Author’s response to reviews


Authors:

Tingting Jiang (ting5680@126.com)
Junxiang Gu (eent_gu@126.com)
Peijun Zhang (eent_zhang@126.com)
Wenwen Chen (eent_chen@126.com)
Qing Chang (eent_chang@126.com)

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Author’s response to reviews:

Dear Editor:

We have enclosed a copy of our revised manuscript, titled "The effect of adjunctive intravitreal conbercept at the end of diabetic vitrectomy for the prevention of post-vitrectomy hemorrhage in patients with severe proliferative diabetic retinopathy: a prospective, randomized pilot study." We would like to thank the reviewers and the editor for their important and instructive comments. The manuscript has undergone a revision accordingly and the point-by-point response are listed on the following pages.

Thank you very much for your careful considerations. We sincerely hope that our efforts have resulted in a better presented manuscript that could be acceptable for publication in BMC Ophthalmology.

Sincerely,
Qing Chang, MD, Ph.D.
Professor of Ophthalmology
EENT Hospital
Shanghai, P.R. China

Point-by-point response to Referee(s)' Comments to Author:

Reviewer reports:

David Steel, MD (Reviewer 1):

1. The manuscript is well written and clear

In this small initial pilot study the authors found that the use of Conbercept at the end of surgery had no effect on any of the outcomes tested. Although a pilot study I think details of masking of outcomes, reasons for the small sample size chosen as well as randomisation methods should be included. Similarly as a non powered pilot I think the conclusions of lack of effect can’t really be stated - the study showed no adverse effects and could be used to power a definitive study but I don’t think the authors can be so definitive about their conclusions as they are - especially regarding early POVCH.

2. The authors could usefully report more on their findings in the few patients with late POVCH - was high frequency ultrasound performed to look for sclerostomy ingrowth or sclerostomy ingrowth seen during re-operation? - see Entry site neovascularization and vitreous cavity hemorrhage after diabetic vitrectomy. The predictive value of inner sclerostomy site ultrasonography. Ophthalmology. 2008 Mar;115(3):525-32 and Entry site treatment to prevent late recurrent postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy. Br J Ophthalmol. 2010 Sep;94(9):1219-25 - both articles provide data on the causes of late POVCH and why a lack of effect may not be seen with anti VEGFs at end of surgery.
Response: Thank you for raising this question. In all the patients undergoing reoperation in our study, the surgeon checked the entry site carefully, and found no neovascularization at the sclerostomy sites through deep scleral indentation. Someone just had a simple vitreous cavity washout while others added retinal laser photocoagulation. We were careful to remove peripheral vitreous as much as possible, especially around the sclerostomy areas through deep scleral indentation during the first surgery. After the second surgery, no one has vitreous cavity hemorrhage again during the follow up. Entry site neovascularization may be considered as a common cause of late recurrent vitreous cavity hemorrhages (VH), however, not all late postvitrectomy hemorrhages for PDR are caused by it.

A high level of VEGF in the vitreous fluid has been identified as a significant risk factor for the outcomes of vitreous surgery in patients with PDR. (Risk evaluation of outcome of vitreous surgery based on vitreous levels of cytokines. Eye 2007;21:377–382.) It is also well known that after vitrectomy, there is a VEGF surge acting as a stimulant for iris neovascularization or fibrovascular proliferation that may lead to VH. (Physiology of vitreous surgery. Graefes Arch Clin Exp Ophthalmol 2009;247:147–63) Therefore, intravitreal anti-VEGF injection at the end of surgery, could inhibit VEGF elevation effectively, inhibiting retinal neovascularization, a potential cause for postoperative VH. Also, Inhibition of VEGF activity could stabilize the vascular permeability. However, faster vitreous clearance rates for medications in vitrectomized eyes have been observed, the anti-VEGF drugs injection may only have their effects during the early postoperative period, which resulting in similar late VH incidence as those of the control group.

Kyung Seek Choi, M.D., Ph.D. (Reviewer 2): The authors reported the effect of intravitreal conbercept injection for preventing of rebleeding after vitrectomy.

1. First of all, there are different condition of eye and surgical indications vary from simple vitreous hemorrhage to retinal detachment.

The authors should describe the intraoperative findings after removal of vitreous hemorrhage and any events related with hemorrhage.

Response: Thank you for raising this question. Due to masking of the retina by vitreous hemorrhage, we evaluated the range of the vasoproliferative membranes during surgery. In the IVC group, the extent of the vasoproliferative membranes was 1.33±1.4 quadrants compared with 1.2±1.47 quadrants in the control group (P=0.8). (Table 4) Various degrees of vitreous-retina adhesion were found in our patients, some had tractional retinal detachment.
2. What is the cause of rebleeding after surgery on early and late period postoperative vitreous hemorrhage?

