ISSN: 2573-9573

Research Article

Journal of Ophthalmology & Clinical Research

Effects of Preoperative Versus Intraoperative Application of Mitomycin C on the Outcome of Pterygium Surgery: A Meta-Analysis

Yijia Huang[1], Junjie Tang[1*], Xiaoyuan Sha[2] and Yulan Luo[3]

[1,2,3,4]*Department of Ophthalmology, The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong Province, China*

[*]Corresponding author

Junjie Tang, Department of Ophthalmology, The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong Province, P.R. China, Tel: +86 13728386438

Submitted: 05 Apr 2021; **Accepted:** 13 Apr 2021; **Published:** 19 Apr 2021

Citation: *Yijia Huang, Junjie Tang, Xiaoyuan Sha and Yulan Luo (2021) Effects of Preoperative Versus Intraoperative Application of Mitomycin C on the Outcome of Pterygium Surgery: A Meta-Analysis. J Ophthalmol Clin Res 5: 77-83.*

Abstract

Background: *The use of mitomycin C (MMC) has been recommended to reduce postoperative recurrence in patients undergoing pterygium surgery. However, the outcomes with preoperative (PO) and intraoperative (IO) application of mitomycin C have not been adequately compared.*

Objective: *This study aimed to evaluate PO MMC versus IO MMC in terms of recurrence and complications for pterygium treatment.*

Methods: *PubMed, EMBASE, and Cochrane Library were systematically searched with the keywords "pterygium," "mitomycin," and "preoperative" and "intraoperative." Randomized controlled trials (RCTs) comparing PO MMC with IO MMC in pterygium surgery were included. A risk of bias tool was used to perform qualitative assessments. Outcome measurements were recurrence and complications of the ocular surface. Review Manager 5.3 was used for statistical analysis.*

Results: *Five RCTs with 390 participants (390 eyes) showing primary or recurrent pterygium were included. Recurrence of pterygium with PO MMC was similar to that with IO MMC (RR = 1.04, 95% CI, 0.61 to 1.76, P = 0.89). There was no significant difference between the two treatments (PO MMC vs. IO MMC) with respect to complications of the ocular surface, including conjunctival complications (RR = 1.04; 95% CI, 0.61 to 1.76; P = 0.89), scleral complications (RR = 0.72; 95% CI, 0.14 to 3.73; P = 0.70), and corneal complications (RR = 1.33; 95% CI, 0.32 to 5.48; P = 0.70).*

Conclusion: *PO MMC was as efficient as IO MMC in controlling the recurrence and complications in pterygium surgery.*

Keywords: Complications, Mitomycin C, Pterygium, Recurrence

Introduction

Pterygium is an ocular surface disease characterized by a fibrovascular tissue resembling an insect wing crossing the limbus and encroaching the cornea [1]. The prevalence of pterygium varies widely worldwide, and the condition is more common in tropical areas and dusty conditions, in which the population is frequently exposed to ultraviolet rays and dust irritation [2-4]. Surgery is the only efficient method to treat pterygium. However, treatment of pterygium with simple excision and the bare sclera technique has been reported to lead to a high recurrence rate (30%-70%) [5]. Various adjunctive treatments have been developed to decrease the recurrence, including conjunctival autograft (CAG), amniotic membrane transplantation, irradiation treatment, and the use of mitomycin C (MMC) [6].

MMC has been used for reducing the recurrence of pterygium [7]. However, postoperative application of MMC eye drops may cause serious complications such as corneal edema, scleral necrosis, and secondary glaucoma [8]. In contrast, intraoperative application of MMC eye drops results in a low recurrence rate with fewer complications [9]. Preoperative subconjunctival injections of MMC have been studied recently, and one report has suggested that sub-

conjunctival injection of MMC before excision may minimize the epithelial and scleral toxicity and protect the physiological function of the ocular surface[10].

Recurrence and complications are factors to be considered when comparing preoperative MMC with intraoperative MMC. Preoperative subconjunctival injection of MMC has been reported to be as effective as intraoperative application of MMC in preventing the recurrence of pterygium and decreasing the incidence of postoperative complications [11]. Theoretically, preoperative subconjunctival injection may protect the cornea from being exposed to MMC and eliminate corneal complications. On the other hand, it may also prolong the duration of MMC exposure to the conjunctiva and sclera. Therefore, this meta-analysis aimed to compare the effects of preoperative and intraoperative MMC on the prognosis of pterygium surgery in two aspects: (1) recurrence and (2) complications of the ocular surface, including the conjunctiva, sclera, and cornea.

