Modified Goldmann prism intraocular pressure measurement accuracy and correlation to corneal biomechanical metrics: multicentre randomised clinical trial

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ABSTRACT

Purpose Clinically evaluate intraocular pressure (IOP) measurements taken with a Goldmann applanation tonometer (GAT) prism and a modified surface Goldmann prism examining measurement differences correlated to central corneal thickness (CCT) and corneal hysteresis (CH) values.

Design Prospective, open-label, randomised, controlled, multicentre reference device accuracy analysis.

Methods A GAT and a modified surface GAT prism measured IOP on 243 unique eyes. The study design and methodology complied with International Standard Organization (ISO) tonometer evaluation guidelines, except the inclusion of thin (<500 µm) and thick (>600 µm) corneas. All eyes were randomised to IOP measurement by one of five standard Goldmann prisms and five modified prisms. Pressures were measured by six investigators, two times with each prism for a total of 1936 IOP measurements. Analysis included a multiple linear regression including CCT and CH correlation.

Results The difference in IOP measurements of the standard and modified Goldmann prisms correlated well to CCT particularly in thin (<500 µm) and thick (>600 µm) corneas (R²=0.404, p=0.007). Corneal hysteresis (CH) also significantly correlated to the difference in prism measurements (R²=0.125, p=0.039). There was no significant overall mean IOP bias between the two prisms (+0.43 mm Hg in modified, p=0.19).

Discussion The paired IOP measurement difference between GAT and a modified surface replacement prism indicated a statistically significant correlation to CCT and CH. A simple modified replacement prism for any Goldmann-type tonometer may significantly improve IOP measurement accuracy by minimising corneal biomechanical errors associated with CCT and CH.

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INTRODUCTION

The standard for measurement of intraocular pressure (IOP) remains Goldmann applanation tonometry (GAT). Intraocular pressure is the clinical indicator in the diagnosis of ocular hypertension, which may lead to glaucoma. Furthermore, it is the only modifiable parameter in the treatment of glaucoma. Errors in IOP measurement may result in potentially sight-threatening conditions. Individual patient variability in corneal thickness, rigidity, curvature and corneal tear film has led to significant errors in GAT IOP measurement. In addition, the corneal biomechanical differences incurred after LASIK surgery and present in children have also led to inaccuracies in GAT IOP measurement.

IOP readings have been demonstrated to be underestimated in thin corneas and overestimated in thick corneas, respectively leading to a potential failure of diagnosis or over-diagnosis of glaucoma. The preferred practice among eye care professionals has changed to consider low central corneal thickness (CCT) values as a risk factor for glaucoma comparison and progression. Standardisation corrections for the various other GAT IOP errors have been attempted in order to yield a comparable IOP between patients. The correction process in practice involves additional data collection and calculation leading to minimal clinical adoption. The IOP corrections by CCT nomograms alone are shown to be ineffective by themselves as a predictive model for glaucoma.

A correcting applanation tonometry surface (CATS) tonometer prism is a Goldmann applanation tonometer (GAT) prism with a modified applanating surface (figure 1). The United States Food and Drug Administration (U.S. FDA) recently cleared the CATS tonometer prism for IOP measurement in existing Goldmann-type applanation tonometers. Alterations to the original GAT prism design include a sinusoidal curved modification of applanating surface with a compensatory increase in prism length. Lengthening of the prism was required to maintain a zero average IOP bias between the GAT and CATS prisms over a large standard population. A zero average bias maintains long established GAT IOP bench marks (ie, borderline high at 21 mm Hg) and was required for clinical adoption as well as tonometer retrofitting without recalibration. The modified Goldmann (CATS) prism significantly decreases individual patient IOP error due to corneal biomechanical and tear-film properties. Improved IOP accuracy with the modified Goldmann (CATS) prism has been demonstrated in direct clinical GAT prism comparison and by surgically placed intracameral transducer pressure comparison.
Any existing Goldmann measurement armature may be retrofitted with the modified (CATS) prism without recalibration. A clinician measures IOP using the same protocol and techniques as those currently employed in GAT measurement. A reduction in corneal biomechanical errors is achieved by partially matching the curvature of the tonometer surface to curvature of the cornea minimising the intracorneal stress during applanation.\(^1\)\(^-\)\(^5\) This process minimises the contribution of total force on the prism face due to corneal deformation, measuring predominantly the IOP force.\(^1\)\(^5\) The annular curvature away from the cornea simultaneously minimises the tear-film error.\(^1\)\(^5\)\(^-\)\(^9\)

The present study was completed to evaluate the modified Goldmann (CATS) prism IOP accuracy compared with the reference GAT prism with known glaucoma risk factors such as CCT and CH in healthy subjects. Study design complies with Guidance for Industry and FDA Staff Tonometers—Premarket Notification [510(k)] Submissions as well as International Standards Organization (ISO) 8612:2009 standards.

**METHODS**

Enrolment included healthy subjects undergoing a series of IOP measurements with the modified (CATS) and standard GAT prisms. The design was a randomised, controlled, prospective, open-labelled, multicentre device comparison. Eligible subjects were screened, enrolled and evaluated according to the study protocol and were recruited from two sites in Arizona, USA. Participation in the study included subjects 18 years or older, meeting the protocol criteria, who provided written informed consent.

**Description of study population**

Healthy adult subjects were enrolled into the study to include high-astigmatism and refractive errors, as well as high IOP. Specifically, both thin and thick corneas with a CCT >600 \(\mu\)m and <500 \(\mu\)m were included. The sample size was calculated at 70 eyes (of those in the thin and thick CCT range) based on statistically significant correlation probability from previous studies.\(^1\)\(^6\)\(^-\)\(^8\)\(^-\)\(^9\)

The following conditions were excluded from participation in the study: corneal scarring, lid, corneal or ocular conditions, disease, disorders or infection that may have confounded the study results. Pregnant or nursing women and contact lens wearers were also excluded as well as ocular surgery within 3 months of enrollment.

