

# Meta-analysis on the recurrence rates after bare sclera resection with and without mitomycin C use and conjunctival autograft placement in surgery for primary pterygium

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## Abstract

**Background/claims**—Bare sclera resection with and without use of mitomycin C and conjunctival autograft placement are three surgical techniques currently in use for the treatment of primary pterygium. The purpose of this study was to determine through a meta-analysis the risk for postoperative pterygium recurrence comparing the three surgical treatment modalities.

**Methods**—A search through Medline for randomised controlled clinical trials comparing at least two of the three surgical techniques in the treatment of primary pterygium, along with a hand search of all references in relevant papers, was conducted. All eligible clinical trials were graded for quality utilising the Detsky score; those studies with a score of 0.5 or greater were included. The main outcome measurements were the pooled odds ratios and 95% confidence intervals for the risk of pterygium recurrence. These were calculated utilising the Mantel-Haenszel method.

**Results**—Five eligible studies with an adequate quality score were retrieved, three comparing bare sclera resection with and without mitomycin C use, one comparing bare sclera resection with conjunctival autograft placement, and one comparing both. The pooled odds ratio for pterygium recurrence in patients who had only bare sclera resection was 6.1 (95% confidence intervals, 1.8 to 18.8) compared with the patients who had conjunctival autograft placement and 25.4 (9.0 to 66.7) compared with the patients who received mitomycin C.

**Conclusions**—The odds for pterygium recurrence following surgical treatment of primary pterygium are close to six and 25 times higher if no conjunctival autograft placement is performed or if no intra/postoperative mitomycin C is used, respectively. Surgeons and clinical triallists should not be encouraged in the use of bare sclera resection as a surgical technique for primary pterygium.

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Pterygium is a fibrovascular growth arising from the conjunctiva onto the cornea. A number of surgical techniques have been described as methods for pterygium treatment,

including bare sclera resection,<sup>1</sup> bare sclera resection followed by mitomycin C application at different time points, doses, and concentrations,<sup>2-5</sup> and pterygium excision plus conjunctival autograft placement.<sup>6-9</sup> The main difference between bare sclera resection and conjunctival autograft placement is that a free conjunctival graft, usually originated from the superior bulbar conjunctiva, is sutured over the denuded sclera following the pterygium resection. Postoperative pterygium recurrence is a relatively common problem. Recurrence rates following bare sclera resection range from 24% to 89%,<sup>10-12</sup> following bare sclera resection with mitomycin application between 0% and 38%,<sup>3-5, 11</sup> and following pterygium resection with conjunctival graft placement between 2% and 39%.<sup>7, 10-14</sup> Despite the fact that these published series do not seem to favour bare sclera resection alone, this technique is still in use both for therapeutic<sup>10</sup> and research purposes<sup>11-15</sup> (presentation No 3212 by Tan *et al* at the Association for Research in Vision and Ophthalmology Meeting, Ft Lauderdale, FL, 24 April 1996).

Meta-analysis is a quantitative evaluation of two or more independent studies intended to integrate their findings.<sup>16</sup> Meta-analysis results provide an overview of the comparative effect of treatments or procedures.<sup>16</sup> The purposes of meta-analysis are to increase the statistical power of primary endpoints, resolve uncertainty about disparate reports, improve estimates on the magnitude of a treatment effect, and provide improvements in the quality of primary research.<sup>17</sup>

We conducted a meta-analysis of published randomised controlled clinical trials comparing the three surgical techniques for primary pterygium treatment previously mentioned. The purpose of this study was to determine the pooled odds ratio and 95% confidence intervals for postoperative pterygium recurrence as a result of bare sclera resection with and without mitomycin C application and conjunctival autograft placement. In brief, an odds ratio is defined as the ratio of the likelihood of developing a disease (in this study a postoperative pterygium recurrence) if a certain exposure is received (in this study receiving only a bare sclera resection) to the likelihood of developing the disease if not receiving a certain exposure.<sup>18</sup>

## Methods

Following an established protocol, a survey of published studies comparing at least two of the

