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EFFECTIVENESS OF MITOMYCIN-C APPLICATION AS AN ADJUNCT IN SURGERIES FOR RECURRENT PTERYGIUM – A META ANALYSIS

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ABSTRACT

Background: Recurrent pterygium poses distinct problem like high postoperative recurrences and many surgical approaches have been tried to decrease recurrences. Currently, mitomycin C (MMC) application and amniotic graft are used as adjunct apart from the standard limbal-conjunctival autograft.

Aim of study: Aim of this study is to determine through meta-analysis, the risk of recurrences and frequency of post operative complications associated with MMC application over bare sclera or along with amniotic graft for recurrent pterygia.

Method: A thorough search of online resources for randomised controlled clinical trials comparing bare sclera technique with or without MMC and amniotic graft with or without MMC application was done. The purpose was to determine the pooled odds ratio and 95% confidence interval for post operative pterygium recurrence.

Results: Among 5 studies, 2 studies comparing bare sclera technique with or without MMC showed pooled odds ratio of 0.105 with 95% CI 0.0131 to 0.847. Study comparing amniotic graft with or without MMC showed odds ratio 0.298 with CI of 0.0817 to 1.089.

Conclusion: Application of MMC on bare sclera reduced recurrence rate to 10% and on amniotic graft it reduced to 30% with no added serious complications.

Keywords: Mitomycin-C, Amniotic graft, Bare sclera, Recurrent pterygia, Meta-analysis.

INTRODUCTION

Pterygium is a fibrovascular growth arising from the conjunctiva onto the cornea. A number of surgical techniques have been described for primary pterygium excision including bare sclera technique¹, bare sclera resection with mitomycin-c (MMC) application², conjunctival autograft³ and recently amniotic membrane grafts⁴. The treatment with these adjuncts have significantly reduced but not eliminated the problem; as far as the recurrent pterygium is concerned, there are greater challenges associated with treatment⁵. Added to high recurrence rate, is the problem of deciding on the best approach of its surgical excision, since a recurrent pterygium is usually associated with

subconjunctival fibrosis and/or corneal thinning and scarring.

Mitomycin-C is an antitumor agent that acts by inhibiting DNA synthesis. The mechanism of action seems to be inhibition of fibroblast proliferation at the level of episclera⁶. Adjunct MMC for pterygium surgery was first described by Kunitomo and Mori⁷ in Japan in 1963 & in US by Singh et al⁸ in 1998 as postoperative topical MMC with concentration of 0.4-1mg/ml. At present, MMC is being mainly used after pterygium excision as an intraoperative application to bare sclera for the management of both primary and recurrent pterygium.⁹ In order to further reduce the recurrence and postoperative complications, an intraoperative MMC treated

sclera is normally covered with a conjunctival or amniotic membrane graft⁴.

Despite the fact that studies on MMC have shown rare but significant conjunctival, scleral, and corneal toxicity¹⁰, its use as an adjunct in primary or recurrent pterygia surgeries seems to be beneficial in few randomised clinical trials¹¹⁻¹⁵.

We conducted a Meta-analysis of published randomised clinical trials analysing the recurrence rates and frequency of postoperative complications with MMC application over bare sclera or along with amniotic graft for recurrent pterygia.

The purpose of this study was to determine the pooled odds ratio and 95% confidence intervals for postoperative pterygium recurrence.

MATERIALS AND METHODS

Selection strategy and selection criteria

Following an established protocol, a survey of published studies comparing at least two of the three surgical techniques in the treatment of recurrent pterygium – bare sclera resection, bare sclera resection with MMC application and amniotic membrane transplantation with MMC – was conducted through an electronic search. We have not analysed technique of limbal-conjunctival autograft with MMC here, because of paucity of Randomised Controlled Trials analysing its effect with or without MMC for recurrent pterygium surgery.

Randomised controlled trials (RCTs) that compared above mentioned techniques and reported recurrence rates and post operative complications were included. Exclusion criteria included non-randomised, non-controlled trials, studies with other adjunct techniques and unpublished data.