Methods

Search Strategy

Literature retrieval was performed on April 10, 2020 by searching the following electronic databases: PubMed, EMBASE, and Cochrane Library. The keywords "pterygium," "mitomycin," and "preoperative" and "intraoperative" combined with their entry terms were used to perform a thorough search without limitations on year, language, or publication status. Irrelevant articles like reviews, animal studies, or meeting articles were excluded by reading the titles and abstract. The full text of the associated clinical trials was downloaded and reviewed. Studies that met the inclusion criteria were included in the meta-analysis. A manual search was supplemented by checking the reference lists of the relevant reports and reviewing the findings.

Inclusion and Exclusion Criteria

The inclusion criteria for the meta-analysis were as follows:

1. Study design: Randomized controlled trial (RCT).
2. Participants: Patients with primary or recurrent pterygium.
3. Intervention and comparison: Preoperative mitomycin C vs. intraoperative mitomycin C
4. Outcome variables: Recurrence and complications of the ocular surface.

Recurrence of pterygium was defined as any new fibrovascular tissue growing beyond the limbus during the follow-up period. Ocular surface complications included drug-related diseases of the conjunctiva, sclera, and cornea.

Exclusion criteria were as follows:

1. Meeting abstracts, duplicated publications, letters, reviews, and clinical studies that were not RCTs.
2. Studies assessing patients with other ocular surface diseases.
3. Studies assessing other interventions, including postoperative MMC or any other adjunctive medication in the surgery.

Data Extraction

Data extraction was performed by two researchers (JT and YH) independently. General information and clinical data were collected, including name of the first author, publication date, population source, trial design, sample size (eye/patient), gender ratio (male/female), means and standard deviations (SDs) of age, group, follow-up duration, recurrence rate, and complications of the ocular surface. Disagreements were resolved by discussion.

Qualitative Assessment

Qualitative assessment was conducted by using the risk of bias (ROB) tool. All the included RCTs were assessed on the basis of the following items: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other bias. For the above items, a judgment of "+" indicated low risk of bias, "-" indicated high risk of bias, and "?" indicated unclear risk of bias.

Statistical Analysis

Outcomes included recurrence and complications of the ocular surface. Review manager 5.3 was used for statistical analysis. Relative risk (rr) was used to analyze dichotomous data with 95% confidence intervals (ci). Statistical heterogeneity was evaluated by the i2 value. When the heterogeneity was moderate or high (i2 > 50%), a random-effects model was used to pool the data; alternatively, if i2 < 50%, statistical heterogeneity was considered acceptable, and a fixed-effects model was used.

Results

Literature Research

The selection process for articles is shown in a flow diagram (Figure 1). On the basis of the search strategies, 790 articles were retrieved through multiple databases before April 2020. No suitable studies could be identified by checking the reference lists of the retrieved papers. Fifteen articles were eliminated because of duplication. Subsequently, after reviewing the titles and abstracts, 82 studies remained. On the basis of the elimination criteria, 76 studies were excluded, including 39 reviews, 27 studies with other interventions, and 10 non-RCTs. The full-text data of the 6 remaining studies were rechecked scrupulously, and one of them was excluded because of inappropriate measurements [12]. Finally, excluding 2 patients who did not complete the follow-up period, a total of 5 RCTs with 390 patients were included [11, 13-16].

