Author’s response to reviews

Title: Goldmann and Error Correcting Tonometry Prisms Compared to Intracameral Pressure

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Author’s response to reviews:

The authors would like to thank the reviewers and editors for the generous and complete review. The suggestions were extremely helpful particularly in the statistical analysis. The appropriate changes were made and we believe you will find the revised manuscript acceptable.

Point by point response to the review:

Reviewer reports:

Carlo Nucci (Reviewer 1): In this paper, McCafferty et al. compared the Goldmann applanation tonometer (GAT) prism and a newly designed prism (correcting applanation tonometry surface, CAT) to intracameral IOP, measured with a trasducer during cataract surgery. They observed that the IOP values recorded with the new CAT prism are more accurate than those measured with the Goldmann's prism in thin cornea and in cornea with lower resistant factor as assessed with ORAC. Cadaveric human globes were also used to determine the intra-operator and inter-operator repeatability of IOP measurements with both prisms, and no differences were detected between the two instruments. The paper is well written, the methods are described accurately and the results presented correctly. However the manuscript is not particularly innovative since most of the conclusions reached with the present experiments have been obtained with previous studies published in TVST 2016 and Clinical Ophthalmology 2017.

Previously published material in TVST 2016 was simply a mathematical model showing the design method to reduce biomechanical errors in applanation tonometry. The three cadaver eyes were to show approximate equivalence in the operability between the GAT and CATS prisms. No superiority was demonstrated except theoretical.

Previously published material in Clinical Ophthalmology 2017 was a direct comparison between GAT and CATS - Examining overall bias and dependence upon clinically measurable factors
relating to biomechanical errors such as CCT. The article was reviewer criticized due to the error inherent in both GAT and CATS prism and no comparison to the true intraocular (intracameral) pressure.

The present article is novel in that it compares both the GAT and CATS prisms to the true intracameral pressure in live human subjects over a manometrically adjusted IOP covering the physiologic range of measurements. Comparisons of tonometer devices and GAT to true intracameral IOP on live human subjects has only been published less than 8 times (that we can find) over the past 30 years, due to the technical difficulty. Furthermore, the intracameral pressure was manometrically adjusted on the live human subjects over the physiologic range of IOP measurement. We can find only one other published study that used manometrically adjusted IOP. This method leaves no doubt (except experimental error) the overall bias and differences between CATS and GAT at measured CCT and CRF values as both are compared to a true reference value of intracameral IOP, not included in any prior study. In addition human cadaveric eye testing was completed to determine intra-operator and inter-operator measurement repeatability errors between the CATS and GAT prisms, also not included in any prior study.

- Introduction line 89. Before presenting the aim of the present study the authors should present the results obtained in the previous two manuscripts on the accuracy of CAT compared to GAT and on the repeatability of the measurements. Than they should present how the present paper differentiates from them.

Line 88 - In addition, two previous studies have examined both the theoretical modeling and direct clinical comparison of a modified GAT (CATS) prism to the traditional flat GAT prism.9,17 Both have demonstrated decreased CATS sensitivity to corneal biomechanical error parameters. The present clinical study was designed to compare both a GAT prism and a modified applanation surface prism (CATS) in live human subjects to a true ‘gold standard’ intracameral pressure which was manometrically adjusted over the physiologic range of IOP measuring bias and sensitivity to corneal biomechanical parameters. Additionally, human cadaveric eye testing was completed to determine Inter-operator and intra-operator measurement repeatability errors.

Line 384 - Additionally, a clinical study of 109 eyes correlating the expected slope correction difference between CATS and GAT IOP measurements to corneal biomechanics related errors corroborate the present findings of decreased sensitivity.9 The aforementioned study did not compare IOP to intracameral pressures and were measured in a narrow pressure range of 17.5+/−2.8mmHg.

- Methods lines 95-107 this section should be presented in the introduction.
Previous critique requested this be moved to the Methods section. The detailed description of the workings of the CATS prism is in the Methods section. However, a modified version included in Introduction:

Line 88- In addition, two previous studies have examined both the theoretical modeling and direct clinical comparison of a modified GAT (CATS) prism to the traditional flat GAT prism.9,17 Both have demonstrated decreased CATS sensitivity to corneal biomechanical error parameters.