Clinical trials were identified through (1) Electronic search of PUBMED, Science direct, MD consult, Google scholar, MEDLINE and EMBASE. (2) Manual searches of the reference list of original article reports through electronic search. Searches were conducted using the keywords “recurrent pterygium”, “Mitomycin-C”,

“Amniotic membrane”. The computerised search covered the period from 1980 to October 2013.

Two reviewers (N.D and C.K.N) confirmed study eligibility and extracted data independently, and data were pooled using standard Meta-analysis techniques.

RESULTS

Total five eligible studies were identified, two that compared bare sclera resection with or without MMC application^{11,12}, three studies that compared amniotic graft placement with or without MMC^{13,14,15}. For statistical analysis and to maintain homogeneity in studies, 5 studies were divided into 2 groups. 1st group consisted of two studies of bare sclera technique with or without MMC and 2nd group with three studies consisting of amniotic membrane transplantation with or without MMC.

Table 1 provides characteristics of clinical trials comparing mitomycin C on bare sclera and on amniotic graft. Table 2 provides a description of the population characteristics of studies included, follow-up periods and recurrence definition. Table 3 & 4 show recurrence rates and complications encountered in different surgical techniques. 3 studies were from English literature and 2 studies from Chinese literature. Full text was available in 3 studies and in 2 studies, only abstract was available.

The results of meta-analysis showed that recurrence rate of bare sclera with MMC were 8% which was lower than bare sclera alone group with 47% recurrence rate. Amniotic Membrane Graft with MMC group was associated with lower recurrence rate (9%) compared to AMG group alone (25.5%).

Heterogeneity was found between the studies in group 1 and group 2. In group 1, $Q=5.2422$ with significant P value ($p=0.0220$) and in group 2, $Q=5.9912$ with significant P value ($p=0.05$). The heterogeneity between the studies were taken into consideration and analysed with due care by random effect analysis of raw data.

DISCUSSION

Pterygium, a worldwide degenerative corneal disease with multifactorial etiology, is particularly common in tropical and subtropical countries.¹⁶ Although different treatment regimens have been proposed for the treatment of pterygium, the main complication of pterygium treatment is recurrence.^{17,18} Recurrent pterygium is more difficult to control, and various treatment modalities including radiotherapy¹⁹, antimetabolite or antineoplastic drugs², conjunctival flap³, and conjunctival or limbal autograft transplantation have been proposed.⁴

Now a days, conjunctival¹⁰ or limbal autografts and amniotic membrane transplants⁵ have been commonly used alone or combined with MMC¹¹ as adjuvant treatment for recurrent pterygium. Use of antimetabolites, especially intraoperative administration of MMC, may be performed in conjunction with amniotic membrane transplantation.^{13,14} Covering bare sclera with amniotic membrane may decrease the risk of scleral ulcer formation as a late complication with the use of antimetabolites.^{20,21}

This study provides evidence of the inherent risk of pterygium recurrence after excision of recurrent pterygium with or without mitomycin C application over bare sclera or amniotic graft. Analysis of group 1 studies showed that for every 100 recurrences in bare sclera alone group, there were only 10 recurrences with application of MMC with a 95% confidence interval of 0.0131 to 0.847 (Pooled OR=0.105). These results show dramatic change in recurrence rate with MMC application.(Graph:1)

Analysis of group 2 studies showing role of MMC on amniotic grafts in preventing recurrences, showed pooled odd's ratio of 0.298 with 95% confidence interval of 0.0817 to 1.089. This implies for every 100 recurrences in Amniotic Membrane Graft alone group, there were only 30 recurrences if MMC was added in AMG. Only one study¹³ revealed no difference with addition of MMC compared to Amniotic Membrane

Transplant alone. The association between exposure (MMC) and control group (AMG alone) was less strong compared to group 1 studies but still carried high significant value in terms of recurrence rates.(Graph:2)

We have found that bare sclera or AMG augmented with MMC was associated with a lower recurrence rate than either of it alone in recurrent pterygium surgeries.

