pterygium to against pterygium recurrence, such as limbal conjunctival autograft and amniotic membrane graft. Amniotic membrane is easy to acquire and convenient to preserve so that it is used widely. MMC is a kind of antimetabolites which can prevent cell proliferation by alkylating DNA double helix, it is used in concentrations of 0.2-0.4mg/mL for various intervals^[5]. Clinical trials had showed that both AMT and MMC could reduce the recurrence rate after surgery^[6,7].

Recently, some published clinical trials compared the recurrence rate of amniotic membrane transplantation (AMT) augmented with mitomycin C (MMC) versus AMT alone. One study^[8] shows that AMT plus MMC did not further reduce the recurrence rate. But some other clinical trials^[9-13] reported that AMT plus MMC can significant reduce the recurrence rate of pterygium. It is difficult to draw conclusions in clinical practice by the conflicting results.

MATERIALS AND METHODS

In order to determine whether MMC application offers any advantages for pterygium surgery in terms of lower recurrence rate and similar incidence rate of postoperative complications, we undertook a meta-analysis of all relevant clinical trials of AMT with MMC and AMT alone, to improve estimates on the magnitude of a treatment effect.

Search Strategy and Selection Criteria Randomized controlled tests (RCTs) that compared AMT plus MMC with AMT alone in all kind of pterygium and that reported recurrence rate or postoperative complications were included. Excluded criteria included non-randomized, non-controlled trials, studies with other adjuvant techniques and unpublished trials. Clinical trials were identified through a systematic search consisting of 1) an electronic search of Cochrane, MEDLINE, EMBASE, Chinese Biomedicine Database, and Chinese National Knowledge Infrastructure; 2) manual searches of the reference lists of original reports through the electronic search; and 3) extensive internet searches, including manufacturers' databases, web sites of professional associations, and the GOOGLE search engine. Searches were conducted using the keywords "amniotic membrane", "MMC", "pterygium". The computerized searches covered the period 1990 to August 2010. The selection criteria were:

Table 1 Characteristics of clinical trials comparing AMT plus MMC with AMT alone

Author	Mean Age(y)	Design	Length (mo)	AMT plus MMC				AMT alone				n
				E	R	P	U	E	R	P	U	
				Gao, 2004	45.7	Randomized	6-12	34	2	8	/	
Ma, 2005	/	Randomized	>12	47	6	/	/	48	6		/	
Shi, 2006	47.3	Randomized	12-24	36	3	4	/	36	12	0	/	
Li, 2007	/	Randomized	12-18	50	3	/	/	49	16	/	/	
Chen, 2007	49.56	Randomized	12-24	248	8	/	/	248	21	/	/	
Tao, 2008	53.5	Randomized	12	29	2	/	1	25	8	/	0	

AMT: Amniotic membrane transplantation; E: Eyes; R: Recurrence; P: Punctata keratitis; U: Ulcer of sclera.

Table 2 Processing skills of each surgeon and patients characters

Trial	Patients characters Unilateral/Bilateral	Primary/Recurred Pterygium	Processing skills amniotic	
			Membrane graft	MMC used
Gao, 2004	Unilateral	Recurred	Preserved in 100% glycerol at 4°C	0.2mg/mL for 5 min
Ma, 2005	Both	Recurred	Unclear	0.025% (0.2mg/mL) MMC for 3min
Shi, 2006	Unilateral	Recurred	Preserved in 100% glycerol at 4°C	0.2mg/mL for 5 min
Li, 2007	Unilateral	Recurred	Preserved in 100% glycerol at 4°C	0.2mg/mL for 5 min
Chen, 2007	Both	Primary	Preserved in 100% glycerol at 4°C	0.2mg/mL for 30s
Tao, 2008	Both	Both	Preserved in 100% glycerol at 4°C	0.02% MMC for 5 min

1) study design (clinical controlled random trials); 2) population (patients with pterygium, including primary and recurrent); 3) intervention (AMT augmented with MMC versus AMT alone); 4) outcome variability (recurrence rate of pterygium, incidence rate of complications); and language (English and Chinese). All published trials which were written by English or Chinese should be taken in the present meta-analysis. Trial eligibility was determined by 2 authors (Liu and Yu) and checked by Cai.

