Author's response to reviews

Title: Microbiological Analysis of Office-based three-port Microincision Vitrectomy Surgery

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Version: 2 Date: 11 December 2013

Author's response to reviews: see over
Responses to Reviewers’ comments

Responses:
We would like to take this opportunity to thank the reviewers for their thorough and constructive comments and encouragement to our paper. Our detailed responses to the comments are as follows.

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Reviewers’ comments:

Reviewer #1:

Major Compulsory Revisions:

1) Imprecise language: The purpose of the study is not clear at first read through the actual text, and this is due in part to some of the vague language (the abstract is more informative). Phrases such as “microbiological analysis of office-based …vitrectomy” or “microbiological profile of office-based vitrectomy, or “bacterial load,” do not clearly express the objectives of the study. In simpler terms, this paper evaluates the vitreous contamination rate of office-based vitrectomy with the Intreector. The authors should revise the title and avoid the use of such language in the text.

Responses:
We appreciate your input. We have taken all your comments and suggestions to heart and have striven to make changes to the wording of the text, to remove redundancies and to clarify vague sentences. The title has also been modified to “Evaluation of the vitreous microbial contamination rate in office-based three-port microincision vitrectomy surgery using Retrector technology” to better reflect the goal of the study.

2. Unclear purpose: The surgeries performed were essentially just sample acquisition for culture and lipidomics. These were vitreous biopsies – little more than a vitreous and tap inject procedure – and not representative of the broad spectrum of vitreoretinal surgery. This should be more explicit. This study therefore most directly addresses the question of whether or not the creation of transconjunctival ports with this particular vitrectomy system leads to high vitreous contamination rates. The setting of the procedure does not seem as relevant - it is hard to imagine that the setting (ie, OR vs. a minor procedure room
with sterile technique) would affect this vitreous contamination rate in a measurable way in an uncontrolled study of 37 patients undergoing only a vitreous biopsy. Although the surgical setting is interesting, the authors should place more emphasis on the instrumentation instead - it may be useful to include diagrams/images further detailing the characteristics of the three port-entry systems.

Response:
Thank you for this comment. The purpose of the study has been rephrased to more clearly emphasize its goal. It now reads as follows: “In this prospective study, we sought to assess the rate of vitreous bacterial contamination and translocation following three-port office-based vitrectomies performed in an office setting using the Retrector® portable vitrector.”

As the reviewer clearly points out, what has been achieved so far in this cohort of patients is a three-port vitreous biopsy and intravitreal injection procedure. However, the same set-up and technique can easily be transferred to more complex retinal procedures such as a limited retinal detachment procedure etc. We also respectfully believe that the setting (OR vs minor procedure room) is pertinent. Just as it is currently not routine to perform a standard 23 or 25-ga three-port vitrectomy in the clinic, the in-office procedure as we describe here is one step in that direction.

We also agree with the reviewer that pictorial and diagrammatic support to further detail our technique is essential. To achieve this means, we have several video recordings of the set-up, procedure and surgical view during a case. If these are of interest to the editors, we would be happy to provide the videos and upload them as supplemental material in conjunction to the manuscript.

3. Data inconsistency: the results in the abstract do not correspond with the text re: culture results of the undiluted and diluted samples. This is a key result and the inconsistency in the reported data is concerning. The abstract also mentions the evaluation of antibiogram sensitivities but this is not reported in the text.

Response:
Thank you for pointing this out. The inconsistencies and discrepancies in results between the abstract and the manuscript have been eliminated and now reflect the final confirmed findings.

As for the antibiogram sensitivities, it is true that they were evaluated in this study. However, since each of the 26 culture positive colonies had its specific antibiogram sensitivity, we felt that this information would weigh down the content of the text and does not contribute additional information to our conclusion. have removed it from the abstract to avoid confusion and discrepancy.
Miscellaneous compulsory revisions

4. The quoted rate of 0.80% for standard MIVS is very high and an outlier. This is misleading when listed in juxtaposition with the single study reporting a 0.17% rate with the Intrector. (see “Discussion”, paragraph 1) Please revisit the references and only use the strongest studies on modern MIVS endophthalmitis rates.

