Author’s response to reviews

Title: Lacrimal passage irrigation in children with Stevens-Johnson syndrome or toxic epidermal necrolysis: A five-year retrospective study

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Author’s response to reviews:

Dear Editor,

We are very pleased to learn from your letter that our manuscript entitled "Lacrimal passage irrigation in children with Stevens-Johnson syndrome or toxic epidermal necrolysis: A five-year retrospective study" (Revise # BOPH-D-18-00613) is allowed a revision. Thank you for your attention and the reviewers for their helpful comments and advices. We have revised the manuscript according to the comments from the reviewers, highlighting all changes in the revised manuscript.

We would like to re-submit the manuscript and that the revision is acceptable for publication in the BOPH and look forward to hearing from you soon.

Yours sincerely,

Correspondence to: Dr. Jing Fang, MD.
Point by Point response to editor and reviewer

Editor Comments:

Question #1 Please clarify whether this is a retrospective study. In the methods section it appears that this was a prospective study as you state “And all the subjects recruited in this study received irrigation during the chronical stage of SJS or TEN to identity whether the lacrimal system was obstructed”.

Response: we apologize for the negligence and thank the editor to point out the descriptive mistake. This is a retrospective study. We have deleted “And all the subjects recruited in this study received irrigation during the chronical stage of SJS or TEN to identify whether the lacrimal system was obstructed” in the Method and rephrased the inclusion criterion. (Please see page 6 line 111 to 117, in highlight)

Question #2 As there is data in this study, please revise the section “Availability of data and materials” in the Declarations. See our Submission Guidelines (https://bmcophthalmol.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article#declarations).

Response: we have revised the section according to your advice. (Please see "Availability of data and materials" in the Declarations, see page 14 line 287 to line 292, in highlight).

Question #3 We would also like to ask for you to provide more justification for the contributions of LP, as currently they do not automatically qualify for authorship. Revising a manuscript does not justify authorship as it is not considered as intellectual input. Additionally please further clarify the role of QX.

Response: we have improved the statement of author contributions. (Please see page 15 line 295 to line 297, in highlight).

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Question #4 An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. According to the ICMJE guidelines, to qualify as an author one should have:

a) made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; AND

b) been involved in drafting the manuscript or revising it critically for important intellectual content; AND

c) given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; AND

d) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Response: we have improved the statement of author contributions.

Question #5 Anyone listed as an author must be included in this section. If you choose to change your author list you will need to fill out a change in authorship form and send it by email to the Editorial office to be approved by the Editor. The form can be found here: https://www.biomedcentral.com/getpublished/editorial-policies#authorship.

Anyone who contributed towards the article who does not meet the criteria for authorship can be acknowledged in the ‘Acknowledgements’ section.

Response: Author list does not need to change. No author is deleted and no new author is added.

Reviewer reports:

Anthony Hall (Reviewer 1): The authors have studied a difficult group of patients and attempted to assess the role of NLD irrigation with steroids and antibiotics in children with SJS or TENS

The paper could be improved in several important ways
Methods

Question #1. Line 111. Were all patients included. I.E. was enrolment consecutive?

Response: We assume there is a misunderstanding concerning the patients involved the study. This is a retrospective research, so all the data are from our medical records, instead of enrollment. We are very sorry for your misunderstanding caused by our unclear description, and we have made some revision in the Method part to clear it. We have deleted “And all the subjects recruited in this study received irrigation during the chronical stage of SJS or TEN to identity whether the lacrimal system was obstructed” in the Method and rephrased the inclusion criterion. (Please see page 6 line 111 to 117, in highlight)

Question #2. Line 114. were there any age restrictions on enrolment?

Response: We appreciate the reviewer’s comments. AS a retrospective research, all data involved in the manuscript are collected from Children’s Hospital of Chongqing Medical University, so the patients were all below 18 years old, and without any other age restriction. We have added the age range according to reviewer’ comments. (Please see page 6 line 106, in highlight)

Question #3 Line 126. was the presence of dry eye assessed again in the chronic stage?