Data Extraction and Quality Assessment Two authors (Song and Yu) independently extracted data from each clinical trials and each type of treatment as following: the authors, year, study design, length of study, treatment methods, number of subjects, recurrence rate, incidence rate of postoperative complications. Any discrepancies which occurred in the process of data extraction were resolved by discussion.

According to the criterion of Cochrane, the qualities of the trials had been graded.

Statistical Analysis and Sensitivity Analysis Because of the different clinical characteristics among study groups and the variation in sample sizes, the different time MMC stayed on the sclera, and the different proficiency of surgery skill. We assumed that heterogeneity was present even when no statistical significance was identified, so we decided to combine data by using a random-effects model to achieve more conservative estimates.

This study was to determine the pooled relative risk (RR) and 95% confidence intervals (CI) for recurrence after each kind of pterygium surgery. The value of *P* below 0.05 was considered statistically significant on the test for overall effect. Pooled estimates were carried out in RevMan software V4.2. We simultaneously took a sensitive analysis to evaluate the impact of component of methodological characteristics on our meta-analysis.

RESULTS

Six eligible trials were included in our final meta-analysis, including 882 eyes with pterygium; 444 eyes in AMT plus MMC groups and 438 eyes in AMT alone groups, all trials reported the result of recurrence rate. Three trials reported complications, include 192 eyes; 99 eyes in AMT plus MMC groups and 93 eyes in AMT alone group. The complications including punctata keratitis, symblepharon, conjunctival cyst and ulcer of sclera.

Characters of Included Trials The years of literature published ranged from 2004 to 2008. Five literatures were written in Chinese, one literature was written in English. The shortest length of follow up was 6 months, the longest over 24 months. The specimen volume in Chen's study were the largest, contained 496 eyes (Table 1).

Most patients were unilateral recurrent pterygium. All surgeons selected preserved amniotic membrane as the grafts, and 2mg/mL for 5 minutes as the most frequently technique used in pterygium surgery (Table 2).

Quality Assessment The baselines of all trials were equivalent, and there were no significant difference and bias. All trials lacked of full description in the aspects; adequate sequence generation, allocation concealment and blind methods (Table 3).

Recurrence Rate Six RCTs reported the recurrence rate, including 882 eyes. The whole Chinese literatures reported that AMT plus MMC led to lower recurrence rate, except one English literature said that whether added MMC the result was the same. The results of meta-analysis showed that recurrence rate of AMT plus MMC group was 5.41%, lower than AMT alone group with 16.89% recurrence rate. AMT plus MMC group was significantly associated with a lower recurrence rate than AMT alone group (RR 0.32, 95% CI 0.19-0.56, *Z* = 4.06, *P* < 0.0001, Figure 1). There was no significant heterogeneity ($\text{Chi}^2 = 6.88$, *P* = 0.23).

Table 3 Trials data

Trials	Adequate sequence generation	Allocation concealment	Blind	Incomplete outcome data addressed	Free of other bias	Baseline equality
Gao, 2004	Unclear	Unclear	Unclear	Yes	Yes	Yes
Ma, 2005	Unclear	Unclear	Unclear	Yes	Yes	Yes
Shi, 2006	Unclear	Unclear	Unclear	Yes	Yes	Yes
Li, 2007	Unclear	Unclear	Unclear	Yes	Yes	Yes
Chen, 2007	Unclear	Unclear	Unclear	Yes	Yes	Yes
Tao, 2008	Unclear	Unclear	Unclear	Yes	Yes	Yes