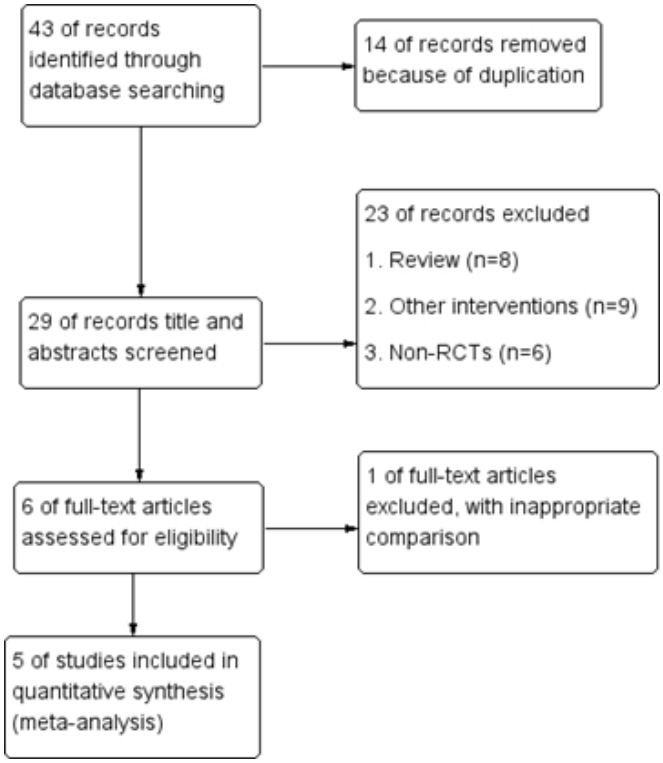

Figure 1: Flow diagram of literature research

Table 1: General characteristic of included studies

Study	Year	Country	Study Design	Sample size eye/patient	Group	Age Mean±SD	M/F	Follow-up (mo)	Recurrence
Ghoneim	2011	Egypt	Randomised controlled trial	70/70	Group 1: 0.1 mL of 0.15 mg/mL MMC 1 day before surgery	Group 1: 33.0±7.1	Group 1: 3/4	12	Group 1: 5.7%
					Group 2: 0.15 mg/mL MMC for 3 min in the surgery	Group 2: 34.0±8.2	Group 2: 16/19		Group 2: 8.6%
Khakshoor	2010	Iran	Randomised controlled trial	82/82	Group 1: 0.05 mg/mL MMC 1 day before surgery	Group 1: 49.4±13.6	Group 1: 1/1	12	Group 1: 0.0%
					Group 2: 0.05 mg/mL MMC for 3 min in the surgery	Group 2: 47.8±13.8	Group 2: 12/11		Group 2: 4.3%
Lotfy	2018	Egypt	Randomised controlled trial	105/105	Group 1: 0.1 mL of 0.15 mg/mL MMC 1 day before surgery	Group 1: 38.9±7.6	Group 1: 12/5	18	Group 1: 3.9%
					Group 2: 0.2 mg/mL MMC for 2 min in the surgery	Group 2: 37.4±7.6	Group 2: 13/5		Group 2: 1.9%

Mandour	2015	Egypt	Randomised controlled trial	83/83	Group 1: 0.1 mL of 0.15 mg/mL MMC for 5 min in the surgery	Group 1: 53.3±11.4	Group 1: 18/17	Group 1: 30.7±4.5	Group 1: 5.7%
					Group 2: 0.1 mL of 0.15 mg/mL MMC 1 month before surgery	Group 2: 55.0±10.0	Group 2: 1/1	Group 2: 29.5±4.3	Group 2: 4.2%
Zaky	2012	Egypt	Randomised controlled trial	50/50	Group 1: 0.1 mL of 0.15 mg/mL MMC 1 day before surgery	Group 1: 35.1±14.0	Group 1: 12/13	12	Group 1: 4.0%
					Group 2: 0.15 mg/mL MMC in the surgery	Group 2: 36.1±13.2	Group 2: 11/14		Group 2: 8.0%

Quality Assessment

The results of ROB assessments for the included publications are shown in Figure 2. For selection bias, all studies showed low risk in randomized sequence generation, and allocation concealment was appropriately reported in three studies. For the blinding of participants, three studies showed high risk because they reported informed consent for operation while the risk for the remaining two studies was unclear. Blinding of outcome assessments was reported correctly in three studies and unclear in the other two. All studies showed low risks of attrition bias and reporting bias. The risk of other biases was unclear.

