Author's response to reviews

Title: Repeatability of Intraocular Pressure Measurements with Icare Pro Rebound, Tono-Pen AVIA and Goldmann Tonometers in sitting and reclining positions

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Author's response to reviews: see over
To Whom It May Concern:

Thank you very much for reviewing the first draft of our manuscript entitled:

“Repeatability of Intraocular Pressure Measurements with Icare Pro Rebound, Tono-Pen AVIA and Goldmann Tonometers in sitting and reclining positions.”

and the constructive feedback. These suggestions helped us to revise our manuscript. We have carefully considered the entire points rose by the two reviewers. The enclosed manuscript has been revised accordingly. We believe that we have addressed all of the comments, as itemized in the point-by-point list of responses, and hope that you will find our revised manuscript suitable for publication in BMC Ophthalmology. Furthermore, we would like thank you for the deadline extension.

Kind regards,

Marc Töteberg-Harms, MD
Reviewer One - Minor essential revisions:

1) Abstract: "Hypothesis was that GAT is superior to ICP and TPA."
Superior in what way? Since you tested repeatability, I would state that here.
Thank you very much for carefully reading the abstract. We have implemented your suggestion accordingly.

2) Please insert a statement regarding the tonometry effect (repeated GAT tend to lower IOP), what about the other two methods? How long was waited between measurements to avoid "idiopathic" IOP reduction?
This information is important for the understanding of the study. We added a statement accordingly.
We provided in Table 3 the differences between measurement 1 and 2 (bias) of each device. They range between -0.2mmHg for ICP (sitting and reclined) to +0.1mmHg for TPA (sitting). Hence, we couldn't find a significant influence between repeated measurements that had influenced the results.
The information was already incorporated in the results section. In addition, we added the following sentence to the methods section:
"Between repeated measurement there was a pause of 3 minutes to avoid a lower IOP of the subsequent measurement caused by the prior applanation."

3) It would have been nice to have CCT measurements in such an experimental setup, although I agree to the authors that in real live no one would perform pachymetry in healthy subjects. However, that information would have improved the paper.
We agree with the reviewer. CCT informations would have been interesting and had add to the value of the study. We added some sentences to the discussion section.

4) The statistic part is very detailed and might be a bit too long, but some readers might not be too familiar with the Mixed-Model for ICC calculation. I therefore understand why the authors put that much effort in this part. No complains regarding statistics itself.
This concern is absolutely correct. The description of the statistical models are very detailed. This is in fact due to not so commonly used mixede models. We would rather not want to shorten the manuscript in describing the statistical models because describing the methods correctly is basic requirement to guarantee comprehensibility and to guarantee that a study can be repeated by another group.

5) Results: 4. paragraph, line 2: ...measurement 1 and 2 of the three methods (Figure 1). Authors should add "...in sitting position."
Thank you very much for pointing this out. We have changed the manuscript accordingly.
6) **Discussion:** The discussion is quite long, in particular on the second page of the discussion, one can find redundant information that has already been presented in the results. We have revised the discussion in order to make it shorter, focused on the main results, and to avoid redundant information.

7) Authors state that "...differences in IOP between GAT and ICT as well as between GAT and TPY in upright and reclining position was investigated..." I am not sure about what is the point in comparing GAT (which only works upright) with the two other methods in reclining position. It is a bit like comparing apples with bananas and no surprise that repeatability is worse in reclining position. Next the authors state that:..."the linear mixed model shows a difference between GAT and ICP of 0.847mmHg in upright and 1.651mmHg in reclining position." This sentence is somewhat confusing, since GAT cannot be performed in reclining position. Please clarify what you mean with that statement.

Perkins can measure IOP in supine position. Results of IOP measurements between Perkins and GAT are nearly interchangeable. Therefore we investigated the difference between GAT-IOP sitting and iCare-IOP lying. We do not used the Perkins because repeated applanation tonometry (other then rebound tonometry) can decrease IOP by enhancing outflow and decreasing aqueous humor volume. Furthermore, GAT is the gold standard for IOP measurement and nearly all results of clinical studies are based on GAT. That was the rational to compare all IOP measurements with GAT.

