Author’s response to reviews

Title: Anti-fibrotic, anti-VEGF or radiotherapy treatments as adjuvants for pterygium excision: a systematic review and network meta-analysis

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Reviewer reports:

Hamidreza Moein (Reviewer 1): In this meta-analysis Zeng et al. systematically reviewed the use of adjuvant treatment including MMC, 5FU, beta-radiotherapy, and bevacizumab after pterygium surgery. They searched published literature in English until March 25, 2016 and chose 34 randomized clinical trials, consisted of 2483 patients, that were eligible to include in their quantitative analysis among 153 abstracts. All the included studies have compared the effectiveness of adjuvant therapies to each other or to placebo in preventing recurrences when given after surgical removal of pterygium. Their analysis demonstrated that MMC decreased the odds of recurrence more significantly as compared to other adjuvant therapies, which did not depend on the technique of the surgery (bare sclera vs. tissue grafting) and primary vs. recurrent pterygium. The results of this study should be reviewed with cautious based on the low quality of the included studies and the limitations that authors mentioned in the manuscript.

This study is well structured and technically sounds. In addition to comparing the results of previous clinical trials on this subject, this review will also help to understand the limitations of
previous studies and help clinicians to design more detailed and higher quality trials in the future. There is a high need for such investigations to better understand the benefit of adjuvant therapies and to help the clinicians to choose the most beneficial adjuvant therapy when indicated. However, to improve the manuscript following comments need to be addressed:

General comments:

1. To have a more conclusive data on anti-VEGF treatment it is highly suggested to search for lucentis/ranibizumab in addition to the bevacizumab and incorporate the results into the current results. Please add lucentis/ranibizumab to your search terms (methods), supplementary file 1, and mention it in the introduction as one of the tested adjuvant treatments even if you did not find an eligible article on that. (Authors may consider the following article as an example if it fits your inclusion criteria: Am J Ophthalmol. 2010 Jun; 149(6):926-931.e2. doi: 10.1016/j.ajo.2010.01.015.)

Thanks for your advice. We have revised it as your instruction (in red font).

2. It is beneficial for the reader to understand why the authors performed both direct and Bayesian network meta-analysis. Please explain the reason and briefly describe the advantages/disadvantages of each method compared to the other.

If results from direct meta-analysis agree with results from Bayesian network meta-analysis, it will further support the results from Bayesian network meta-analysis. Many new drugs/treatments are often compared with placebos or standard drugs/treatments without directly comparing between these new drugs/treatments. Bayesian network meta-analysis can obtain indirectly treatment efficacy and differences from these new drugs/treatments, however, evidence level from Bayesian network meta-analysis is lower than direct meta-analysis. When both evidences exist, first consider evidence form direct comparison; in the absence of direct comparison, judiciously and carefully product or consult existing indirect comparative evidence from Bayesian network meta-analysis in order to select the best treatment options.

Specific comments:

1. Figure 2: Please spell out placebo and bevacizumab completely on the figure. Spell out the abbreviations in the figure legend and expand the figure's legend by describing more about the circles and connections, and about what you want to show in that figure.

Thanks for your advice. We have revised it as your instruction (in red font).
2. Although the figure helps to visualize the amount of studies and comparisons between different adjuvant therapies to some extent (qualitatively) but showing the quantitative data will be beneficial. You can add a table that presents the number of included studies in each comparison group and mention the number of participants in each treatment group as well. (e.g., In the table show 14 studies compared MMC to placebo; Total number of participants who received placebo in these 14 studies were "X"; Total number of participants who received MMC in these 14 studies were "Y")

Thanks for your advice. We have revised it as your instruction (in red font).

3. In the supplementary figure 2 and 3, number of studies for MMC vs. placebo is demonstrated 15 but in the results section of the manuscript and supplementary file 4 it is 14. Please double check and correct accordingly.

One study (Ozsutcu2013) compared three treatments (MMC, bevacizumab and placebo), 14 studies compared two treatments (MMC and placebo), which makes the number of studies for MMC vs. placebo is 15.

Mohammad taher Rajabi (Reviewer 2):

I reviewed the manuscript entitled as "Anti-fibrotic or anti-VEGF treatments as adjuvants for pterygium excision: a systematic review and network meta-analysis Adjuvants in pterygium excision". It is a good manuscript comparing all adjunct therapies to prevent recurrence of pterygium. There are some comments that the authors are recommended to consider before decision;

1. It is recommended to add "radiotherapy" to the title. As the title does not present that the radiotherapy have been considered in comparison.

Thanks for your advice. We have revised it as your instruction (in red font).
2. Although the authors have down the best to compare these modalities in prevention of recurrence in primary pterygium, however it is not clear which of them is better in recurrent cases, or how many of these cases were the recurrent pterygium. Number of studies in recurrent cases was limited. Comparisons only contained bevacizumab to placebo, and MMC to placebo. We could not obtain effective results in recurrent cases from the present studies. (One study compared bevacizumab (n=22) to placebo (n=22), five studies compared MMC (n=147) to placebo (n=137) in recurrent pterygium. Four studies compared MMC (n=276) to placebo (n=93) in primary and recurrent pterygium, and the number of recurrent cases in these studies was not available)