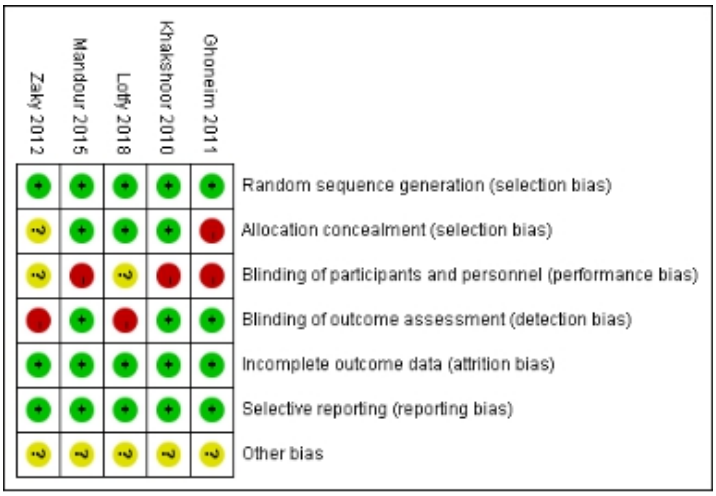

Figure 2: Risk of bias for the included publication

Data Analysis

Outcome measurements included evaluations of pterygium recurrence and complications of the conjunctiva, sclera, and cornea. Complications of the conjunctiva included conjunctival granuloma, conjunctival cyst, conjunctival irritation, conjunctival vascularization, and graft melting, or retraction. Complications of the sclera included scleral dellen, scleral melting, and thinning. Corneal complications included delayed corneal epithelial healing, superficial punctuate keratitis, corneal melting, and infection.

Recurrence was recorded in 5 RCTs with a total of 390 patients. Although the intraoperative MMC group showed a higher recurrence rate than the preoperative group, there was no statistical difference between the recurrence rates with the two therapeutic strategies (RR = 0.77; 95% CI, 0.30 to 1.98; P = 0.59) (Figure 3). Conjunctival complications were recorded in 4 RCTs with 340 patients. There was no significant intergroup difference in the incidence of conjunctival complications (RR = 1.04; 95% CI, 0.61 to 1.76; P = 0.89) (Figure 4). Scleral complications were recorded in all studies. Events related to scleral complications were similar between the two therapies (RR = 0.72; 95% CI, 0.14 to 3.73; P = 0.70) (Figure 5). Corneal complications were also noted in all five studies, with no significant difference when MMC was given preoperatively or intraoperatively. (RR = 1.33; 95% CI, 0.32 to 5.48; P = 0.70) (Figure 6).

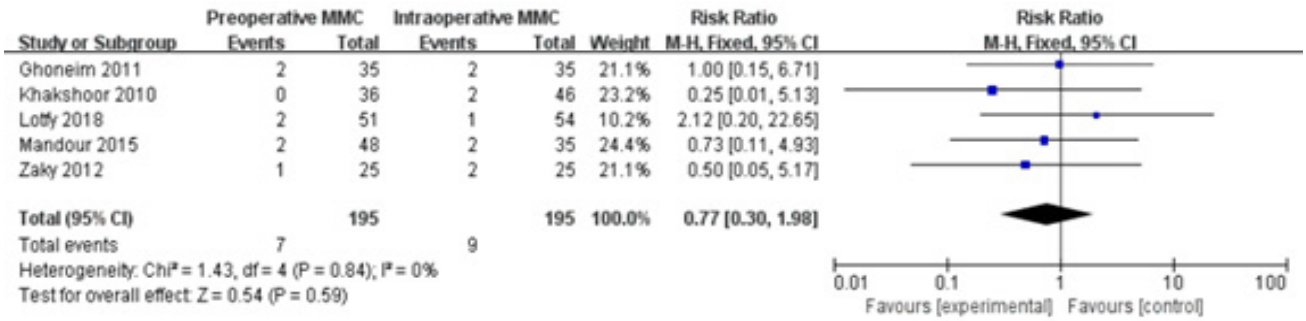

Figure 3: Forest plot for recurrence of preoperative MMC versus intraoperative MMC in pterygium surgery