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Table 1 Characteristics of patients included in studies

| Ref* | Age (years) |       | Sex (%) |        | Race (%) |    |     | Follow up (months) |       |
|------|-------------|-------|---------|--------|----------|----|-----|--------------------|-------|
|      | Mean        | Range | Male    | Female | AA       | AS | HS  | Mean               | Range |
| 11   | 45.6        | 23–79 | 45.3    | 54.7   | 1        | 5  | 94  | 9.3/13.5/<br>12.3† | 6–22  |
| 14   | 37.4        | 25–68 | 38.2    | 61.8   | 100      |    |     | 15.93/14.47‡       | 9–33  |
| 23   | 36.7        | 14–65 | 43.8    | 56.3   | 2        | 2  | 96  | 3/16.3‡            | 1–21  |
| 15   | NS          | 19–81 | 65.4    | 34.6   | NR       |    |     | NR                 | 1.5–8 |
| 24   | 51.8        | 25–71 | 77.8    | 22.2   |          |    | 100 | 8.3/8.9‡           | 4–15  |

## \*Recurrence definition:

11=fibrovascular regrowth past limbus in area previously compromised.

14=regrowth similar to original with symptoms.

23=fibrovascular regrowth past limbus at least 1.5 mm with conjunctival drag.

15=vascular regrowth past limbus.

24=NR.

AA=African-American; AS=Asian; HS=Hispanic; NR=not reported.

†Bare sclera resection group/mitomycin C group/conjunctival autograft group.

‡Bare sclera resection group/treatment group.

Table 2 Surgical technique and postoperative treatments

| Technique | Polishing  | Conjunctival flap | Postoperative treatment  |
|-----------|------------|-------------------|--|
| (11)      |            |                   |  |
| BS        | Yes        | No                | Topical antibiotics/steroids 4–8 weeks   |
| BS+MC     | Yes        | No                | Topical antibiotics/steroids 4–8 weeks<br>Topical mitomycin C 0.02% twice daily 5 days             |
| (14)      |            |                   |  |
| CG        | Yes        | Autograft*        | Topical antibiotics/steroids 4–8 weeks   |
| BS        | Yes        | No                | Topical antibiotics/steroids 3–4 weeks   |
| CG        | Yes        | Autograft*        | Topical antibiotics/steroids 3–4 weeks   |
| (23)      |            |                   |  |
| BS        | No mention | No                | Topical antibiotics/steroids 3 weeks   |
| BS+MC     | No mention | No                | Topical antibiotics/steroids 3 weeks<br>Topical mitomycin C 0.1% or 0.04% four times daily 2 weeks |
| (15)      |            |                   |  |
| BS        | No         | No                | No mention   |
| BS+MC*    | No         | No                | No mention   |
| (24)      |            |                   |  |
| BS        | No         | No                | Topical antibiotics/steroids 3 months  |
| BS+MC*    | No         | No                | Topical antibiotics/steroids 3 months  |

BS=bare sclera resection; BS+MC=bare sclera and postoperative mitomycin C application; BS+MC\*=bare sclera and intraoperative mitomycin C application. Studies with references 23 and 24 referred to the use of 5 minute intraoperative mitomycin C application at concentrations of 0.01% and 0.02% respectively.

\*Conjunctival autograft taken from the superior bulbar conjunctiva of the operated eye.

three surgical techniques in the treatment of primary pterygium—bare sclera resection, bare sclera resection with intraoperative or postoperative mitomycin C application, and conjunc-

tival autograft placement—was conducted through a Medline search between 1966 and 1995, along with a hand search of all references in relevant papers. Only controlled clinical trials including a preintervention patient randomisation process were included. Studies evaluating patients receiving mitomycin C were included regardless of treatment regimen. Exclusion criteria included uncontrolled studies, non-randomised studies, studies combining non-selective results from surgery on primary and recurrent pterygia, studies using concurrent treatment modalities (that is,  $\beta$  therapy), and incomplete information from published data. Also, the quality of each clinical trial was graded according to the method outlined by Detsky *et al.*,<sup>19</sup> and studies with a score less than 0.5 were excluded. When two published studies included data from the same group of patients the study showing results of a larger number of patients or with a longer follow up period was included. Data were collected from each study by two independent observers who performed the study calculations. Calculations were performed utilizing the Mantel–Haenszel method<sup>20</sup> as outlined by Pagano and Gauvreau,<sup>21</sup> and briefly included the following:

- (1)  $2 \times 2$  tables from raw data included in published studies. If any cell of the  $2 \times 2$  table were to be zero, 0.5 would be added to each cell for calculations as suggested by Kahn and Sempos<sup>22</sup>
- (2) odds ratio and 95% confidence intervals for each study
- (3) test of study population homogeneity to ensure independent study data could be combined, as outlined by Pagano and Gauvreau<sup>21</sup>
- (4) pooled odds ratio and 95% confidence intervals.