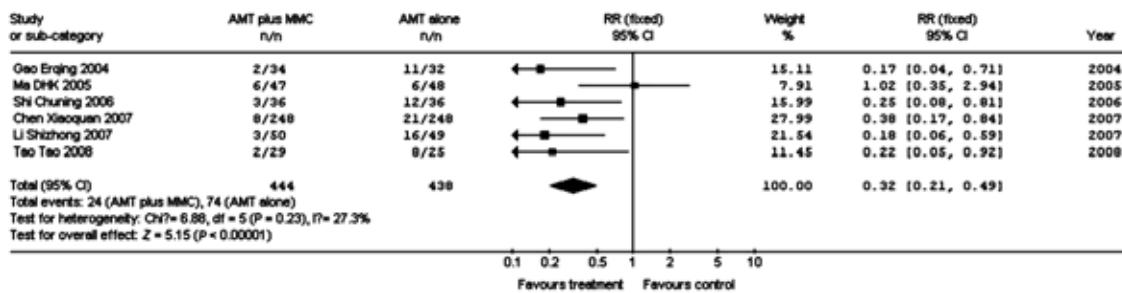


Figure 1 Meta-analysis of AMT plus MMC group and AMT alone group.

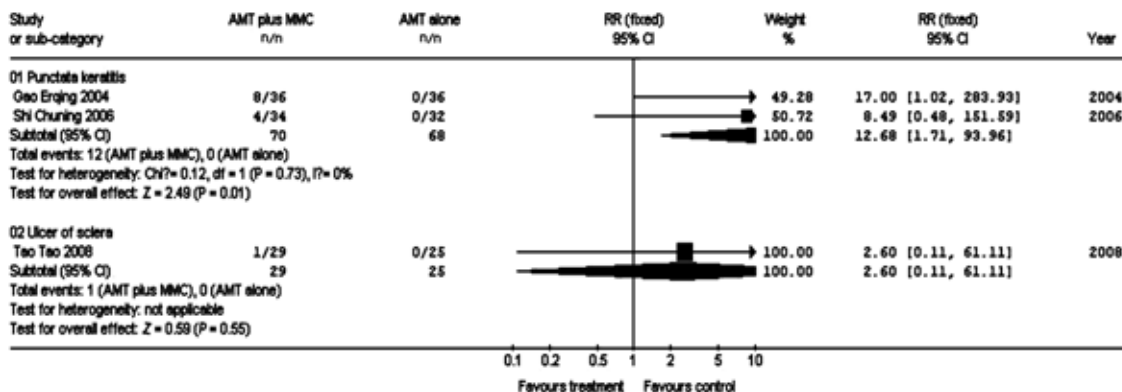


Figure 2 Meta-analysis of AMT plus MMC group and AMT alone group in another trial.

Complications Three RCTs reported postoperative complications of pterygium, including 192 eyes. Punctata keratitis was the most common early postoperative complication. The result of meta-analysis showed that AMT plus MMC group was significantly higher than AMT alone (RR 12.11, 95% CI 1.62-90.76, Z = 2.43, P = 0.02). There is no significant heterogeneity (Chi² = 0.12, P = 0.73).

One trial reported the incidence of symblepharon and conjunctival cyst after surgery in AMT alone group, but pyogenic granuloma and symblepharon in AMT plus MMC group. One patient in AMT plus MMC group had partial detachment of AM with because of subsequent delayed reepithelialization.

One trial reported a severe postoperative complication, ulcer of sclera with AMT plus MMC (RR 2.60, 95% CI 0.11-61.11, Z = 0.59, P = 0.55, Figure 2).

DISCUSSION

Pterygium has been known as a common frequently ocular disease characterized by inflammation, angiogenesis, and cellular proliferation^[14], but the mechanism of its origin and development is still unknown. Surgical excision had been considered as a traditional treatment, but evidence has shown that a high recurrence as bare sclera with simply excision. To resolve this problem, amniotic membrane transplantation