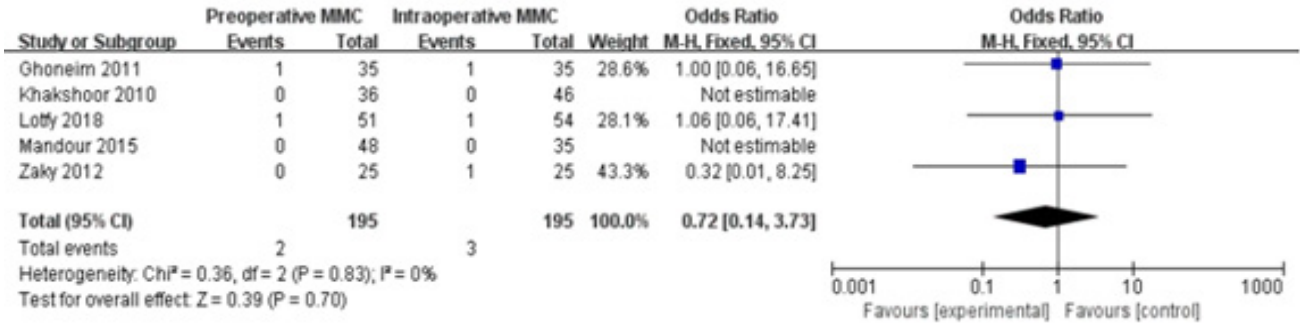

Figure 4: Forest plot for scleral complications of preoperative MMC versus intraoperative MMC in pterygium surgery

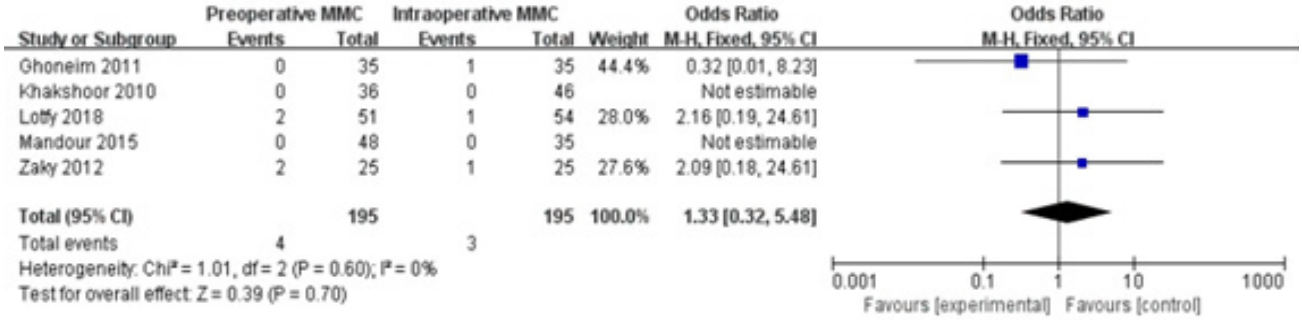

Figure 5: Forest plot for conjunctival complications of preoperative MMC versus intraoperative MMC in pterygium surgery

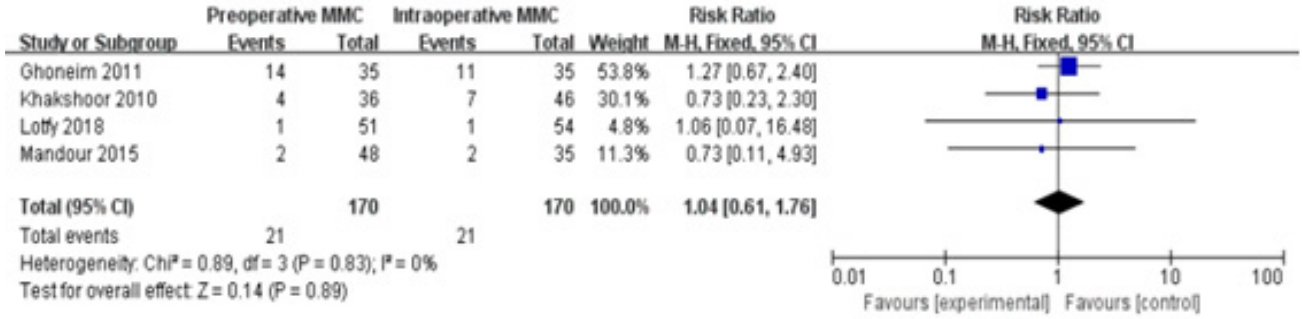

Figure 6: Forest plot for corneal complications of preoperative MMC versus intraoperative MMC in pterygium surgery

Discussion

In this meta-analysis, in comparison with intraoperative MMC, preoperative MMC did not significantly decrease the recurrence rate and ocular surface complications in pterygium surgery. This meta-analysis collected data from five RCTs including 390 eyes with pterygium. Among the five included RCTs, four were conducted in Egypt while the fifth was performed in Iran. Assessments of the gender and age distribution showed that pterygium mainly occurred in the working-age population and was more frequently noted in males; therefore, the condition definitely had a significant socioeconomic impact.