Response:
The sentence has been modified to reflect the most recent data on the subject from 2009 onward. It reads: Comparatively, modern endophthalmitis rates for standard 23-ga and 25-ga MIVS are reported at around 0.02-0.10%, although values ranging from 0.02%-0.80% have been reported throughout the years.”

5. Note that with a single surgeon and prospective uncontrolled design, it is hard to make definitive conclusions from this study. In the present prospective study, it is likely that the single experienced surgeon can pay meticulous attention to sterile procedure and limit vitreous contamination. The authors should include some comment re: the external validity of this study as a limitation.

Response:
This limitation has been added in the discussion section.

6. Note: “avoiding hypotony” (see under “patients and methods, vitrectomy”) is misleading, as all these eyes likely had hypotony after removal of a “minimum of 0.5ml” of fluid.

Response:
Thank you for this comment. This has been modified to “…manual aspiration, all the while visually monitoring for and avoiding globe collapse. “ You are completely correct in pointing out that we could not check accurately for IOP and hypotony intra-operatively. Our goal rather was to use visual cues to avoid globe collapse.

Minor essential revisions:

7. The authors describe their sterile technique and surgical technique in good detail. Please include further details from the figure 1 caption in the paper’s text (ie, not a positive pressure room, no surgical gown).

Response:
This information has also been added into the manuscript text.

8. The authors appropriately describe their culture/assay. The low conjunctival
culture yield is concerning but the techniques the authors used are consistent with those of other similar studies and the authors appropriately acknowledge this.

Response:
Thank you for this comment.

9. Please proofread the paper for grammatical and spelling errors prior to resubmission.

Response:
Thank you for this comment. The paper has been reviewed again meticulously to remove any grammatical and spelling errors.

Discretionary Revisions

10. Findings don’t entirely support conclusions: The authors imply in the manuscript (not in the abstract) that the findings from the study relate to postoperative endophthalmitis risk. As the authors acknowledge, this has been evaluated in a retrospective series of thousands of patients by Koch et al. It is not clear how the present study relates to endophthalmitis rates with the Intrector. Are there any studies that correlate intraoperative vitreous contamination with postoperative endophthalmitis? Ie, what is the positive predictive value/negative predictive value of intraoperative culture for postoperative endophthalmitis? There is limited literature to this effect, but if the authors wish to make inference on endophthalmitis rates based on their intraoperative culture, they should address this. Perhaps referencing the cataract literature if there is no relevant PPV literature. Do the authors believe that intraop contamination or postoperative contamination through unsutured sclerotomies is more relevant? This is mentioned in the abstract but not in the manuscript text.

Response:
A sentence has been added into the abstract to corroborate the manuscript’s discussion on possible postoperative endophthalmitis risk under the section “Conclusion”. Similar, the discussion of intraoperative vs postoperative contamination has also been added into the manuscript’s “Discussion” section to corroborate the abstract.
Thank you also for reviewer’s excellent remark on vitreous contamination and postoperative endophthalmitis. We have added a paragraph to discuss this topic more in depth in the “Discussion” section of the manuscript, with citations from both vitrectomy and cataract surgery literature on the topic. Although no studies large enough have been conducted to be able to yield positive and negative predictive values, Egger et al in their 1996 article give an example amongst their 25 patients: 32% had vitreous contamination at the beginning of vitrectomy surgery, 20% had vitreous contamination towards the end of surgery, yet none
developed endophthalmitis postoperatively. This study is discussed in the updated discussion section.

11. It would be informative, but not critical, to note the percentage of patients with a PVD preoperatively. In those without a PVD, was this induced surgically?

**Response:**
We did not record this information.

12. Were the conjunctival isolates typical for normal conjunctival flora? Please comment briefly on this.

**Response:**
This has been acknowledged in the results section. “All of these isolates (100%) were gram-positive and identified as organisms found as part of the normal ocular flora.”