- Figure 1 is the same of figure 1 in Clinical Ophthalmology 2017 and figure 3 is the same of figure 6 in TVST 2016.

Removed

- Methods line 136, was refractive surgery an exclusion criteria?

YES. Line 132- Subjects were selected in accordance with the following exclusion criteria: Ocular surgery within the last 3 months; pregnant or nursing: only one functional eye; poor or eccentric fixation; high corneal astigmatism (>3.5 diopters); corneal scarring; corneal surgery; microphthalmos; buphthalmos; severe dry eyes; blepharospasm; nystagmus; keratoconus; or any other corneal or conjunctival pathology or infection.

- Page 10 line 196, GAT instead of CAT

Changed

- Methods. It is not clear if the human cadaveric eye testing were performed on 3 eyes or on 21, three for each IOP level tested.

21 cadaveric eyes. Line 208 - Twenty one (21) enucleated human globes were obtained from the Georgia Eye Bank (Atlanta, GA). Line 249 - Twenty one (21) total cadaver eyes were utilized. Three (3) eyes were measured at each of the following seven (7) intracameral pressures (5, 10, 20, 30, 40, 50, 60mm Hg). Measurements were completed five (5) times by two (2) different examiners (10 total) with each prism.

- Pag. 12 lines 252-253 the example is not clear
Twenty one (21) total cadaver eyes were utilized. Three (3) eyes were measured at each of the following seven (7) intracameral pressures (5, 10, 20, 30, 40, 50, 60mm Hg). Measurements were completed five (5) times by two (2) different examiners (10 total) with each prism.

- Pag 17 line 348 the sentence "all globes……..post mortem" could be eliminated

Removed

- Pag 17 line 350 the sentence "Twenty ……two prisms" could be eliminated

Removed

Reference 9 is incomplete.

Completed

Giovanni Montesano (Reviewer 2): The authors present a detailed analysis comparing two applanation tonometer prisms in terms of accuracy. Measurements from both devices have been compared to an invasive measure of the ocular pressure via cannulation. The experimental setup is thorough and the description of the methodology is accurate. However, I have major concerns, especially regarding the statistical analysis.

- Lines 116 - 125: instead of performing a post hoc power analysis it would be better to model the variability considering the intrasubject correlation of observations. Mixed models might be helpful in this context and should be considered, using random effects to model the correlations;

Line 196- A multivariate regression analysis with a linear mixed-effects model was carried out to compare sensitivities of the GAT and CATS IOP reading errors to CCT and CRF.

- Lines 193 - 201: the authors should specify what kind of modeling was used to study the correlation of the error with the intracameral IOP value. The graph suggests a curved relationship but no reference to a polynomial or any other kind of curved model is made.
The lines demonstrating the differences in IOP measurement of the CATS and GAT prisms compared to intracameral pressure are a closest fit polynomial forced through zero. The zero intercept is justified since the prisms are unable to measure a negative pressure and would only read zero.

All CCT and CFR analysis: the authors are not addressing the main question with their correlation analysis. First, they calculate separate correlations for GAT and CATS and then, since they cannot find significant differences in neither of the two they attempt to show the difference with a t-test by dividing the range of the corneal parameters in two groups. It would be better to actually test the difference of the slopes between the two tonometers. This could be easily achieved by the use of linear models. In this case, two random effects (one for the subject and one for the eye to account for the repeated measures, the second nested in the first) should be used. The actual model should include the parameter of interest and a dummy factor indicating if the measure has been taken with a GAT or a CATS. Then, an interaction term between the two parameters would represent the difference in slope and could be tested. For example, for the CCT modeling the difference between the applanation and the intracameral IOP, the model would look like this (Prism is a dummy variable indicating the GAT or the CATS tonometer):

\[
\text{Difference} = \text{Intercept} + \text{Prism} + \text{CCT} + \text{Prism} \times \text{CCT}.
\]

Here I did not report the random effects (that MUST be included). The last term is the interaction that would test the difference in slope. The same could be repeated for the CFR and, possibly, for the true IOP to assess the different effects of these parameters on the error. Furthermore, a multivariate model with two way or three way interaction terms could be used to assess the effect of all these parameters contemporarily (but this global model could be limited by the number of observations).