Plenty of studies have contrasted the therapeutic effects of MMC with other agents in pterygium surgery, such as 5-fluorouracil, cyclosporine, and bevacizumab, and the results showed that MMC could prevent recurrence after pterygium excision [17,18]. MMC is a toxic chemical, and it can inhibit the generation of collagen and migration of fibroblasts to affect wound healing; however, it also causes irreversible damage to the cells on the ocular surface [19,20]. The concentration of intraoperative MMC application has been widely studied to reduce its toxicity [21]. To further reduce the side effects of MMC, the time point of MMC administration was studied and the outcomes of preoperative subconjunctival injection of MMC were evaluated [22,23]. To the best of our knowledge, this is the first meta-analysis to compare the outcomes of preoperative MMC and intraoperative MMC for pterygium surgery. The recurrence rate after intraoperative MMC combined with CAG for primary pterygium ranged from 2% to 35% [24-26]. The results of this meta-analysis indicated that the effect of preoperative MMC was similar to intraoperative MMC in controlling the recurrence. Regarding complications of the ocular surface, preoperative MMC administration was performed to protect the corneal epithelium, since subconjunctival injections of MMC could directly act on the fibroblasts and avoid direct contact with the surface of cornea, but the results of the analysis demonstrated that preoperative MMC did not substantially reduce complications of the ocular

surface, especially corneal complications [27].

Limitation of the Study

This meta-analysis was a purely pairwise meta-analysis comparing the recurrence and complications of preoperative MMC versus intraoperative MMC in pterygium surgery. The results were analyzed subjectively and conclusions were obtained critically. However, this meta-analysis had some limitations. First, only 390 patients from two countries were included in this meta-analysis. The insufficient sample size and population composition could have influenced the results. Notably, only recurrence and complications of the ocular surface were assessed in this meta-analysis. More indicators should be analyzed to evaluate the clinical benefit of preoperative MMC in pterygium surgery, including the changes in intraocular pressure and improvements in best corrected visual acuity.

Conclusion

To sum up, this meta-analysis illustrated that preoperative MMC was as efficient as intraoperative MMC in controlling the recurrence rate and protecting the ocular surface from complications. More large-sample RCTs from different countries with more clinical indexes are needed to further reveal the advantages of preoperative MMC in pterygium surgery.

Disclosure of Conflict of Interest

The authors declare that they have no competing interests.

