Author's response to reviews

Title: Use of Mitomycin C to Reduce the Incidence of Encapsulated Cysts Following Ahmed Glaucoma Valve Implantation in Refractory Glaucoma Patients: A New Technique

Authors:

Minwen Zhou (zmw8008@163.com)
Wei Wang (will.wong@qq.com)
Wenbin Huang (cyhwenb@gmail.com)
Xiulan Zhang (zhangxl2@mail.sysu.edu.cn)

Version: 3
Date: 28 April 2014

Author's response to reviews: see over
Dear Dr. Cruz,

Enclosed please find the revised version of our manuscript “Improved Technique of Mitomycin C Application May Decrease the Encapsulated Cyst Incidence Following Ahmed Glaucoma Valve Implantation in Refractory Glaucoma Patients” (Manuscript ID: 7102138001153575).

We appreciate your supportive comments and the Reviewers’ thoughtful and constructive critiques, which had been extremely helpful in our revision. We have considered each of the reviewer’s comments, and have responded carefully and thoroughly as summarized in the following pages, which we believe that the article is thereby strengthened.

Thank you again for your further consideration of this manuscript.

Sincerely yours,

Xiulan Zhang, MD, PhD
Professor of Ophthalmology, Vice director of Glaucoma Department, Director of Clinical Research Center, Director of Institution of Drug Clinical Trials, Zhongshan Ophthalmic Center, State Key Laboratory of Ophthalmology, Sun Yat-sen University
54S.Xianlie Road, Guangzhou, China 510060
Email: zhangxl2@mail.sysu.edu.cn.
Tel: +86-20-87330484
Fax: +86-20-87333271;
Reviewer #1
1. Change ‘the effective’ to ‘an effective’

Answer: Thank you. I had corrected it to ‘an effective’.

2. Are refs 1,5,6 appropriate supporting references for the efficacy of Ahmed implants? Are they superior papers to the Ahmed data from the Ahmed versus Baerveldt Study or Ahmed Baerveldt Comparison Study?

Answer: Thank you for highlighting this point. We cited the success rates of these studies of AGV implantation because several reported success rates ranging from 49% to 70.59%. The famous ABC and A versus B studies reported success rates of AGV implantation of 83.6% and 57%, respectively, at one year. We have added these two references in the manuscript.

3. Reference 4 is inadequate to cite as supporting evidence for the use of MMC in tubes. This paper is a retrospective review of use of MMC in Ahmed tubes in a paediatric population and describes poorer surgical outcomes in the group that received MMC. The authors should either cite primary sources that support the point they are trying to make or it would be reasonable to cite the Cochrane review on this topic: http://summaries.cochrane.org/CD004918/aqueous-shunts-for-glaucoma. Also there a few publications on coating Ahmed implants with MMC. This is a sufficiently similar concept to what is being described that some discussion of these papers would be useful in the introduction.

Answer: Thank you for your helpful reminder and suggestion. We cited two other references to support the effective use of Ahmed glaucoma valve implantation in treating refractory glaucoma.

4. Leading on from the Cochrane review findings, which did not find good evidence to support the use of MMC in tube surgery, many (perhaps most) surgeons around the world do not use MMC during Ahmed tube surgery. Thus it risks being misleading to describe its use as the traditional technique. If by traditional the authors mean the
commonest then perhaps the commonest thing to do with MMC is to leave it in the bottle and not use it at all during Ahmed surgery. It would be better to say they compared technique A and technique B.

Answer: Thank you for raising this important question. We agree with the comments. To date, there is no evidence to support the use of mitomycin C (MMC) in tube surgery, and controversy surrounds its use. However, some famous studies (e.g., trabeculectomy versus tube) used MMC at a dosage of 0.3 mg/ml to 0.4 mg/ml. The focus of the present study was on how MMC is used in tube surgery. In addition, we changed the expression “improved technique” to “new technique.”

5. I’m not sure that a retrospective chart review represents ‘recruitment’. The authors need to clarify if ALL the patients that met the inclusion/exclusion criteria and had surgery between Oct 2008 and January 2013 were included for analysis. If any not included state they must state why so that the reader can be clear if this represents a potential source of bias. Were any surgical notes or hospital charts missing or was the data 100% complete?

Answer: Thank you for pointing this out and for your thoughtful and incisive critique. I apologize for not clarifying this issue. Consecutive patients followed up at the Zhongshan Ophthalmic Center from October 2008 and January 2013 were included in this study. This has been clarified in the revised manuscript (page 3, paragraph 2, lines 24–28).

6. “Different surgical technique was used based on surgeon discretion.” This isn’t enough detail. Did the single surgeon (XZ) change his technique half way through the time period over which results are drawn? If he changed his technique so the 41 eyes receiving traditional technique were consecutive operations and 38 eyes receiving new technique were also consecutive please state this as this would be reassuring to the reader that this source of bias is somewhat reduced. If surgeon changed technique intermittently throughout the time period being studied this should be stated with some explanation as to how and why the surgeon decided which technique he would
use for each case.

Answer: Thank you for raising this important question. We are sorry we did not make it clear. From October 2008 to January 2010, we employed the traditional method in our hospital, and we converted to the new technique from January 2010. This information has been added in the revised manuscript (page 4, paragraph 1, lines 1–2).

7. 200ml of BSS seems like a lot. Is this correct and is there a reason why the surgeons irrigate using BSS rather than water or saline?