An interventional prospective case series comparing limbal-conjunctival autograft (L-CAT) with or without MMC showed least recurrence rate in MMC group.¹⁶ L-CAT theoretically is a natural substitute to cover bare sclera and hence associated with low recurrences but recurrent surgeries on conjunctiva pose difficulties in harvesting healthy conjunctival graft. We have not analysed this technique here because of paucity of RCTs analysing its effect with or without MMC for recurrent pterygium surgery.

As per complications are concerned, Superficial punctate keratitis was found in only one study in MMC group. Otherwise the mentioned complications (table 4) are nonspecific and do not seem directly related to the effects of MMC. Moreover these complications are more in control group than treatment group suggesting protective role of MMC in preventing complications other than recurrences.

There are many case series, prospective studies and reports of complications arising from MMC application²¹⁻²⁴; no such serious complications like scleral or corneal melt were reported in our study group. The reason could be difficult to analyse but needs more data to conclude these findings.

As per quality assurance and strength of studies is concerned, heterogeneity was found, which do weaken the result. Things like unpublished data, research in language other than English, Chinese and publication bias might appear like an island in a sea of darkness which may partly make the analysis incomplete. Hence, we tried doing a good home work before interpreting the findings.

Table 2: Characteristics of patients included in the studies

Sl. No	Ref*		Age (yrs)		Sex		Follow-up months	
			Mean	Range	Male	Female	Mean	Range
1	11	Cases	40.8	21-59	28	17	34.55	6-54
		Control	40.7	21-62	27	18	29.64	7-50
2	12	Cases	23.5¥	/	19	46	12months	
		Control	-	-	23	42		
3	13	Cases	53.4+11.3	30-78	26	22	28.6+22.7	12-87
		Control	53+11.7	26-82	21	26	27.9+20.2	12-84
4	-	/	47.3	/	/	/	12-24months	
5	-	/	/	/	/	/	>12 months	

***Recurrence definition**

11 – When a fibrovascular growth, in the position of previously excised pterygium, crossing the limbus & extending onto the cornea for any distance.

12 - Grading system for pterygium extension onto the cornea. Grade 1, 2 & 3 are 0-2, 2-4 and >4mm extension into cornea from limbus.

13 – (1) Conjunctival or potential recurrence was defined as the ingrowth of fibrovascular tissue to the excised area, reaching to the limbus but not invading the cornea and was also considered partially successful and (2) Corneal or true recurrence, which was considered treatment failure and was defined as the invasion of fibrovascular tissue into the cornea

¥ - Average age.

Table 3: Recurrence rates among different studies

Sl. No	Study	Group-1	Recurrence	%	Group-2	Recurrence	%
1	Leonardo et al	45	6	12.5	45	16	35.6
2	Nitin Verma	65	2	3	65	31	48
3	* Ma, Dh	47	6	12.8	48	6	12.5
4	*Shi et al	36	3	8	36	12	33.3
5	*Li et al	50	3	6	49	16	32.6

*amniotic membrane graft with or without MMC.

Table 4: Post-operative complications among different studies

1.		Study group	Control group
	Leonardo et al		
	SPK*	7 (15.6%)	-
2.	Nitin Verma		
	Granuloma	2	14
	Hyperaemia	7	31
	Subconjunctival haematoma	3	5
3.	Ma. DH		
	Pyogenic granuloma	1(2.2%)	Conj. Cyst 1(2.1%) Conj Hg 2(4.2%)
	Symblepharon	1(2.2%)	2(4.2%)
4, 5	-	-	-

CONCLUSION

To summarise, this is the first ever Meta analysis done, analysing the surgeries for recurrent pterygium using MMC as adjuvant. From above analysis, it is clear that MMC application over bare sclera stood highly scientific and rationale. So, we should strongly discourage bare sclera technique alone in a recurrent pterygium surgery. This fact is more or less well established from other meta analyses which tested MMC effectiveness on primary pterygium surgery.^{25,26}

With respect to the surgeries with amniotic graft concerned, addition of MMC as an adjunct overweighs advantages compared to complications per se due to MMC. Hence, MMC is strongly recommended in high risk groups. There appears to be low magnitude of recurrence both in control and cases of group 2 studies. Here, amniotic graft has major contribution in low recurrence but addition of MMC makes the figures encouraging. In this regard, new research should focus on long term effects of mitomycin-C in recurrent pterygium surgeries.

