Author’s response to reviews

Title: Vitreous Hemorrhage and Rhegmatogenous Retinal Detachment that Developed after Botulinum Toxin Injection to the Extraocular Muscle: Case Report

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Author’s response to reviews:
The authors' response letter has been included as a supplementary file.

Sep. 11, 2017

Dr. Cecilia Devoto
Editor-in-Chief
BMC Ophthalmology
Email: em@editorialmanager.com

Dear Dr. Devoto,

Thank you very much for your review, and for pointing out several important issues in our manuscript entitled, "A Case of Vitreous Hemorrhage and Rhegmatogenous Retinal Detachment that Developed after Botulinum Toxin Injection to the Extraocular Muscle” (BOPH-D-17-00420). We hereby submit a revised manuscript to BMC Ophthalmology ® for publication.

We found the reviewers’ comments to be very thoughtful and appropriate. Therefore, we tried our best to answer their questions, and revised the manuscript according to the suggestions given by the associate editor and the reviewers. After addressing the comments, we believe that the
quality of our manuscript has substantially improved. All contributing authors of this study have reviewed the revised manuscript, and have agreed to all of the changes made to the manuscript as well as to the way his or her name is listed. We hope that our revisions will help the readers of BMC Ophthalmology® better understand our manuscript. For ease of reference when reviewing, we have provided both a clean copy of the revised manuscript and another copy with all revisions highlighted in yellow.

Once again, we would like to thank the editor-in-chief, section editors, associate editors, and the reviewers for their constructive suggestions that helped strengthen our manuscript. We hope that our revised manuscript will meet the requirements for publication in BMC Ophthalmology®. Thank you in advance for your kind consideration, and we look forward to hearing a positive reply from you soon.

Sincerely,

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Response to Editorial Reviewers’ Comments

Reviewer Comments:

Reviewer #1:

Dear Kim et al,

Thanks a lot for your interesting manuscript.
Though this report describes an important consideration and rare complication, apart from the comments by the reviewers' there are some important drawbacks. I agree with the suggestions by both reviewers, and they should be appropriately addressed.

1. The English language needs appropriate corrections throughout as marked in the highlighted file.

-> Thank you for your comment. We made the following corrections:

(page 3, 1st para, lines 2-3) We corrected as follows: "In addition to cosmetic uses,"

(page 3, 1st para, line 3) We removed the phrase “into the extraocular muscle.”

(page 4, 1st para, line 27) We deleted the word “bilateral.”

(page 4, 1st para, line 29) We changed the expression “alternative cover test” to “alternate cover test” throughout the manuscript.

(page 4, 1st para, lines 34) We corrected as follows: “angle of deviation did not improve,”

(page 4, 1st para, line 35) We changed the word “RLR” to “RMR” throughout the manuscript.

(page 5, 2nd para, line 65) We deleted the misspelled “am” as follows: "am electroretinogram (ERG) test"

2. Further some of the terms are not used appropriately:

- alternate cover test is mentioned as alternative cover test

-> We realized that we had misspelled the English term. So we changed the phrase “alternative cover test” to “alternate cover test” (page 2, 2nd para, lines 7 and 15-16; page 4, 1st para, lines 29 and 45-46).

- right medial rectus is abbreviated as RLR,

These are serious concerns to accepting the manuscript.

-> We changed the term “RLR” to “RMR” (page 2, 2nd para, lines 9 and 16; page 4, 1st para, lines 35 and 46).
3. There is no need to bold the titles in references.

-> As you suggested, we removed bold processing in reference titles.

4. Last the manuscript describes basically a concern of inadvertent globe perforation and rhegmatogenous retinal detachment, which is well reported in the literature. They do not mention any concern about the Botulinum toxin going into the eye. Please add relevant literature.

The following manuscript can be a good reference.


-> Following your advice, we cited a paper published by Pehere N et al. and mentioned potential toxicity of botulinum toxin in the discussion section:

(page 5, 2nd para, lines 69-74) “Pehere N et al. reported a case of unintentional injection of botulinum toxin into the eyeball that recovered without any complications other than a slight increase in intraocular pressure [18]. In our case, small amount of botulinum toxin, which might have been injected into the eyeball, did not affect the final visual acuity or intraocular pressure. To sum up, these reports suggest that, in most cases, botulinum toxin injected inadvertently into the eyeball does not appear to be toxic.”

Reviewer #2

Niranjan Pehere (Reviewer 1): Dear authors:

Thanks for submitting your work. I have a few queries:

1. The decision to give botox after 6 months of observation looks controversial. Generally botox is given in early phase. Later fibrosis sets in and both may not be effective.

-> At first, we diagnosed paralytic strabismus in the patient, and followed up for 2 months. However, the patient did not visit the outpatient clinic since then, so further follow-up was unavailable. The patient re-visited at 6 months after the first symptom had developed. We described this in the manuscript as follows:
The patient was diagnosed with paralytic strabismus, and we planned to observe her for about two to three months to check changes in the amount of deviation. However, as the patient failed to visit outpatient clinic since then, further follow-up was unavailable. She revisited at 6 months after the development of her first symptom.

2. As a part of surgery for the RD, what intravitreal bevacizumab was given?

-> Several studies have been conducted regarding the possibility that increased VEGF levels in PVR may be associated with pathogenesis of PVR. Of course, no study has yet reported that intravitreal injection of bevacizumab inhibits recurrence of PVR-related RD or improves visual prognosis. However, since these studies were conducted on a small number of patients, more prospective studies, including a lot of patients, are needed. We used bevacizumab in anticipation of counteracting the potential VEGF-mediated changes, and thus ameliorating postoperative PVR.