A third masked examiner evaluated disagreements comparing results from the two independent examiners. The three evaluators agreed on the final calculations.

Table 3 Quality assessment of studies included (method by Detsky *et al.*<sup>19</sup>)

|   | Reference No |      |      |     |      |      |      |      |
|---|--------------|------|------|-----|------|------|------|------|
|   | 4            | 5    | 11   | 14  | 23   | 29   | 15   | 24   |
| 1   |              |      |      |     |      |      |      |      |
| (A) Random allocation   | No           | Yes  | Yes  | Yes | Yes  | No   | Yes  | Yes  |
| (B) Description of randomisation                                    | I            | I    | A    | P   | I    | I    | I    | P    |
| (C) Potential bias in treatment assignment                          | Yes          | No   | No   | No  | No   | Yes  | No   | Yes  |
| 2   |              |      |      |     |      |      |      |      |
| (A) Description of outcome measures                                 | Yes          | Yes  | Yes  | Yes | Yes  | Yes  | Yes  | Yes  |
| (B) Criteria objective  | P            | P    | Yes  | Yes | Yes  | P    | P    | P    |
| (C) Outcome assessors masked to treatment                           | No           | No   | Yes  | No  | Yes  | No   | Yes  | Yes  |
| 3   |              |      |      |     |      |      |      |      |
| (A) Inclusion/exclusion criteria defined                            | No           | No   | P    | No  | No   | P    | Yes  | Yes  |
| (B) Mention of patients not included                                | No           | No   | No   | No  | No   | No   | No   | No   |
| 4   |              |      |      |     |      |      |      |      |
| (A) Therapy described for treatment group                           | Yes          | Yes  | Yes  | Yes | Yes  | No   | Yes  | Yes  |
| (B) Therapy described for control group                             | Yes          | Yes  | Yes  | Yes | Yes  | Yes  | Yes  | Yes  |
| 5 (A)   |              |      |      |     |      |      |      |      |
| 1 Statistical analysis test stated                                  | Yes          | No   | Yes  | Yes | Yes  | Yes  | Yes  | Yes  |
| 2 p Value stated  | No           | No   | Yes  | Yes | No   | Yes  | Yes  | Yes  |
| (B) Statistical analysis appropriate                                | Yes          | NA   | Yes  | Yes | P    | Yes  | Yes  | Yes  |
| (C) If negative trial, CI and post hoc power calculations performed | NA           | NA   | No   | No* | NA   | NA   | NA   | NA   |
| (D) Sample size justification before study                          | No           | No   | No   | No  | No   | No   | No   | No   |
| Final score   | 0.39         | 0.46 | 0.73 | 0.6 | 0.53 | 0.42 | 0.67 | 0.71 |

A=adequate; P=partial; I=inadequate; CI=confidence intervals; NA=not applicable.

\*Sample size limitations are discussed.

Table 4 Data for 2x2 tables constructed from raw data originated from eligible studies

| Study                                  | Bare sclera resection<br>Recurrence<br>No of eyes |    | Conjunctival graft<br>Recurrence<br>No of eyes                            |    |
|--|---|----|---|----|
|  | Yes   | No | Yes   | No |
| Lewallen <i>et al</i> <sup>14</sup>    | 6   | 9  | 3   | 14 |
| Chen <i>et al</i> <sup>11</sup>        | 15  | 2  | 9   | 14 |
|  | Bare sclera resection<br>Recurrence<br>No of eyes |    | Bare sclera resection with<br>mitomycin C use<br>Recurrence<br>No of eyes |    |
|  | Yes   | No | Yes   | No |
| Singh <i>et al</i> <sup>23</sup>       | 16  | 6  | 1   | 41 |
| Frucht-Pery <i>et al</i> <sup>24</sup> | 14  | 16 | 1   | 29 |
| Cano-Parra <i>et al</i> <sup>15</sup>  | 14  | 22 | 1   | 29 |
| Chen <i>et al</i> <sup>11</sup>        | 15  | 2  | 9   | 15 |