(AMT) is used widely nowadays. Intraoperative application of mitomycin C (MMC) to the scleral bed is another strategy which has been proved effectively reducing the recurrence rate, but with a high risk of complications such as delayed would healing, one literature reported that topical MMC treatment during recurred pterygium surgery might lead to a deleterious effect on corneal endothelium at one month^[15]. Some even combined the AMT with MMC intraoperative using for pterygium. Previous studies have evaluated the recurrence rate and safety of AMT augmented with MMC compared with AMT alone. But all these randomized clinical trials showed conflicting results in recurrence rate. This study provides evidence of recurrence rate of AMT augmented with MMC compared with AMT alone. We found that AMT augmented with MMC was associated with a lower recurrence rate than AMT alone in pterygium surgery. But it seemed that there was a trend of higher postoperative complication incidence rate, short term and long term of follow up. It was also easy to find out that the significant different result from the domestic studies and abroad study, which could be considerate by the factors of the low recurrence rate of the AMT alone group, and the shorter length on MMC using would also leading to a higher recurrence rate on recurred pterygium. Six trials were included in our study. No high quality

literature was found as lack of details of design, such as sequence generation, allocation concealment of the randomized controlled trials, blinding method was not referred. These made us difficult to remove the other factors, including patients' psychological factors, doctors' subjective factors, scientific of grouping and so on.

There still exists some disadvantages and limitations in our meta-analysis, included acknowledge and covert duplication of data, publication bias. A low number of studies was retrieved by our research, the reasons as following: 1) it may caused by the factor that MEDLINE research may seized only a part of relevant published papers, published papers is also only a part of all relevant studies; 2) our study including the literatures which were written in English or Chinese, so some high quality trials not written in English or Chinese may be excluded.

The recurrence was usually occurred in about 12 months^[16], weather it will be delayed by MMC is still a problem need to be resolved. Some severe complications such as severe secondary glaucoma, corneal edema, corneal perforation, sclera dellen, scleral perforation, conjunctival cyst, corectopia, iritis, sudden mature cataract, incapacitating photophobia and pain^[17-19], which were not at all involved in our study. The reason might be the ocular protection of amniotic membrane. Another important reason might be the length of follow-up is not enough to reveal all the complications^[20].

To sum up, although it is too early to draw the conclusion that the benefits of AMT plus MMC outweigh the risks, but we are lucky to find that AMT augmented with MMC really lead to a significant lower recurrence rate. We should conquer the difficulties and carry more high quality randomized controlled trials of the effectiveness of AMT augment with MMC compared with MMC alone and AMT alone. New research should focus on complications of AMT plus MMC by a long term follow up.

REFERENCES

- 1 West S, Muñoz B. Prevalence of pterygium in Latinos: Proyecto VER. *Br J Ophthalmol* 2009;93(10):1287-1290
- 2 Shiroma H, Higa A, Sawaguchi S, Iwase A, Tomidokoro A, Amano S, Araie M. Prevalence and risk factors of pterygium in a southwestern island of Japan; The Kumejima Study. *Am J Ophthalmol* 2009;148(5):766-771
- 3 Srinivasan S, Dollin M, McAllum P, Berger Y, Rootman DS, Slomovic AR. Fibrin glue versus for attaching the conjunctival autograft in pterygium surgery: a prospective observer masked clinical trial. *Br J Ophthalmol* 2009;93(2):215-218
- 4 Hirst LW. The treatment of pterygium. *Surv Ophthalmol* 2003;48(2):145-180
- 5 Majmudar PA, Epstein RJ. Antimetabolites in ocular surface neoplasia. *Curr Opin Ophthalmol* 1998;9(4):35-39
- 6 Enock ME, Omoti AE, Dawodu OA, Fuh UC, Eguaoje IE. Effectiveness of intra-operative mitomycin C in reducing the recurrence of pterygium in Irrua, Nigeria. *Niger Postgrad Med J* 2010;17(1):55-59
- 7 Essex RW, Snibson GR, Daniell M, Tole DM. Amniotic membrane grafting in the surgical management of primary pterygium. *Clin Experiment Ophthalmol* 2004;32(5):501-504
- 8 Ma DH, See LC, Hwang YS, Wang SF. Comparison of amniotic membrane graft alone or combined with intraoperative mitomycin C to prevent recurrence after excision of recurrent pterygia. *Cornea* 2005;24(2):141-150
- 9 Tao T, Duan ZG, Yang CJ, Yu LY, Li MZ. Observation of amniotic

membrane transplantation combined with mitomycin C to prevent pterygium recurrence. *Chin J Ocular Trauma Occup Eye Dis (Chin)* 2008;30(6):500-501