A multivariate regression analysis with linear mixed-effects revealed a statistically significant (\(p = 0.021\)) difference in sensitivity to CCT between the GAT and CATS.

Figure 7 illustrates the decreased slope sensitivity to CRF in the CATS prism. It demonstrates a linear error sensitivity of 0.37 mmHg/CRFunit with the GAT and -0.043 mmHg/CRFunit with the CATS prism which is nearly statistically significant in the linear mixed effects analysis (\(p=0.055\)).

To compare the sensitivities of CATS and GAT to the corneal biomechanical properties (CCT and CRF), we conducted a multivariate regression analysis using a MATLAB General Linear Mixed-Effects (GLME) model on the departures from intracameral transducer IOP of the tonometer IOP readings. Equation 1 captures the linear mixed-effect model used in the analysis.
Eq 1: \( y_{hij} = \pi_h + \theta_{i(h)} + \beta_0 + \beta_1 \cdot CATS + \beta_2 \cdot CCT + \beta_3 \cdot CATS \cdot CCT + \beta_4 \cdot CRF + \beta_5 \cdot CATS \cdot CRF + \epsilon_{hij} \)

h indicates the patient for a measurement (48 patients, 5 bilateral).

i indicates the eye of the patient for a measurement (58 total eyes measured).

j keeps track of repeated measurements on the same eye.

\( y_{hij} \) is the IOP difference from intracameral of measurement j on eye i of patient h.

\( \pi_h \) is the random effect corresponding to the patient measured.

\( \theta_{i(h)} \) is the nested random effect corresponding to the eye measured.

CCT is the central corneal thickness in microns.

CRF is the corneal resistance factor in CRFunits.

CATS is a dummy factor corresponding to which tonometer is used.

CATS=1 when the CATS was used and CATS=0 when the GAT was used.

\( \beta_0 \) is the fixed offset effect when using the GAT including the grand mean error from true IOP.

\( \beta_1 \) is the fixed offset effect when using the CATS relative to when using the GAT.

\( \beta_2 \) is the fixed first-order effect of CCT when using the GAT.

\( \beta_3 \) is the fixed first-order effect of CCT when using the CATS relative to when using the GAT.

\( \beta_4 \) is the fixed first-order effect of CRF when using the GAT.

\( \beta_5 \) is the fixed first-order effect of CRF when using the CATS relative to when using the GAT.

\( \epsilon_{kj} \) is the inherent error/variability of y not explained by the factors in the model.

- It is not clear what the rationale for using cadaveric eyes is. From the methods, it looks like only three eyes have been used (since the main goal is stated to be the measurement of the test repeatability and reproducibility) but then in the Results it looks like all the eyes have been used. Please clarify these aspects.
Human Cadaveric Eye Testing (in vitro study)

Cadaveric eye testing was completed human globes to determine practitioner intra-operator and inter-operator repeatability of pressure measurements with both the CATS and GAT prisms.

Twenty one (21) total cadaver eyes were utilized. Three (3) eyes were measured at each of the following seven (7) intracameral pressures (5, 10, 20, 30, 40, 50, 60mm Hg). Measurements were completed five (5) times by two (2) different examiners (10 total) with each prism.

It is not clear where the cannula has been placed during surgery. This is important since it might affect the corneal properties (as opposed to the cadaveric eyes measurements where the cannula was implanted through the sclera). This limitation is noted by the authors in the discussion. Nonetheless it should be better explained in the methods.

The incision was 1.2mm at a ‘near clear’ corneal location almost tangential to the limbus. The cannula and tubing were adjusted and secured throughout the measurements to eliminate any visible endothelial folds minimizing potential changes to the biomechanical properties of the central cornea.

Minor comment: the English language is overall correct but some typos are present and might limit the comprehension of the manuscript.

Line 75: "relavent" should be "relevant";
Changed

Line 102: "In mathematically modeling" should be "In mathematical modeling"
Changed

Line 174: "though" should be "through"
Changed