3. Was macula on or off when RD was noticed?

-> Patient's fovea was attached. We added the following description:

Optical coherence tomography (OCT) examination revealed subretinal fluid nasal to the fovea, but central fovea was attached.

4. Poor English- page 4, line 31-32

-> We corrected the mentioned part as follows:

“The patient was diagnosed with paralytic strabismus, and we planned to observe her for about two to three months to check changes in the amount of deviation. However, as the patient failed to visit outpatient clinic since then, further follow-up was unavailable. She revisited at 6 months after the development of her first symptom.”

5. Gap of 19 weeks following botox inj and RD surgery is too long.

-> Initially, only a mild vitreous hemorrhage was seen, and the tear was not large; therefore, the patient was observed after receiving barrier laser photocoagulation around the lesion. At first, subretinal fluid and vitreous hemorrhage improved over time. However, 12 weeks after botulinum toxin injection, we found tractional membrane which was suggestive of PVR development, and the patient's visual acuity could not be restored. Since the patient was hesitant to receive surgery, we observed her for 4 more weeks. After that, the patient decided to receive surgery, and pars plana vitrectomy was performed. The following paragraph was added to the manuscript:
(page 4, 1st para, lines 40-45) “The patient was diagnosed with RRD with macula off, but because of small subretinal fluid and tiny retinal break, we decided to observe it first. Barrier laser photocoagulation around the retinal hole was performed. However, the patient’s visual acuity continued to decrease without improvement of vitreous hemorrhage, and at 12 weeks after botulinum toxin injection, a newly developed tractional membrane from macula to inferonasal periphery was noted, suggesting PVR development.”

6. We need details of where was the retinal break

-> We described the location of retinal break in more detail, as follows:

(page 4, 1st para, lines 37-40) “Based on funduscopic examination, a retinal hole was located 4DD (disc diameter) inferonasally from the optic disc, and both preretinal and vitreous hemorrhage were present in front of the lesion. Optical coherence tomography (OCT) examination revealed subretinal fluid nasal to the fovea, but central fovea was attached.”

7. You need to discuss possible reasons for the scleral perforation and ways to avoid it. That’s the key message of the case report.

-> In the discussion section, we discussed possible reasons for scleral perforation in addition to ways to avoid this complication, as follows:

(page 5, 3rd para, lines 81; page 6, 1st para, lines 82-88) “Although the procedure was done under EMG guidance, the patient underwent scleral perforation. Her axial length which was taken before PPV was 25.15 mm, which suggests that the patient might have had moderate myopia. Myopia is known to be a risk factor for scleral perforation in various surgical interventions, including strabismus surgery [22] and retro- or peribulbar anesthesia [23]. Therefore, we concluded that the risk factor was obscured due to past history of refractive surgery. Accordingly, when planning botulinum toxin injection into extraocular muscle, surgeon should be fully aware of patient's refractive error as well as history of any kind of refractive surgery, in order to prevent inadvertent scleral perforation.”

(page 6, 2nd para, lines 96-98) “To prevent such serious complications, surgeons should thoroughly review the patient’s past history and perform detailed examination to identify various risk factors, such as myopia and scleral scar, when planning botulinum toxin injection into extraocular muscle.”

Reviewer #3

Ilana B. Friedman (Reviewer 2): I congratulate the authors on their Manuscript entitled "A case of vitreous hemorrhage and rhegmatogenous retinal detachment that developed after botulinum toxin injection to extraocular muscle." The manuscript is well written. It describes a rare
complication that could be of interest to readers of the journal. There are a couple of points upon review of the manuscript.

1. Firstly in both the abstract and body of the case report in Lines 6 and 14 As well as in the case presentation they use the term alternative cover test as opposed to the proper terminology which is ALTERNATE cover test.

-> We realized that we had misspelled the English term. So we changed the phrase “alternative cover test” to “alternate cover test” (page 2, 2nd para, lines 7 and 15-16; page 4, 1st para, lines 29 and 45-46).

2. In addition, while the injection was done under EMG guidance this was not elucidated until the discussion and should be noted. Given that there is more than 1 method for botulinum toxin injection with respect to direct visualization versus EMG I believe another cautionary statements should be included in that the patient had previous history of refractive surgery which might have alerted the surgeons to the fact that they were previously a high myope and at greater risk of perforation of the sclera due to their refractive error. This might change the approach to direct visualization in order to ensure that there is not an inadvertent perforation even if guided by EMG.

-> We agree with you in that if the patient had previously undergone refractive surgery, such history should be taken into account when planning the surgery. The discussion section was supplemented as follows:

(page 5, 3rd para, lines 81; page 6, 1st para, lines 82-88) “Although the procedure was done under EMG guidance, the patient underwent scleral perforation. Her axial length which was taken before PPV was 25.15 mm, which suggests that the patient might have had moderate myopia. Myopia is known to be a risk factor for scleral perforation in various surgical interventions, including strabismus surgery [22] and retro- or peribulbar anesthesia [23]. Therefore, we concluded that the risk factor was obscured due to past history of refractive surgery. Accordingly, when planning botulinum toxin injection into extraocular muscle, surgeon should be fully aware of patient's refractive error as well as history of any kind of refractive surgery, in order to prevent inadvertent scleral perforation.”