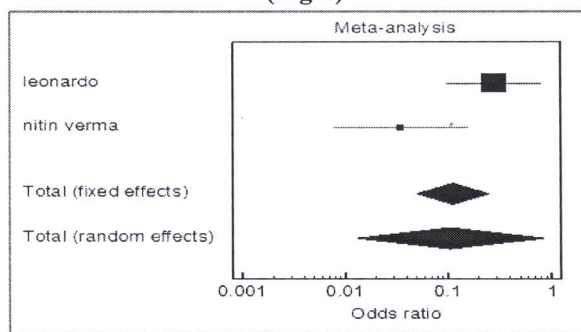
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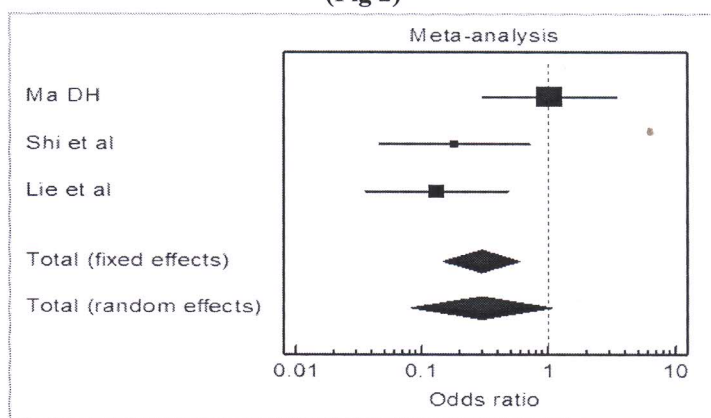
(Fig-1)



Group 1 - Meta analysis of studies with and without MMC on bare sclera

Figure 1: Individual study and pooled odds ratio and 95% confidence interval calculated from data provided by original studies comparing bare sclera resection with or without mitomycin C. Leonardo et al¹¹ OR:0.279 (0.0972 to 0.800), Nitin verma et al¹² OR:0.0348 (0.00785 to 0.154). (OR=individual study odds ratio, 95% confidence interval for individual studies are in parenthesis.) Pooled odds ratio: 0.105 (95% confidence interval 0.0131 to 0.847). If the value 1 is not within the 95% CI, then the Odds ratio is statistically significant at the 5% level ($P < 0.05$).

(Fig 2)



Group 2 - Meta analysis of studies with or without mitomycin C on amniotic graft.

Graph 2: Individual study and pooled odds ratio and 95% confidence interval calculated from data provided by original studies comparing amniotic graft with or without mitomycin C. Ma DH et al¹³ OR: 1.024 (0.305 to 3.428), Shi et al OR: 0.182 (0.0462 to 0.716), Lie et al OR: 0.132 (0.0355 to 0.488) (OR=individual study odds ratio, 95% confidence interval for individual studies are in parenthesis.) Pooled odds ratio: 0.298 (95% confidence interval 0.0817 to 1.089). If the value 1 is not within the 95% CI, then the Odds ratio is statistically significant at the 5% level ($P < 0.05$).

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Table 1: Study details and number of participants

Sl. No	Author	Year of publishing	Design	Treatment group	Control group	Total number of participants
*1	L. Mastropasqua et al	1996	Random	45	45	90
*2	Nitin Verma et al	1998	Random	65	65	130
**3	Ma DH et al	2005	Random	47	48	95
**4	Shi C N et al	2006	Random	36	36	72
**5	Li SZ et al	2007	Random	50	49	99

*Methods adopted were bare sclera as control and with MM-C (0.02%) as treatment group.

**Both groups had amniotic graft and additional MM-C in treatment group.