8) Authors state that only eyes with IOP between 9 and 27mmHg were included. 27mmHg seems to be quite high for healthy controls. Can that still be considered normal? We do not agree with this concern. First of all, a definition of normal IOP does not exist per se. The study of Leydhecker et al. (Leydhecker W, Akiyama K, Neumann HG: Der intraokulare Druck gesunder MenschAugen, Klin Monatsbl Augenheilkd 133:662, 1958) is generally referred to whenever normal IOP distribution is discussed. They investigated IOP with the Schiøtz tonometry on more than 10.000 normal individuals. IOP was 15.8±2.6 mmHg (mean ± SD). Based on this study normal IOP is accepted as to be between 11 and 21 mmHg (mean ± 2 SD). First, their population was not Gaussian distributed, but rather skewed to the right. So higher IOP (over 21 mmHg) has still to be included into their normal distribution and an upper limit cannot be defined by adding simply 2 or even more standard deviations to the mean. Furthermore, a couple of studies have shown, that IOP over the cut-off of 21 mmHg is present in a normal collective by a percentage of close to 10% (e.g. Hollows FC, Graham PA: Intraocular pressure, glaucoma and glaucoma suspects in a defined population, Br J Ophthalmol 50:570, 1966). Glaucoma specialist often refer to ocular hypertension in patients with elevated IOP but without any typical glaucoma changes (i.e. normal optic disc, normal RNFL, and normal visual fields). That in mind, their IOP is above,
what is considered to be normal, but they do not have glaucoma. For sure they are of higher risk of developing glaucoma over time but they do not have glaucoma and not all of them will develop glaucoma. Hence, we do not agree with the reviewer in this point and we believe that IOP up to 27 mmHg can still be considered normal IOP.

9) Last sentence of the discussion: Why would a hand-held DCT be a better device to compare measurements to GAT? Since GAT cannot measure in reclining position, there is no need for a hand-held DCT for comparison. We see the point and deleted the information on DCT from the discussion.

10) Conclusion: Last sentence: I could not find any information regarding conversion factors for the three devices in this manuscript. It is recommended to only conclude on your own data. Authors might want to add a calculation for conversion between devices. That might indeed be helpful in clinic. We agree, this would be helpful. Conversion of GAT by CCT has widely be investigated. Those studies have sample sizes of >500 eyes. And still, none of the developed formulas is accurately applicable. We believe it is more important to have an idea of how much different tonometers over- or underestimote IOP compared to a reference tonometer to clinicy judge if the measured pressure leads to a clinical disicssion. IOP should not be converted between devices at the moment. This will never be accurate. Thus, our advice was only to use a tonometer other than GAT whenever IOP measurements with GAT is not possible. We added a sentence regarding conversion factors to the conclusion.

Reviewer Two – Major Compulsory Revisions
The study "Repeatability of Intraocular Pressure Measurements with Icare Pro Rebound, Tono-Pen AVIA and Goldmann Tonometers in sitting and reclining positions" was revised appropriately. The authors compared repeatability between Goldmann tonometer (GAT), ICare Pro and Tono-Pen AVIA readings. Comparisons between those devices were previously reported, since at least 2010, however repeatability among them was not specifically studied before.

The reviewer is right, several comparative studies have been published but most of them used the iCare and not the iCare Pro rebound tonometer. The iCare Pro is was introduced in 2011 and is still not available in the U.S. for example.

1) However, two major flaws should be addressed: stylistic construction of the text and sample size calculation. For instance, considering the parameters presented for the sample size calculation and a commonly used standard deviation for IOP (of 2.0), at least 220 subjects would be necessary. Thank you very much for this important concern. Standard deviation of IOP measurements of all devices were between 2.7 and 3.5mmHg. We have re-done the sample size calculation with the online tool from the biostatistics service of Massachusetts General Hospital, Harvard Medical School.
However, our results vary from those given by the reviewer. The reviewer did not provide any further information for his calculation (e.g. power, significance level, standard deviation) that would make it possible to prove his results:
„A total of 36 patients have entered this study. With a probability of 80 percent this study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 2.4 mmHg based on standard deviation of 3.5 (or 1.8 mmHg based on a standard deviation of 2.7).“

2) Moreover, I suggest that only the essential Bland-Altman plots should be presented, once tables are quite explicative.
Thank you very much for this concern. BMC Ophthalmology is an open access journal and thus not limited to space restrictions. Hence, we have not deleted any plots. Nevertheless, if the editorial board agrees to this concern we will present only essential Bland-Altman plots in the manuscript and provide the remaining plots as additional material.