Author’s response to reviews

Title: Reoperation Following Vitrectomy for Diabetic Vitreous Hemorrhage With versus Without Preoperative Intravitreal Bevacizumab

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Author’s response to reviews:

Response letter

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Dear Editor,

We much appreciate the editor’s and reviewer’s positive and constructive comments and suggestions regarding our manuscript entitled “Reoperation Following Vitrectomy for Diabetic Vitreous Hemorrhage With versus Without Preoperative Intravitreal Bevacizumab” (BOPH-D-18-00514R1).

We have studied the reviewers’ comments carefully and have made revisions according to the comments.

Point-by-Point Response
Reviewer: 2
1. I am very satisfied with this revision. I have only one further comment on it.

I am a little concerned with the diagnosis of TD. Did the authors confirm the accuracy of the diagnosis of TD by B-scan?

Reply: Thank you very much for your comments. B-scan is a very sensitive tool with a high sensitivity level to even a slight separation of the retina from the underlying retinal pigment epithelium. Of course, in some complicated cases, we also adjusted the gain for the B-scan or used color Doppler ultrasonography to confirm the accuracy of the diagnosis of TD.

We have corrected our statement located on line 7 on page 2, line 4 on page 5 and line 2 on page 11 in the revision.

Reviewer: 3

Revised

1. Abstract

a. Methods: The way the groups are described is confusing. I would suggest rewording it something like, "...were divided into a group that received preoperative IVB and a group that did not receive preoperative IVB." To call one group a PPV group is confusing since both groups had PPV.

Reply: Thank you for your careful review and suggestion. We are very sorry that our statement is confusing.

We have modified the description in the revised version, located on line 5-6 on page 2.

b. Results: Similarly, this could be worded better, i.e. "There were 17.4% of eyes in the VH group that did not receive preoperative IVB that later required additional vitrectomy, while only 7.7% of the eyes in the VH group that received preoperative IVB required additional vitrectomy." I would word the sentence about the TRD groups the same way. Instead of "in group TRD without IVB," say, "in the TRD group that did not receive preoperative IVB."

Reply: Thank you for your suggestion. We have made the correction in the revised, located on line 10-14 on page 2.

2. Background

a. Line 7-8. Cryopexy is no longer a "conventional method to treat PDR." I think the authors mean to describe historical methods of PDR treatment. As such, it would be better to say, "Historically, treatment for PDR has included PRP, cryopexy, etc."

Reply: Thank you for your advice. We have modified the description in the revised version, located on line 3-4 on page 3.

b. Line 21. Should be "have been used widely" rather than "has been used widely."

Reply: Thank you for your careful review. We are very sorry that our grammatical errors. We have corrected the error located on line 8 on page 3 in the revision.

c. Line 24. Anti VEGF does not help the actual blood clear faster. Rather, it helps the neovascular vessels regress preventing further bleeding. The VH still has to be cleared by the eye—this may happen faster than otherwise since there will likely be no further active hemorrhage after the injection, but the anti-VEGF does not clear the media. This should be clarified.

Reply: Thank you for your careful review and suggestion.

We have made the correction, which is located on line 8-10 on page 3 in the revision.

d. Line 38-39. "In recent 10 years" is an unusual way to phrase this. Perhaps the authors mean, "The
use of IVB as an adjunct before vitrectomy has been routinely recommended over the last 10 years."

Reply: Thank you for your advice. Since we are from non-English speaking countries, many of our statements are not commonly used, and your expression is more accurate.

We have made the correction, which is located on line 15-16 on page 3 in the revision.

e. 2nd page of background Line 9-10. What is it about the surgical instruments with small gauge PPV that makes surgery safer? I don't disagree, I just think this needs more description. i.e. smaller, yet more elegantly designed and sturdy.

Reply: Thank you very much for your comments. We have added the description located on line 5 on page 4 in the revision.

f. 2nd page of background Line 17 ish to the end of the paragraph. The purpose is not well described. Isn't the purpose to evaluate the reoperation rate in patients with VH and TRD when preop IVB is given and when it is not given? The way it's worded makes it sound like the authors are trying to compare "reoperation of preoperative IVB in VH patients compared with TRD patients without preop IVB." This should be reworded. For example: "The purpose of this study was to evaluate the reoperation rate in patients with VH or TRD in patients that received preoperative IVB versus those who did not receive preoperative IVB."

Reply: Thank you for your advice. We have made the correction, which is located on line 9-10 on page 4 in the revision.

g. I would also delete the last sentence of the background.

Reply: Thank you for your advice. The last sentence seems to be a bit redundant.

We have deleted the last sentence of the background on page 4.

3. Methods
a. Line 53. I like "IVB+PPV group." I would call the "PPV group", "PPV alone group," or "PPV without IVB." I would make this change throughout the paper.

Reply: Thank you for your suggestion. We have chosen "PPV alone group" and made the changes throughout the paper.

b. The timing of when the Avastins were given (median time before PPV etc.) are given later. This should be included in the methods section when the injection technique is described.

Reply: Thank you for your advice. We have made the correction, which is located on line 6-8 on page 5 in the revision.

4. Results
a. Line 25 (1st sentence). Should be "We reviewed 1080 patients with VH who had underwent..."

Reply: We are sorry for the mistakes in numerous spelling/grammar/formatting. The manuscript has been checked by Grammarly and modified by the Scribendi website.