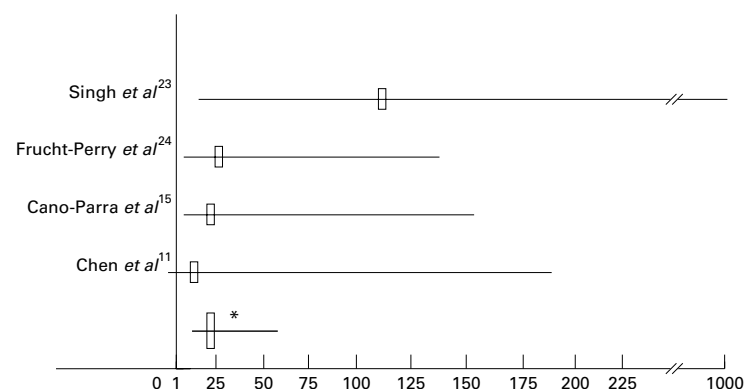


Figure 1 Individual study and pooled odds ratios and 95% confidence intervals calculated from data provided by original studies comparing bare sclera resection with postoperative mitomycin C versus placebo. Singh *et al*<sup>23</sup> OR: 109.33 (12.18–980.34), Frucht-Pery *et al*<sup>24</sup> OR: 25.38 (4.68–136.4), Cano-Parra *et al*<sup>15</sup> OR: 18.45 (2.24–150.27), Chen *et al*<sup>11</sup> OR: 12.5 (0.81–192.92). (OR = individual study odds ratio, 95% confidence intervals for individual studies are in parenthesis.) Cumulative odds ratio: 25.4 (95% cumulative confidence intervals 9.02 to 66.69)

**Results**

Five eligible published studies were identified, three that compared bare sclera resection without and with mitomycin C application,<sup>15 23 24</sup> one that compared bare sclera resection with conjunctival autograft placement,<sup>14</sup> and one comparing the three techniques.<sup>11</sup>

An initial objective of the study was to perform meta-analysis calculations comparing bare sclera resection with mitomycin C use and conjunctival autograft placement; however, only one eligible study was identified.<sup>11</sup> Also, we originally intended to evaluate the role of  $\beta$  irradiation and three studies evaluating different treatment groups were retrieved; one com-

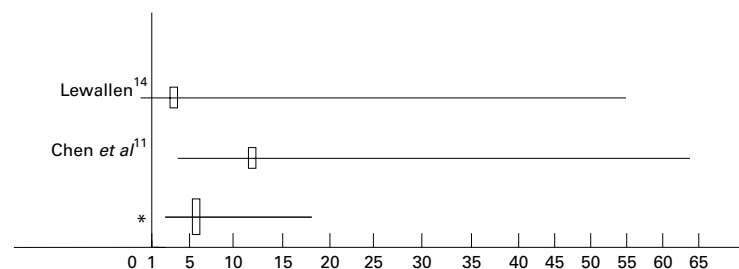


Figure 2 Individual study and pooled odds ratios and 95% confidence intervals calculated from data provided by original studies comparing bare sclera resection versus conjunctival autograft placement. Lewallen *et al*<sup>14</sup> OR: 3.11 (0.17–55.21), Chen *et al*<sup>11</sup> OR: 11.67 (2.14–64.04). (OR = individual study odds ratio, 95% confidence intervals for individual studies are in parenthesis.) Cumulative odds ratio: 6.1 (95% cumulative confidence intervals 1.82–18.75).

paring bare sclera resection with mitomycin C and  $\beta$  irradiation applications,<sup>25</sup> one comparing bare sclera resection with or without  $\beta$  irradiation,<sup>26</sup> and one comparing bare sclera resection with  $\beta$  irradiation and conjunctival autograft placement.<sup>27</sup> Since no two studies compared similar treatment groups no analysis attempt was performed.

Table 1 provides a description of the population characteristics of studies included, follow up periods, and pterygium recurrence definitions. Table 2 gives a general outline of the surgical technique and the postoperative treatment utilised in the studies included. Table 3 shows the individual quality scoring of the studies included, along with that of three studies excluded for non-randomisation and scores below 0.5.

Ten studies were totally and one partially excluded from this analysis. Studies by Haya-saka *et al*,<sup>4</sup> Riordan-Eva *et al*,<sup>28</sup> Schrage *et al*,<sup>29</sup> and a part of Singh *et al*<sup>23</sup> partially because of no patient randomisation; Mahar *et al*<sup>5</sup> because of a quality score below 0.5; Güler *et al*,<sup>30</sup> and Sebban and Hirst<sup>13</sup> because of combined treatment results from primary and recurrent pterygia; Dowlut and LaFlamme,<sup>27</sup> and Chay-akul<sup>25</sup> because of the concomitant use of  $\beta$  irradiation; Singh *et al*<sup>3</sup> because of results included in a subsequent study<sup>23</sup>; and Vaniscotte *et al*<sup>31</sup> because of insufficient information.

