Author’s response to reviews

Title: Comparison of Intraocular Pressure as Measured by Three Different Non-contact Tonometers and Goldmann Applanation Tonometer for Non-glaucomatous Subjects

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Manuscript Number BOPH-D-17-00287 “Comparison of Intraocular Pressure as Measured by Three Different Non-contact Tonometers and Goldmann Applanation Tonometer for Non-glaucomatous Subjects”

Thank you for reviewing this manuscript and for the immensely helpful comments of the reviewers. Please find enclosed the manuscript, which has been revised according to the comments raised by the referees.

Dear Editor,

Thank you for your kind letter.

We now send you the first revised version of our manuscript. We hope that we have adequately answered the reviewers’ comments and questions, and that you and the reviewers will be satisfied with the result. We enclose a list of the modifications to the revised manuscript and our replies to the comments of the referees. We appreciate the thoroughness with which the reviewers assessed our manuscript and hope that it is now suitable for publication in BMC Ophthalmology.

We look forward to hearing from you soon.

Enclosure: Response to Reviewer 1
Response to Reviewer 2

One copy of the revised manuscript

With best regards,
Yours sincerely,
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Reviewer 1:

Thanks for the opportunity to revise your manuscript. I found it very interesting and the information presented here is of potential interest for the readers. I have just a small comment: why the authors did not randomized the use of the three NCTs? This must be explained and discuss. I understand that they want use the NCTs before touching the cornea (GAT and ultrasound), but they could randomized the order the machines were used to avoid any kind of systematically error.

-> First, we express our sincere appreciation to you for the opportunity to revise our manuscript. Indeed, we had initially planned to randomize the order of the three NCTs to avoid any type of systematic error. However, we could not randomize the use of the machines due to the relatively short study period. We were only able to obtain these three machines during the demonstration period for about 10 days. We were running out of time for randomization and ultimately had to perform the measurements in a fixed sequence. As we mentioned in the Discussion [Page 10, Lines 5 to 9] of the manuscript as first submitted:

“Considering the order of the tonometer measurements, the greatest IOP values of C-IOP could be due to the “massage effect,” though the NCTs were less affected than was the GAT [24, 25],
and regardless, the five-minute interval between each measurement, enough time to recover from enhanced aqueous outflow due to corneal compression, would minimize such effect.”

We tried to resolve this problem using a five-minute interval between each measurement to minimize the “massage effect,” but we were unable to ensure that the lack of randomization did not influence the outcome. We regret that we did not perform the randomization, and we appreciate your comment. We have added the following sentences to the Discussion [Page 13, Lines 5 to 9] of the revised manuscript:

“Additionally, we were unable to randomize the order in which the NCTs were used due to restraints on access to the equipment. Therefore, we were unable to avoid potential systematic errors and are unable to ensure that the lack of randomization did not influence the outcome. We did implement a five-minute interval between each measurement to minimize the ‘massage effect’.”

Reviewer 2:

The authors seek to compare intraocular pressure measurements among three different non-contact tonometers and goldman tonometry in healthy subjects. In principle, this is a well-written paper and the authors are addressing an important issue. However, I have some concerns that need to be addressed.

Specific comments:

The authors did not randomize the sequence of the measurements within the three non-contact tonometers. How can the authors be sure that this does not affect the outcome? This needs to be addressed in the discussion.

-> Thank you for your comments. Indeed, we had initially planned to randomize the order of the three NCTs to avoid any type of systematic error. However, we could not randomize the use of the machines due to relatively short study period. We were only able to obtain these three machines during the demonstration period for about 10 days. We were running out of time for randomization and ultimately had to perform the measurements in a fixed sequence. As we mentioned in the Discussion [Page 10, Lines 5 to 9] of the manuscript as first submitted

“Considering the order of the tonometer measurements, the greatest IOP values of C-IOP could be due to the “massage effect,” though the NCTs were less affected than was the GAT [24, 25], and regardless, the five-minute interval between each measurement, enough time to recover from enhanced aqueous outflow due to corneal compression, would minimize such effect.”
We tried to resolve this problem using a five-minute interval between each measurement to minimize the “massage effect,” but we were unable to ensure that the lack of randomization did not influence the outcome. We truly regret that we were unable to randomize the order in which measurements were performed, and we appreciate your insightful comment. We have added the following sentences to the Discussion [Page 13, Lines 5 to 9] of the revised manuscript:

“Additionally, we were unable to randomize the order in which the NCTs were used due to restraints on access to the equipment. Therefore, we were unable to avoid potential systematic errors and are unable to ensure that the lack of randomization did not influence the outcome. We did implement a five-minute interval between each measurement to minimize the ‘massage effect’.”