Answer: We thank the reviewer for drawing our attention to this important issue. In our hospital, in order to irrigate the MMC thoroughly we usually use 200 ml of BSS.

8. How was decision to use ST or IT quadrant made? Given these are different quadrants it isn’t true to say the same technique was used.

Answer: Thank you. When we performed the AGV implantation surgery, the flap of the conjunctiva and Tenon’s capsule was usually created in the superior. However, in the patients who had undergone previous eye surgery, such as trabeculectomy, causing scarring of the conjunctiva of the superior temporal quadrant, we used an inferior temporal quadrant incision (page 4, paragraph 3, lines 12–15).

9. Why ligate the tube? The valved design of the Ahmed prevents the need for routine ligation. Please explain this for the reader.

Answer: Thank you. As we all know, the Ahmed device contains a one-way valve designed to prevent postoperative hypotony and a shallow anterior chamber. However, in clinical practice, hypotony still occurred in some patients. To reduce the incidence of hypotony, we ligate the tube. As a result, there was a relatively lower incidence of this complication. Thus, when we perform AGV implantation surgery, we usually ligate the tube to prevent hypotony and a flat anterior chamber.

10. Do the authors think that varying concentration and duration of MMC application may be the main reason for different effect? Some explanation as to how surgeons
decided what concentration and duration of MMC application is needed in this section.

Answer: Thank you for your careful review and valuable suggestion. The concentration and time of MMC depended on the judgment of the risk of failure of the surgery by the surgeon. This information has been incorporated in the revised manuscript (page 4, paragraph 3, lines 22–23).

11. Were these determined a priori? If so this should be stated.

Answer: Thank you for pointing out this critical issue. We determined the concentration and duration of MMC before surgery according to the age, diagnosis, and conjunctiva status of the patients.

12. Figure 2 does not add clarity to the presentation of results over the same data in table 2.

Answer: We entirely agree with the reviewer and have deleted Figure 2.

13. Figure 3 is not the clearest way to present data on medication usage. Could this be incorporated in table 2 so the reader can see the extent to which the post-op IOPs in table 2 may be affected by supplemental medication usage?

Answer: Thank you for your suggestions. As advised, we have deleted Figure 3 and incorporated the glaucoma medication data in Table 2.

14. I was interested to see that the complications of over drainage (flat AC, choroidal effusion and hypotony maculopathy) were more common in the group that had an MMC soaked piece of cotton wrapped around the plate. This is reasonable supporting evidence that the different technique may indeed be responsible for some clinical effect. Unfortunately an increased complication rate is not an improvement, so again I think the techniques should be called ‘technique a’ and ‘technique b’ with the reader allowed to make their own mind up as to which precise balance of surgical success and complications is preferable.
Answer: Thank you for your suggestions. As advised, we have changed the expression “improved technique” to “a new technique.”

15. It would be interesting to know if Fisher’s exact test would consider the 9 complications of over drainage versus 2 in the ‘traditional’ technique arm to approach statistical significance.
Answer: Thank you. We used the Fisher’s exact test to examine the statistical significance of the complications between the two groups.

16. Please also state when these complications of over drainage occurred. Were they before or after the ligating suture dissolved or was lasered? Can the authors comment on what they believe the reasons for over drainage were given that the Ahmed implant is valved to prevent over drainage. Is it possible that the valve mechanism was damaged directly by MMC or by the increased handling of the implant associated with the wrapping of the implant by the surgeon?
Answer: Thank you for raising this important question. In clinical practice, we observed that the complications of over drainage occurred when the viscoelastic in the anterior chamber was absorbed. We did not ligate the tube previously, and we found that the incidence of a flat anterior chamber was relatively high. Ligating the tube decreased this complication, but it still occurred in several patients in the current study. We do not know the exact cause, but we do not think the complication is due to the direct application of MMC. This issue needs to be investigated further.

17. Results should include some description of MMC concentration and duration between the 2 groups. Presumably this would have been recorded in the operative notes so should be available for analysis. This could be the main reason for the results presented.
Answer: Thank you. We accept your comment. In this study, the MMC concentration and duration were comparable between the two groups. We have added the relevant data in Table 1.
18. I’m not sure the last sentence is necessary. It’s difficult to imagine a larger study with fewer patients.

Answer: Thank you. As advised, we have deleted this sentence in the revised manuscript.

19. The discussion needs some comment as to the limitations of non-randomisation introducing bias and different MMC concentrations and times making comparisons limited.

Answer: Thank you for your helpful reminder and suggestion. Accordingly, we have added information on the limitations in the revised manuscript (page 9, paragraph 4, lines 28–30; page 10, paragraph 1, lines 1–3).

Reviewer #2
1. However, Visual acuity was not addressed before or after and it should be a marker for success (or failure – i.e.: NPL).

Answer: Thank for your advice. Accordingly, we have added information on the visual acuity at each time point in the revised manuscript (page 7, paragraph 4, lines 20–22) and in Table 4.

2. Although Failure was specified, the reasons why eyes/patients were removed from the analysis were not (re-do? Lost to follow-up/lack of attendance? New surgery?)

Answer: Thank you for pointing this out and for your thoughtful and incisive critique. As advised, we have added the reasons for failure in the manuscript (page 7, paragraph 3, lines 19–21) and in Table 3.