10 Li SZ. Effect analysis of amnion membrane transplantation combined with mitomycin C in the treatment of pterygium. *J Bethune Military Medical College (Chin)* 2007;10(5):290-291

11 Gao EQ, Jin M. Effect analysis of frozen amnion membrane transplantation combined with mitomycin C in the treatment of pterygium. *Guangzhou Med J (Chin)* 2004;35(5):50-51

12 Shi CN, Zhou GL. Application of mitomycin C in amniotic membrane transplantation to treat recurrence pterygium. *Guangzhou Med J (Chin)* 2006;37(5):37-39

13 Chen XQ, Chen FX, Lai JW. Clinical study on mitomycin C combined with amniotic membrane transplantation in the treatment of pterygium. *Chin J Difficult Complicat Cases (Chin)* 2007;6(7):412-414

14 Efstathios TD, Demetrios AS. Pathogenetic mechanisms and treatment options for ophthalmic pterygium: Trend and perspectives. *Int J Mol Med* 2009;23:439-447

15 Irit B, Igor K, Alex PL, Alana S, Eliya L, Wiwan S, Allan RS. The effect of mitomycin C on corneal endothelium in pterygium surgery. *Am J Ophthalmol* 2009;147(3):447-452

16 Hirst LW, Sebban A, Chant D. Pterygium recurrence time. *Ophthalmology* 1994;101(4):755-758

17 Avisar R, Apel I, Avisar I, Weinberger D. Endothelial cell loss during pterygium surgery: importance of timing of mitomycin C application. *Cornea* 2009;28(8):879-881

18 Rubinfeld RS, Pfister RR, Stein RM, Foster CS, Martin NF, Stoleru S, Talley AR, Speaker MG. Serious complications of topical mitomycin-C after pterygium surgery. *Ophthalmology* 1992;99(11):1647-1654

19 Diaz L, Villegas VM, Emanuelli A, Izquierdo NJ. Efficacy and safety of intraoperative mitomycin C as adjunct therapy for pterygium surgery. *Cornea* 2008;27(10):1119-1121

20 Wan Norliza WM, Raihan IS, Azwa JA, Ibrahim M. Scleral melting 16 years after pterygium excision with topical mitomycin C adjuvant therapy. *Cont Lens Anterior Eye* 2006;29(4):165-167

羊膜移植联合丝裂霉素 C 治疗翼状胬肉的 Meta 分析

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摘要

目的: 比较羊膜移植联合丝裂霉素 C (mitomycin C, MMC) 与羊膜移植在翼状胬肉治疗中的有效性和安全性。

方法: 我们进行 Meta 分析进行比较。计算机扩大检索 Cochrane 图书馆, MEDLINE, EMBASE, CBMdisc, CNKI 等数据库获得数据。通过 Cochrane 协作网提供的 RevMan 4.2 软件进行数据统计分析。

结果: 羊膜移植联合 MMC 显著降低了翼状胬肉的复发率。但是否会增加术后的并发症仍需更多的临床试验证实。入选的 6 项临床试验均报道了翼状胬肉术后的复发率, 包括 882 眼, 3 项临床试验报道了术后并发症情况。Meta 分析的结果显示羊膜移植联合 MMC 组复发率为 5.41%, 只进行羊膜移植组复发率为 16.89%, 相对危险度为 0.32, 95% 可信区间为 0.19 ~ 0.56, Z 值为 4.06, P < 0.001。2 项研究报道了术后早期点状角膜炎的发生情况, 羊膜移植联合 MMC 组与羊膜移植组的发病率分别为 17.14% 和 0.00%, 相对危险度为 12.11, 95% 可信区间为 1.62 ~ 90.76。

结论: 与羊膜移植相比, 羊膜移植联合 MMC 联合治疗翼状胬肉显著降低了术后复发率。

关键词: 翼状胬肉; Meta 分析; 羊膜; 丝裂霉素 C