Response: We appreciate the reviewer’s comments. Because this is a retrospective study, there is only one record of presence of dry eye assessment in the chronic stage. (Please see Table 2, line 5 to 6, in highlight). And no other record showed that the presence of dry eye in the cases was assessed again in the chronic stage. We appreciate the reviewer to point out the important concern. We will pay attention to this problem in the clinical practice and medical records of patients in the future.

Question #4. Line 129. How were patients randomised? This is especially important to determine of there were any possible biases in enrolment.

Response: We are sorry again for your misunderstanding caused by our unclear description. This is a retrospective research, and without enrollment. The groups were not randomly divided, but based on whether received irrigation. We have rephrased the sentence to avoid confusion in the Method part. (Please see page 6 line 125 to 126, in highlight)
Question #5. Line 140. (1) when was the late irrigation performed? (2) Was this through the lower punctum or the upper or either? (3) How was obstruction defined? (4) How was epiphora determined?

Response: We appreciate the reviewer’s comments.

(1) The subjects received lacrimal passage irrigation twice a week since identified as acute stage for totally four weeks (Please see page 6 lines 126 to 127, in highlight).

(2) Generally, the irrigation was performed through the upper canaliculus to avoid the lower canaliculus damage. If the lower punctum was covered by pseudomembrane, the irrigation performed through both upper and lower punctums. We have added the sentence to describe this step. (Please see page 7 line 134 to 137, in highlight)

(3) The nasolacrimal duct was defined as obstruction when the irrigation solution was refluxed through the upper or lower punctum. We have rephrased the sentence about the obstruction of lacrimal passage. (Please see page 7 line 138 to 140, in highlight)

(4) Epiphora was determined if the discharge of tears was blocked and confined in the eyes. We have added the definition of epiphora. (Please see page 7 line 140 to 141, in highlight)

Results

Question #6 How many of the patients had obstruction acutely? I.E. At the time of the twice weekly lavage with steroid and antibiotics, were patients obstructed then and if so, how was this managed? this is important to determine what, if any, is the role of mechanical syringing and what, if any, is the role of the steroids and antibiotics.

Response: We appreciate the reviewer’s comments. Totally, there were 16 patients had obstruction in the chronical stage. Two patients were in the irrigation group, and fourteen were in the control group. The data were showed in Table 2 (Please see Table 2, line 2, in highlight). In this retrospective study, we didn’t find a case that had obstructed during the acute stage when received the irrigation. There maybe two reasons we think that lead this result. In one hand, the sample size is too small, if we enlarge the size, may have the different result. In our further study, we would pay attention to this situation. In another hand, in the acute stage, the adhesion of the nasolacrimal duct may not happen so fast. The role of mechanical syringing is to make the nasolacrimal duct unobstructed by the flush pressure, and we have added this point to the manuscript. Besides, a timely irrigation can also avoid the occlusion of the upper and lower puncta caused by pseudomembranes. The role of steroids is to reduce the adhesions in the
mucosa of lacrimal system involved in SJS or TEN. The role of antibiotics is to reduce the intraoperative infection.

We have made some revisions according to the reviewer's advice. (Please see page 11 line 219 to 229, in highlight)

Question #7 Discussion. Discussion is needed regarding possible enrolment bias. were just bad patients enrolled as it was thought they might benefit. were milder patients enrolled as they may have been easier to syringe? This needs to be addressed.

Response : We agree with the reviewer’ opinion that the data involving the different individuals may have possible bias because of the severity of symptoms. In this retrospective study, according to their medical records (please see Table 1), all patients included were had eye damage, and the moderate-severe SJS/TEN cases were more commonly to have eye damage, so we had enrolment bias indeed and unavoidable. During our future research, we need to collect more samples including more mild patients with eye damage to avoid the bias. We have added some sentences in the Discussion part according to the reviewer's advice. (Please see page 12 line 251 to 253, in highlight).

