Author’s response to reviews

Title: Efficacy of intravitreal ranibizumab combined with Ahmed glaucoma valve implantation for the treatment of neovascular glaucoma

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Version: 6
Date: 27 September 2015

Author’s response to reviews: see over
Dear April Rada

Thank you very much for your letter and the comments from the referees about our manuscript (MS: 1586084483169159). We have checked the manuscript and revised it according to the comments.

Yours

Min Tang

Response to Angeline M Nguyen:

Thanks very much for your comments.

Major compulsory revisions:

1) There is no information provided about how patients were educated about their options for intravitreal injection. Please provide details about the education process and some explanation of how patients came at their final decisions.

Ranibizumab was allowed to be used in Ophthalmological clinic in China from 2012, just before the beginning of our study. Chinese Medical Care dose not afford this therapy, and patients should pay by themselves. It belongs to off-label use in NVG here.

NVG patients through preliminary screening (those who needed an operation) would be educated about IVR on its effect, side-effect, risks, price and so on, then they chose to accept IVR before AGV implantation or AGV implantation only at the discretion of themselves and signed an informed consent.

From my point of view, the patients made their decisions mainly according to their economic base. As a non-randomized study, to certain extent, bias would be inevitable between the two groups.

We added patient education and grouping method to revised MS. Line 47-50

2) Patients were not excluded on the basis of having had prior intravitreal injection outside of three months. Please explain the rationale for this.

IVR was used in picnic just before the beginning of our study, and mostly in AMD or PCV. No subject in our study had used Ranibizumab before. Our original intention was to exclude those who had intravitreal hormone (usually TA) inside three months. We believe these drugs have their function and probably affect the IOP mainly inside first three months. Finally, no subject in our study had used TA before. But with Ranibizumab more and more widely being used in China, this problem will be complex in future.

We supplied this content to revised MS. Table 1

3) Are patients also excluded if the basis of having had prior PRP? If not, then was neovascularization of the anterior segment suppressed as much as possible with PRP prior to glaucoma surgery? Please clarify.

PRP is a necessary step in NVG treatment. We found many patients here had done incomplete PRP or even none pre-surgery, and it might one of the causes of NVG occurrence. We tried to do PRP for patients before IVR or AGV if possible, and evaluated again whether they needed IVR or AGV, or could be enrolled. As to those who could not accept PRP due to very high IOP or corneal edema pre-surgery, we applied this therapy just after surgery, usually 1 or 2 weeks later. Our study
did not take PRP before as a criterion for exclusion, but patients would not be enrolled if their IOPs were controlled by PRP before AGV implantation (IOP <= 21 mm Hg). We added this content to revised MS. Table 1 and Line 31-32 and Line 56-61

4) Please include in Table 1 the number of patients who had received prior injection at different intervals prior to the study.
Prior injection, PRP and NVI/NVG degree and angle-closure degree were added. Table 1

Minor essential revisions:
1) Success and failure of treatment should be defined in the Abstract.
Because of the limitation of length, we only added surgical success definition in the abstract. We defined success and failure in detail in Methods. Line 102-110

2) Please include criteria for diagnosis of NVG in the method.
Diagnosis of NVG was included in the method. Line 28-30

3) Since this is ultimately a negative study, it would help to mention power calculations.
We added survival analysis for success rate and Kaplan-Meier graph. Figure 1

4) Line 32 The assumption is that patients are only included in the study if their IOP is >= 22 despite maximizing glaucoma medications. Please state this more clear in the methods.
The mean of three consecutive outpatient IOP measurements just before surgery was used as the baseline IOP. IOP > 21 mm Hg, with or without anti-glaucoma medications or panretinal photocoagulation (PRP) before; (1 mm Hg = 0.133 kPa, Goldmann applanation tonometer) We added in Line 28-32 and Line 94-95

5) For the injection group, what was the rationale for the 3-14 day interval prior to surgery? Was surgery performed after confirmation of regression of iris/angle neovascularization? Were there other considerations used such as IOP and severity of optic nerve damage? Please clarify.
We decided the interval mainly by IOPs. On one hand, we needed some time to observe the effect of IVR; on the other hand, we would not want to bring additional damage to patients' optic nerve because of high IOPs. So our criteria were as follow:
3 days after IVR
1) IOP <= 21: exit from the study
2) 21 < IOP < 40: surgery on day 14th
3) IOP >= 40 surgery immediately
We added in Line 68-72

6) Line 52-54: Provide criteria for requiring additional adjunctive therapy. Also, include need for PRP as a criterion for dropout.
PRP is a routine therapy for severe DR or CRVO or BRVO. Even a complete PRP pre-surgery could be insufficient during follow-up to a patient. Some patients may need additional laser therapy if their retinal conditions go worse. So we did not take PRP as a criterion for dropout.
7) Limitation of the study should be stated.
   We stated in the discussion of revised MS. **Line 265-267**

8) Table 2: The title should be renamed to exclude the word “decline”.
   **Table 2** was renamed.

Discretionary revisions:
1) Because of the limitation of length, we explained these contents in discussion.
2) We changed in **Line 95-96**
3) Because of the limitation of length, we did not explain in detail.
4) We changed in **Line 100-102**
5) We changed to LogMAR in revised MS. **Table 4**
6) We changed in **Line 189**

Response to Pradeep Ramulu:
Thanks very much for your comments.