We have made the correction, which is located on line 10 on page 6 in the revision.

b. Line 56 under primary outcomes. The numbers here are different than in the abstract. Here it says 71.8% of patients with VH who had preop IVB had no reoperation vs. 69.7% of VH patients who did not have preop IVB. The p value is not significant. In the abstract the numbers for the same group are 17.4% of the VH without preop IVB that required another PPV vs. 7.7% of eyes in the VH group with preop IVB. The p value is 0.025. Which is it? What is the actual result?

Reply: Thank you for your careful review.

"However, in the patients without TRD, there were 69.7% (76/109) of patients without IVB that had a
single vitrectomy, while only 71.8% (84/117) of patients with preoperative IVB had no reoperation (IVB+PPV vs. PPV: OR=0.894, 95% CI 0.617 to 2.048, P = 0.703)” Here, we are talking about no reoperation, that is, no re-injection, no vitrectomy, no silicone oil removal, no reoperation for neovascular glaucoma.

“There were 17.4% of eyes in the VH group that did not receive preoperative IVB that later required additional vitrectomy, while only 7.7% of the eyes in the VH group that received preoperative IVB required additional vitrectomy.” Here, we are talking about the rate of re-vitrectomy.

We have made the correction, which is located on line 18-22 on page 6 in the revision.

c. Line 6. I don't think a repeated anti-VEGF treatment should be included as a reoperation.
Reply: Thank you for your advice. In developed countries, intravitreal injections can be performed in the office and can be reimbursed for expenses, so they are not classified as re-operations. In China, anti-VEGF treatment needs to be performed in the operating room, and the cost is not covered by medical insurance, which incurs additional costs. Therefore, in this study, re-injection will be included as a reoperation.
I am sorry that I have not made any changes in this regard. I hope you can understand.

5. Discussion
a. Line 20. The Discussion talks about the use of endotamponades. The numbers for each group should be listed in the results. What % of patients needed SO in each group? Gas?
Reply: Thank you for your suggestion.
We have added Fig. 2 to show the intravitreal tamponade at the end of surgery.

b. Line 15 on 3rd page of the Discussion: anti VEGF does not promote absorption of VH—it prevents more bleeding.
Reply: Thank you for your suggestions and correct my misunderstanding.
We have made the correction, which is located on line 13 on page 10 in the revision.

General comments: I like the idea of this study. It is an extremely relevant topic. Does IVB lower re-op rates in VH and/or TRD patients? This is a great question. I think several points need clarification. Why do the authors include glaucoma surgeries and anti-VEGF injections as re-operations? Glaucoma (unless it is NVG) is not VEGF mediated and anti-VEGF injections are not operations. Also, the fact that you had to use SO and remove it later may be completely unrelated to the use of IVB. The TRD or the VH may have just been associated with worse neovascular traction in that case (where SO endotamponade and later removal was required). It is impossible to account for the initial severity of the pathology in a retrospective review and this needs to be mentioned in the discussion as a limitation. The most important question to me is how many patients needed reop for recurrent VH, recurrent RD/TRD, and perhaps NVG. Reoperations to remove oil, or inject anti-VEGF or treat glaucoma seem less relevant. This should be more clearly highlighted in the paper.
Reply: Thank you for your comments. In fact, the anti-glaucoma surgery in our article refers to the operation of neovascular glaucoma, not glaucoma after conventional vitrectomy. We have made the corrections, which is located on line 17 on page 5, line 3 on page 7 and line 20 on page 10 in the revision. As for the anti-VEGF injections, as I said above, anti-VEGF treatment needs to be performed in the operating room, and the cost is not covered by medical insurance in China, which incurs additional costs. Therefore, in this study, re-injection will be included as a reoperation.
It is impossible to explain the initial severity of pathology in retrospective studies, which has been added to the limitations of the article on line 22 on page 10.
“preoperative anti-VEGF treatment of diabetic vitreous hemorrhage could reduce the chance of POVCH, reduce the chance of re-vitrectomy, and reduce the incidence of neovascular glaucoma”
which has been clearly highlighted on line 1-4 on page 10.

I also think the authors should hypothesize in the paper a bit more about why the TRD group with preop IVB has more re-operations.

As it stands, the authors suggest that we should consider IVB for VH cases but maybe not TRD's, but the numbers contradict each other in places (if I am reading it correctly—could be me!), and, in addition, the main point of the study is not fully developed in the discussion. If the above suggestions are implemented, the numbers clarified, the limitations flushed out a bit, and the main purpose more clearly nailed down—this could be a very helpful paper.
Reply: Thank you for your advice. We added the speculative reason for “TRD group with preop IVB has more re-operations” in the discussion section on line 17-20 on page 8.
The numbers are contradictory because one number is the rate of re-vitrectomy, one number is the rate of no reoperation, and my expression is not clear, so I apologize for your troubles.
Thank you again for your careful, serious and responsible review.

We tried our best to improve writing and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for Editors’ and Reviewers’ warm work earnestly and hope that the correction will meet with approval.

We appreciate your consideration of our manuscript, and we look forward to receiving comments from the reviewers.
Thank you again and best regards.

Sincerely,

Zongduan Zhang