Reviewer #2: No major compulsory revisions. Minor essential revisions.

The authors need to correct

1) p3 ...a first conjunctival specimen..... should be .....the first conjunctival ...

**Response:**
This has been corrected as suggested.

2) p4 the authors might clarify their assertion hypotony was avoided in spite of removal of 0.5ml. Were these eyes myopic?, did the authors apply digital pressure to maintain the IOP? Or was the reduction in IOP not clinically relevant?

**Response:**
Thank you for this comment. Reviewer 1 also pointed out this assertion and the sentence has been modified accordingly.

3) p5. Could the authors check cautery not diathermy was used if there was a wound leak?

**Response:**
Thank you for pointing out this description, which might be vague. We have verified that bipolar cautery was indeed used. The phrasing has been modified to “If a leak was noted, thermocauterization was applied to coapt the conjunctiva overlying the sclerotomy site.”
4) p5. It would be difficult to mask the order of the samples if the first sample was collected in a 1.0ml syringe and the second sample in a 10.0 ml syringe. I am not sure if it is necessary to assert the samples were masked in any event!!

Response:
Thank you for pointing out this description. The sentence on masking has been removed.

5) p6. ?? average follow-up time since vitrectomy, should it not be mean follow up??

Response:
This has been corrected to “mean follow-up”.

6) p6 ? ...."None of the patient swore" think that is a typo!!

Response:
This has been corrected.

7) p6. As these patients were from a pool of wet AMD, did none use topical antibiotics prior to sampling; I suspect some of the patients did have topical antibiotics in the past ??? associated with their intra vitreal therapy, so might be best to say patients had not used topical antibiotics in the previous x weeks.

Response:
Thank you. This sentence has been modified to “None of the patients wore contact lenses or used topical antibiotics in the 4 weeks prior to sampling. “

8) p6 The authors should reserve the term species for different bacterium and strains for a single bacterium. thus 6/18 patients had 2 strains [ these should be listed] and 11/18 patients had 1 species identified...... Similarly Table 2 "strains" should be replaced with "species”

Response:
Thank you for clarifying the difference. The terminology has been corrected to be more accurate throughout the text of the manuscript, including in table 2. We decided not to list in the manuscript text the 2 species isolated from the 6/18 patients who had 2 species on their conjunctiva as each of these patients has a different combination of the 2 species isolated (e.g. it could be Staphylococcus and Corynebacterium, Propionibacterium and Corynebacterium etc, hence to not
further burden the text, the reader is referred to table 2 for the breakdown of species identified).

9) p6 The sentence beginning "From the 37 undiluted midvitreous samples collected....." is poorly constructed; perhaps a better sentence might be" Only 1 of the 37 undiluted midvitreous samples was culture positive, equating to a contamination rate of 2.7%. The bacterium isolated was Propionibacterium sp. This patient’s conjunctiva also.......None of the 37 diluted midvitreous samples were culture positive......

Response:
Thank you for the suggestion of sentence construction, which has been adopted.

10) p7 The use of office-based vitrectomy has continued to evolve since its inception in the early 1980s. I think the authors need to clarify the reference (5) to the office based vitrectomy and risk of endophthalmitis. In the study quoted a single port was used, unlike the current study. Also the authors may choose to elaborate on the idea of continual irrigation with povidone-iodine contributing to the lower rates of culture positive, see Shimada et al 2013

Response:
Reference [5] from Koch et al. has been clarified. On p7, it has been made clear that Koch’s study only studied single port Intrector procedures, which were partly performed in the OR setting, while our study is a three-port procedure completely set up in the office setting.

To elaborate on the idea of intra-operative povidone-iodine irrigation as suggested by the reviewer, the following paragraph has been added to the manuscript: “Shimada et al. have even advocated for the repeated irrigation of 0.25% povidone-iodine unto the surgical field during a procedure to reduce vitreous contamination. However, as per the authors, the safety and efficacy of such a practice needs further statistical confirmation from a larger scale study necessitating enrollment of more than 50,000 eyes.”