Question #8 The Cause of any possible benefit of syringing needs to be addressed. Was it the mechanical lavage that proveded the benefit or was it the steroids or the antibiotics?

Response : We appreciate the reviewer’s comments. We have discussed the possible benefit of syringing in the discussion section. The benefit of syringe is a combination of physical irrigation, steroids and the antibiotics. The mechanical lavage maybe involve in the physical flush pressure of irrigation and the anti-inflammatory and anti-infective effect of eye drops. We have added a sentence in the discussion part according to the reviewer’s advice. (Please see page 12 line 232 to 234, in highlight).

Charles Bouchard (Reviewer 2):

Question #1 I understand that this is a retrospective review. Please explain why it was decided to irrigate some patients and not others.
Response: We appreciate the reviewer’s comments. We usually gave the patients irrigation once they had pseudomembranes covered their puncta in our clinical practice. We have added this point in the Methods section. (Please see page 6 lines 122 to 124, in highlight).

Question #2 Also, any indication that dry eye/corneal disease worsened in any patients who had their lacrimal system irrigated with dexamethasone due to tear deficiency?

Response: We agree to the reviewer's opinion that irrigation with dexamethasone has the risk of dry eye/corneal disease worsened. Usually, the moderate-severe SJS/TEN cases needed to accept systemic glucocorticosteroid treatment no matter patients had eye damage or not. In this study, however, all patients did not be recorded dry eye/corneal disease worsened through irrigated with dexamethasone. This result may be due to a small number of subjects. In our further study, we need to observe more patients to confirm this question. We have added a paragraph to state the risk. (Please see page 12 line 236 to 241, in highlight).

Question #3 There are significant grammatical errors throughout the manuscript that should be fixed prior to publication.

Response: We thank the pertinent suggestion of the reviewer. We have made some revision of this manuscript according to the suggestion.

Question #4 Were any complications from this procedure noted?

Response: There is no complication from this procedure, and we have added this point in Method part. (Please see page 7 line 141, in highlight)

Question #5 It is hard to garner conclusions from Table 2 - is there a way to reorganize the information so that significant trends or important conclusions can be easily made from it?

Response: We appreciate the reviewer’s comments and have reorganized Table 2 following your advice. We hope the revision could be easier to understand.

Question #6 Has this procedure been done before in this patient population? If so - this information with references should be included in the Background section. If not, how was it decided to perform this procedure?
Response: We appreciate the reviewer’s comments. There has no report that using lacrimal duct irrigation as a usual treatment in the SJS and TEN up to now. However, this procedure that using the topical dexamethasone to reduce recurrence of lacrimal duct obstruction was frequently adopted in lacrimal passage probing in china, and had been reported. (Xu J, Hong J, Sun X, Liu Z, Mashaghi A, Inomata T, Lu Y, Li Y, Wu D, Yang Y et al: Combined Lacrimal Passage Probing and Tobramycin/Dexamethasone Ophthalmic Ointment Infiltration: A Minimally Invasive Surgical Procedure for Incomplete Nasolacrimal Duct Obstruction. Medicine 2015, 94(36):e1483.)

Zafer Onaran (Reviewer 3):

Question #1 Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Response: We have made revisions including manuscript, graphs and supporting materials according to the suggestions of editor and all reviewers.

Question #2 A well designed study evaluating the lacrimal drainage system obstruction in TEN and SJS. The successful results of the lacrimal irrigation in the acute phase of these diseases could encourage the readers to apply this method on their patients. One thing that needs to be clarified is the p value that cant be understood (p = 1.56E-05 ) in the text.

Response: We have changed all p = 1.56E-05 into p< 0.01 in our revision manuscript. (Please see page 2 line 36, page 8 line 168, page 9 line 186, in highlight)