The study did not include subjects with irregular astigmatism or astigmatism more than 3.5 diopters. Although this is reasonable for the current study, this issue needs to be discussed. In particular, it means that the findings of the current study hold only true for the selected group of subjects.

-> Thank you for your comments. As you mentioned, we also agree that exclusion of subjects with irregular astigmatism or astigmatism of more than 3.5 diopters is reasonable for our study, but it could also be a limitation of our study. We have added the following sentence to the Discussion [Page 12, Line 18 to Page 13, Line 2] of the revised manuscript:

“We also excluded subjects with irregular astigmatism or astigmatism of more than 3.5 diopters, and thus, our findings may hold true only for subjects with similar refraction characteristics.”

We have also changed the sentence in the Discussion [Page 12, Line 18 to Page 13, Line 2] of the manuscript first submitted from the following:

“The sample size of this study also was relatively small; future studies will need to include larger populations of ocular hypertensive and glaucoma subjects, for which any bias between instruments could have clinical implications.”

to

“Furthermore, the sample size of this study was relatively small for the subgroup analysis; future studies will need to include larger populations of ocular hypertensive and glaucoma subjects, with and without irregular/severe astigmatism, for whom any bias between instruments could have clinical implications.”

in the Discussion [Page 13, Lines 2 to 5] of the revised manuscript.
Did the authors perform a power and sample size calculation prior to study start? What was the power of the study to detect differences between groups in the selected sample size? This is especially important for the sub-group analysis. Do the authors need to correct for multiple testing?

-> Thank you for your astute comments. We had planned to perform a power and sample size calculation prior to the start of the study, but we finally omitted the calculation when analyzing the results of this study. Furthermore, during the analysis process, we realized that subgroup analysis might be necessary for our study. We decided to perform the subgroup analysis despite the low number of subjects. We totally agree with your comment and regret that our subgroup analysis has inexorably weak statistical power due to subdivision of the subject pool. We have decided to keep the subgroup analysis, but have added the following:

“Furthermore, the sample size of this study was relatively small for the subgroup analysis; future studies will need to include larger populations of ocular hypertensive and glaucoma subjects, with or without irregular/severe astigmatism, for whom any bias between instruments could have clinical implications.”

in the Discussion [Page 13, Lines 2 to 5] of the revised manuscript.

Although it is briefly mentioned in the discussion, I feel that the limitations of the study should be discussed in more detail. In particular, the fact that no patients with high IOPs have been included is of importance also in respect to the conclusion of the study. Furthermore, the CCT correction and the possible impact on the study results need to be discussed in more detail.

-> We completely agree with your comments. We have changed the sentence in Discussion [Page 13, Lines 8 to 11] of the initially submitted manuscript from

“Despite the relatively small sample size of this study, the instruments’ good IOP-measurement performance for ocular normotensive non-glaucomatous subjects suggests they will prove useful for rapid IOP testing in clinical practice.”

to

“Despite the relatively small sample size of this study and the absence of high IOPs, the instruments demonstrated good performance in measuring IOP in ocular normotensive non-glaucomatous subjects. These results suggest the instruments will prove useful for rapid IOP testing in clinical practice.”

in Discussion [Page 13, Lines 17 to Page 14, Line 1] of the revised manuscript. Additionally, we have changed the sentence in Discussion [Page 13, Lines 2 to 4] of the initially submitted manuscript from

“One other limitation was the fact that we did not carry out CCT correction separately with each tonopachymeter.”

to

“One other limitation was the fact that we did not carry out CCT correction separately with each tonopachymeter; future studies should also investigate the results of CCT correction and comparison of CCT values from the ultrasound pachymeter with those from each tonopachymeter.”

in Discussion [Page 13, Lines 9 to 13] of the revised manuscript.