The authors show the data of postoperative hemorrhage on Table 4. There were many severe graded vitreous hemorrhage cases in IVC group on Day 1.

The authors evaluated postoperative bleeding cases based on 4 weeks after surgery, early and late. I think the grade of hemorrhage of POD 1 day affect the status of POD 1 week.

Response:

Thank you for raising this question. Reactivation of fibrovascular tissue remnants at the retinal sites may represent the cause of early postoperative vitreous hemorrhage (POVH) while anterior hyaloidal fibrovascular proliferation, or sclerotomy site neovascularization, may represent the cause of late POVH. In addition, vitreous hemorrhage is closely related to blood glucose control. The grade of POVH 1 day may have some effect on the status of POVH 1 week but not so much. The clearance of POVH is related to the severity of recurrent bleeding and to the speed of clearance of vitreous cavity blood. The speed of clearance may be partly related to the thoroughness of anterior vitrectomy. In our study, there were many severe graded vitreous hemorrhage cases in IVC group on Day 1, while 1 week later, the vitreous hemorrhage cleared in most of the patients, indicating the effect of the conbercept injection to some extent.

3. Are there any other treatment for the patients who has rebleeding after surgery?

Response:

Thank you for raising this question. If the vitreous hemorrhage couldn’t cleared spontaneously, vitreous cavity washout would be done. There is no any other treatment for the patients who has rebleeding after surgery.

4. I think that intravitreal anti-VEGF have increased clearance in vitrectomized eye. The authors use 0.5 mg of conbercept.

How's the pharmacokinetics of intravitreal conbercept in vitrectomized eye. Is it enough to prevent postoperative vitreous hemorrhage?
Response:


5. The authors evaluate the effect of conbercept for one year, late postoperative vitreous hemorrhage. After single injection of conbercept, did it work during 1year?
Response:

Thank you for raising this question. Conbercept could bind not only VEGF-A, but also VEGF-B, and placental growth factor (PIGF)—all with high affinity. The preclinical studies have shown that conbercept has advantages over ranibizumab and bevacizumab in that it has a longer half-life and a stronger binding affinity to VEGF-A. (Serum levels of vascular endothelial growth factor before and after intravitreal injection of ranibizumab or conbercept for neovascular age-related macular degeneration. Retina. 2017;37:971–7. The pharmacology study of a new recombinant human VEGF receptor-fc fusion protein on experimental choroidal neovascularization. Pharm Res. 2009;26:204–10)

However, it can be concluded that a single intravitreal injection of conbercept produces transient rather than sustained effects specially in vitrectomized eyes. Preoperative intravitreal injections of conbercept has been reported to decrease the risk of postoperative early VH based on a 24-month follow-up data.( Efficacy comparison of intravitreal injections of conbercept and ranibizumab for severe proliferative diabetic retinopathy . CAN J OPHTHALMOL. 2019,54(3)

In a previous study, the results showed that the intravitreal injection of conbercept at the end of the vitrectomy for PDR without tractional retinal detachment lead to a better postoperative visual acuity, thinner central retinal thickness and less frequent VH recurrences at 24 weeks.( Safety and efficacy of intravitreal conbercept injection after vitrectomy for the treatment of proliferative diabetic retinopathy eye 2019) It also has been suggested that intravitreal conbercept at the end of surgery had limited effect on reducing macular edema after surgery, and had an upward trend in foveal thickness and macular volume in periods longer than 6 months.( Effect of intravitreal conbercept vs triamcinolone acetonide at the end of surgery on macular structure and function in patients with severe proliferative diabetic retinopathy Int J Clin Exp Med 2017;10(10):14511-14518)

In our pilot study, intraoperative IVC did not appear to have an encouraging effect on the rate of postoperative VH and visual recovery. However, there was not an upwards trend in mean macular thickness; even when measured 6 months after surgery. This may be due to the small sample size of our study. Meanwhile, in our study, there is a discrepancy between the foveal thickness and the vision acuity in the injection group. The reduction in macular thickness was not accompanied by significant improvement in vision acuity. The decreasing CRT was associated with macular atrophy and destruction of the outer structure of the retina, which all lead to poor vision prognosis.

6. The authors should describe the fundus status after surgery including fluorescein angiography for new vessels and non-perfusion areas.
Response:

Thank you for raising this question. Fluorescein angiography was not performed on all the patients because some patients were allergic to contrast agents. For those who had finished Fluorescein angiography 6 months after surgery, no obvious neovascularization and no perfusion area were observed.