Major compulsory revisions
1) It is not entirely clear from the MS why these 2 groups of patients exist. In other words, why did some patients receive preop ranibizumab while others did not? At one point, the authors imply that those that did not refused the ranibizumab.
   Ranibizumab was allowed to be used in Ophthalmological clinic in China from 2012, just before the beginning of our study. Chinese Medical Care dose not afford this therapy, and patients should pay by themselves. It belongs to off-label use in NVG here.
   NVG patients through preliminary screening (those who needed an operation) would be educated about IVR on its effect, side-effect, risks, price and so on, then they chose to accept IVR before AGV implantation or AGV implantation only at the discretion of themselves and signed an informed consent.
   From my point of view, the patients made their decisions mainly according to their economic base. As a non-randomized study, to certain extent, bias would be inevitable between the two groups.
   We added patient education and grouping method to revised MS. **Line 47-50**

2) An important consideration in who dose/dose not receive ranibizumab is the presence/severity of NVI/NVA. Are data available on this finding? For example, if ranibizumab was not given to those with more severe NVI/NVA, then the findings may be biased.
   We did not take The severity of NVI/NVA as a standard for grouping. Really this factor could affect the result. In revised MS we added prior injection, PRP and NVI/NVG degree and angle-closure degree of the two groups to **Table 1**.

3) Also, it is important to known what percentage of patients in each group had received preop PRP, as that would also be expected to control neovascularization, and perhaps obviate the need for ranibizumab.
PRP is a necessary step in NVG treatment. We found many patients here had done incomplete PRP or even none pre-surgery, and it might one of the causes of NVG occurrence. We tried to do PRP for patients before IVR or AGV if possible, and evaluated again whether they needed IVR or AGV, or could be enrolled. As to those who could not accept PRP due to very high IOP or corneal edema pre-surgery, we applied this therapy just after surgery, usually 1 or 2 weeks later. Our study did not take PRP before as a criterion for exclusion, but patients would not be enrolled if their IOPs were controlled by PRP before AGV implantation (IOP \( \leq 21 \) mm Hg).

We added this content to revised MS. **Table 1** and **Line 31-32** and **Line 56-61**

4) The proper method to analyze these data is survival analysis, in which patients who had less than 1 year of followup were not excluded.....

We used survival analysis in revised MS. **Figure 1** and **Line 137-139**

5) The authors state that only 30% of control group failed, though the failure criteria are IOP > 21, and the mean IOP throughout the first 6 months is consistently greater than 21 mm Hg, suggesting that the failure rate should be even higher. The reason for this discrepancy should be explained.

We believe several relative high IOPs data affect the results.

For example: at 12 months, in control group, IOP: 12 18 18.5 19.5 19.5 19.5 20 20 20.5 20.5 21 21 25 26.5 28 29 29.5 30 mean: 22.1 std: 4.7 min: 12 max: 30 success rate: 13/19

6) In such studies, it is almost impossible that every patient provides data for every postoperative timepoint, due to missed appointments, sickness, etc. The authors need to detail how often this happened and how it was dealt with statistically.

Such phenomenon is inevitable in long time follow-up. In our study, we provided the follow-up time points were 2w \( \pm \) 1d, 1m \( \pm \) 3d, 3m \( \pm \) 5d, 6m \( \pm \) 7d, 12m \( \pm \) 14d, we would remind every subject by telephone or letters when the dates were coming, and if subjects could not finish follow-ups in time, they would be regarded as dropout cases. Totally the rate of dropout was 14.0%. **Line 95-96 126-132**

7) It is not clear to me what the authors mean with regards to “mildly ligating” the tube. What is the purpose of this? How dose when regulate the lever of ligation? With what suture dose this ligation take place?

We believe “mildly ligating” has two functions: Firstly, it can fix the tube on the surface of sclera; secondly, it can limit the aqueous outflow in the early stage (1~2 weeks after AGV), and it will not affect long time outflow, for we use 8.0 absorbable suture forming a light indentation. Many surgeons in China do like this.

8) I do not understand the VA data, as they are presented neither as a Snellen value or logMAR value. The authors should use a VA scale that would be understood by all ophthalmologists.

We used logMAR value in Revised MS in **Table 4**.

9) The Tables have a lot of confusing elements. For example...

We rectified all the Tables.
10) Survival data should be presented as Kaplan-Meier graphs, and not only in Table format. We added survival analysis for success rate and Kaplan-Meier graph. Figure 1

Minor compulsory revisions
11) The first sentence of discussion should be omitted, as it is not a result of the paper. We omitted the sentence. Line 179

12) While an IOP < 6 has broadly used as a criterion for failure, many eyes with IOPs of 5 or less do just fine. The number of eyes “failure” by this criterion should be specified, and it should be mentioned if sequelae of these low IOPs were present. We defined $6 \leq IOP \leq 21$ as a criterion for success, as this criterion has been broadly used. In our study, no IOP < 6 was found during follow-up. Table 2

13) In Line 147 the authors say that 3 pts had blood clots, and in line 157 they say blood clots developed in 4 patients. 3 patients in injection group and 4 patients in control group Line 160 and Line 167

14) The reasons for using MMC as part of the surgery should be described. The effect of using MMC in AGV implantation for NVG is still doubted. As we know, most surgeons here still tend to use MMC. In fact, we can not tell it is helpful or not, for we have few data from clinical trials in China.