References

1. Hilgers JH (1960) Pterygium: its incidence, heredity and etiology. Am J Ophthalmol 50: 635-644.
2. Panchapakesan J, Hourihan F, Mitchell P (1998) Prevalence of pterygium and pinguecula: the Blue Mountains Eye Study. Aust N Z J Ophthalmol 26: S2-5.
3. Ang M, Li X, Wong W, Zheng Y, Chua D, et al. (2012) Prevalence of and racial differences in pterygium: a multiethnic population study in Asians. Ophthalmology 119: 1509-1515.
4. Viso E, Gude F, Rodríguez-Ares MT (2011) Prevalence of pinguecula and pterygium in a general population in Spain. Eye (Lond) 25: 350-357.
5. Sodhi PK, Verma L, Ratan SK (2004) The treatment of pterygium. Surv Ophthalmol 49: 541-542.
6. Hacıoğlu D, Erdöl H (2017) Developments and current approaches in the treatment of pterygium. Int Ophthalmol 37: 1073-1081.
7. Mastropasqua L, Carpineto P, Ciancaglini M, Enrico Gallenga P (1996) Long term results of intraoperative mitomycin C in the treatment of recurrent pterygium. Br J Ophthalmol 80: 288-291.
8. Rubinfeld RS, Pfister RR, Stein RM, Foster CS, Martin NF, et al. (1992) Serious complications of topical mitomycin-C after pterygium surgery. Ophthalmology 99: 1647-1654.
9. Donnenfeld ED, Perry HD, Fromer S, Doshi S, Solomon R, et al. (2003) Subconjunctival mitomycin C as adjunctive therapy before pterygium excision. Ophthalmology 110: 1012-1016.
10. Chang YS, Chen WC, Tseng SH, Sze CI, Wu CL (2008) Subconjunctival mitomycin C before pterygium excision: an ultrastructural study. Cornea 27: 471-475.
11. Ghoneim EM, Abd-El Ghny AA, Gab-Allah AA, Kamal MZ (2011) Preoperative subconjunctival injection of mitomycin C versus intraoperative topical application as an adjunctive treatment for surgical removal of primary pterygium. Middle East Afr J Ophthalmol 18: 37-41.
12. Khan FA, Awais M, Niazi Sh P, Akhter N, Ishaq M (2017) Effectiveness of Preoperative Subconjunctival Injection of Mitomycin-C in Primary Pterygium Surgery. J Coll Physicians Surg Pak 27: 88-91.
13. Zaky KS, Khalifa YM (2012) Efficacy of preoperative injection versus intraoperative application of mitomycin in recurrent pterygium surgery. Indian J Ophthalmol 60: 273-276.
14. Lotfy A, Gad AAM, Abdelrahman A, Samir A, Abdulhalim BH (2018) Conjunctival Autograft Combined With Either Preoperative Mitomycin C Injection or Intraoperative Local Mitomycin C Over the Medial Rectus Muscle Tendon in Primary Pterygium Surgery. Eye Contact Lens 44 Suppl 2: S192-s195.
15. Khakshoor H, Razavi ME, Daneshvar R, Shakeri MT, Ghate MF, et al. (2010) Preoperative subpterygeal injection vs intraoperative mitomycin C for pterygium removal: comparison of results and complications. Am J Ophthalmol 150: 193-198.
16. Mandour SS, Marey HM, Farahat HG, Mohamed HM (2015) Preoperative Versus Intraoperative Subpterygial Mitomycin C Injection for Prevention of Pterygium Recurrence. J Ocul Pharmacol Ther 31: 340-343.
17. Zeng W, Liu Z, Dai H, Yan M, Luo H, et al. (2017) Anti-fibrotic, anti-VEGF or radiotherapy treatments as adjuvants for pterygium excision: a systematic review and network meta-analysis. BMC Ophthalmol 17: 211.
18. Hwang S, Choi S (2015) A Comparative Study of Topical Mitomycin C, Cyclosporine, and Bevacizumab after Primary Pterygium Surgery. Korean J Ophthalmol 29: 375-381.
19. Bass PD, Gubler DA, Judd TC, Williams RM (2013) Mitomycinoid alkaloids: mechanism of action, biosynthesis, total syntheses, and synthetic approaches. Chem Rev 113: 6816-6863.
20. Singh G, Wilson MR, Foster CS (1988) Mitomycin eye drops as treatment for pterygium. Ophthalmology 95: 813-821.
21. Frucht-Pery J, Siganos CS, Ilsar M (1996) Intraoperative application of topical mitomycin C for pterygium surgery. Ophthalmology 103: 674-677.
22. Dos Santos Martins TG, de Azevedo Costa ALF, Furuzawa KM, Chammas R, Alves MR (2019) Evaluation of antimitotic and antiangiogenic effect of preoperative subconjunctival application of mitomycin C in primary pterygium: a randomized trial. Int Ophthalmol 39: 2435-2440.
23. Alsmman AH, Radwan G, Abozaid MA, Mohammed UA, Abd Elhaleim NG (2017) Preoperative subconjunctival combined injection of bevacizumab and mitomycin C before the surgical excision of primary pterygium: clinical and histological results. Clin Ophthalmol 11: 493-501.
24. Tsim NC, Young AL, Jhanji V, Ho M, Cheng LL (2015) Combined conjunctival rotational autograft with 0.02% mitomycin C in primary pterygium surgery: a long-term follow-up study. Br J Ophthalmol 99: 1396-1400.
25. Frucht-Pery J, Raiskup F, Ilsar M, Landau D, Orucov F, et al. (2006) Conjunctival autografting combined with low-dose mitomycin C for prevention of primary pterygium recurrence. Am J Ophthalmol 141: 1044-1050.
26. Wu WK, Wong VW, Chi SC, Lam DS (2007) Surgical man-

agement of double-head pterygium by using a novel technique: conjunctival rotational autograft combined with conjunctival autograft. Cornea 26: 1056-1059.

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