Table 4 shows the 2 x 2 tables data constructed based on information provided by the study. Homogeneity testing determined a  $\chi^2$  of 1.23 for the bare sclera versus conjunctival autograft and 3.06 for bare sclera with or without mitomycin C use. For a  $\chi^2$  distribution with 1 and 3 degrees of freedom respectively, and at an alpha level of 0.05, the obtained  $\chi^2$  determined that it was acceptable to combine information from the studies using the Mantel-Haenszel method.

The pooled odds ratio for postoperative pterygium recurrence in patients who only had bare sclera resection was 6.1 (95% confidence intervals, 1.82 to 18.75) compared with those who had conjunctival autograft placement, and 25.4 (9.02 to 66.69) compared with those who received mitomycin C. Individual and pooled odds ratios and confidence intervals are depicted in Figures 1 and 2.

**Discussion**

This study provides evidence of the inherent risk for pterygium recurrence of bare sclera resection alone when compared with other currently available surgical techniques. Our results show with a 95% confidence interval that the odds for a pterygium recurrence is at least nine times higher if mitomycin C is not applied intraoperatively or postoperatively. Despite the fact that when comparing bare sclera resection with conjunctival autograft placement only two eligible studies were retrieved, we provide evidence with a 95% confidence interval with the fact that there is an increased risk of pterygium recurrence with bare sclera resection of at least 1.8 times greater, a figure that could be in excess of 18. These results should strongly discourage

surgeons and clinical researchers in the use of bare sclera resection, if recurrences are to be prevented, bearing in mind that the Declaration of Helsinki states that in clinical trials no suboptimal treatment can be offered to a control group.

Conjunctival autograft placement and bare sclera resection with mitomycin C use have both advantages and limitations. Conjunctival autograft placement following pterygium resection offers the theoretical advantages of reconstructing the architecture of the corneoscleral limbus and transplanting limbal stem cells which may facilitate corneal epithelial healing.<sup>32</sup> It is also a time consuming procedure. Mitomycin C is an antibiotic-antineoplastic agent that selectively inhibits DNA, cellular RNA and protein synthesis<sup>3</sup> and can have serious complications following administration.<sup>33</sup> Identification of an ideal dose and concentration of mitomycin C is beyond the scope of this study.

Our study has several limitations inherent in meta-analysis. A low number of studies was retrieved by our search as a result of several factors. Medline searches may yield only two thirds of relevant published papers.<sup>34 35</sup> Among the identified studies, only a few randomised controlled clinical trials provided the quality standards for eligibility. This underscores the need for the development and publication of adequately planned and conducted clinical research in this area. Publication bias (the lack of publication of trials with negative results) is also a limitation to any meta-analysis. Unidentified eligible studies, as well as future publications should increase the power of this survey. As for any meta-analysis evaluating a surgical technique, the study populations, the individual surgeon expertise, as well as the postoperative treatment are different in every study. The test of homogeneity performed provides confidence in establishing that, statistically speaking, the samples can be combined because they could come from a same theoretical population from which each sample from each study is a representation. An evaluation of the individual population risk factors and recurrence rates was out of the scope of this meta-analysis. Also, according to the authors' description of the surgical technique and postoperative management, all studies followed standard surgical and postoperative procedures (Table 2), although some differences were noticeable. Mitomycin C concentration, administration, and dosing were different between the studies evaluated. Follow up periods and definitions of pterygium recurrence are also slightly different among studies evaluated. Recurrences are usually evident 1–2 months after surgery,<sup>35</sup> a period covered by all eligible studies. Included for analysis are studies by Singh *et al*,<sup>23</sup> Frucht-Pery *et al*<sup>24</sup> reporting a total of four recurrent cases. Bearing in mind all the study's limitations, we consider that our study had eligibility criteria adequate for meta-analysis. We believe that the differences between the eligible studies should only minimally affect the general results and conclusions of this study.

At present we are unable, through meta-analysis, to determine if there is a significant difference in the recurrence rate between bare sclera resection with mitomycin C and conjunctival autograft placement. In this regard, Singh *et al*<sup>23</sup> reported that to detect 2% and 5% recurrence rate differences, adequately designed clinical trials require sample sizes of 736 and 211 patients respectively. Only one study with a small sample size was detected in our search.<sup>11</sup> New research in this area should focus on answering, through randomised controlled clinical trials with adequate sample sizes, if significant differences exist with regard to safety and efficacy issues of techniques which, like bare sclera resection with mitomycin C and conjunctival autograft placement, have a lower risk for postoperative pterygium recurrence.

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