**Protocol**

Each enrolled subject received a standard ophthalmic examination from one of six investigators. CCT was measured by an assistant investigator with a Zeiss HD-OCT-5000 spectral domain ocular coherence tomographer (Zeiss, Jena, Germany). Corneal topography was completed with a Zeiss Atlas model 9000 (Jena, Germany) using the central 3 mm diameter of the cornea for analysis in accordance with ANSI Z80.23. An Ocular Response Analyzer was used to measure corneal hysteresis (CH) (Reichert, Depew, New York, USA) according to its instruction for use. Each investigator was masked to the results of the assistant investigator’s results and were also masked to the randomised and alternated use of the CATS and reference GAT prism devices, chosen by a random number generator. Topical anaesthetic drops were applied prior to each measurement with fluorescein (fluorescein sodium and benzoxine hydrochloride ophthalmic solution 0.25%/0.4%; Bausch & Lomb, Tampa, Florida, USA). A calibrated Haag-Streit model 900 application tonometer armature (Mason, Ohio, USA) was used to measure IOP with one of five cleaned and disinfected Haag-Streit reference GAT prisms and one of five CATS prisms. Pressure measurements were made two times with each GAT and CATS prism (one measurement consisted of averaged measurements at 180 and 90 degrees for astigmatism correction). Sequential measurements more than 2 mm Hg different required a third measurement. All three measurements were then averaged, if the third was within the range of the first two, otherwise the measurements were discarded. Four measurements were taken (two with each prism, four total).

**Test product**

Five modified surface Correcting Applanation Tonometry Surface (CATS) Tonometer prisms.

**Control product**

Five flat surface Haag-Streit Goldmann Applanation Tonometer (GAT) prisms.

**Objectives**

The clinical study’s primary performance objective was to examine improved IOP accuracy in accordance with expected standard Dresdner CCT correction for GAT IOP measurement. A secondary objective was to examine IOP measurement correlation with corneal hysteresis.

**Endpoints**

The primary endpoint was CCT corrected accuracy of IOP measurement readings, as measured by applanation tonometry. The criteria for success was the difference in IOP readings between modified (CATS) and GAT demonstrating a statistically significant correlation to CCT in accordance with standard published Dresdner CCT correction. Using the modified (CATS) tonometer prism and the Goldmann tonometer (GAT) prism to measure IOP enrolment continued until a minimum of 70 eligible eyes were identified equally in the high CCT (>600 \(\mu\)m) and low CCT (<500 \(\mu\)m) cornea categories. The sample population from a previous sister study of 172 eyes, which was limited to corneas with nominal CCTs (between 500 \(\mu\)m and 600 \(\mu\)m), was included in the CCT correlation to ensure continuity across the spectrum of probable CCT values.\(^2\) The study set of 173 eyes was run concurrently with the present study (70 eyes) using the identical protocol and clinical investigators. The only difference between the two patient populations was the range of CCT values.

**Statistical methods**

The Full Analysis Set (FAS) was used for the analysis of the primary endpoint. All eligible eyes were included in the FAS.
Continuous variables were used for descriptive statistics including mean, SD, median and range. An assessment of change from GAT to CATS IOP measurements baseline was provided using two-sided CIs and α=0.05 or one-sided CIs and α=0.025. The primary endpoint was analysed using a homoscedastic, two-tailed t-test (α=0.05) separately in both the high and low CCT value categories. A linear regression analysis of the difference in paired GAT and CATS IOP measurements was correlated to CCT. Linear regression analysis included the present set of 70 eyes and the previously published set of 173 eyes for a total of 243 unique eyes. Both data sets were collected concurrently using the same protocol in which CCT measurement determined the subject’s enrollment into each study. The secondary endpoint was evaluated using a homoscedastic, two-tailed t-test (α=0.05) separately in both the high and low CH value categories. High was defined as higher than mean and low was defined as lower than mean. A linear regression analysis of the difference in paired GAT and CATS IOP measurements was correlated to CH using the full set of 243 unique eyes. A multiple linear regression analysis was completed on the FAS using a general linear mixed effects model examining CCT, CH, IOP, age, gender and astigmatism.

RESULTS

Two hundred forty-three (243) unique eyes were measured. There were 173 eyes in the nominal CCT category (between 500 µm and 600 µm) and 33 eyes in the high CCT category (>600 µm) and 37 eyes in the low CCT category (<500 µm) (table 1). Measurements within all categories were completed in accordance with the ANSI Z80.10–2014 guidelines. There were 91 (37%) men and 154 (63%) women who completed the study with an average age of 59.9±19.0 years. Forty-five (45) eyes had high astigmatism (>3.0 dioptres) and 198 eyes had low astigmatism (≤3.0 dioptres). Fifty-nine (59) eyes were measured in the high IOP category (>23 mm Hg), 112 eyes were measured in the moderate IOP category (16 mm Hg to 23 mm Hg) and 72 eyes were measured in the low IOP category (<16 mm Hg).

Accuracy of IOP

Figure 2 shows the modified (CATS) versus GAT prism scatter-plot of all data according to FDA Tonometer Guidelines. The scatterplot indicates excellent correlation between the CATS and GAT IOP measurements throughout the useful range of measurement IOPs with a correlation coefficient of $R^2=0.91$, slope=$+0.93$ and y-intercept of $+2.15$. Bland-Altman paired difference plots were previously demonstrated as substantially equivalent ($±5$ mm Hg) with ANSI Z80.10–2014 tonometer testing using limited CCTs (500 µm to 600 µm). Overall, the mean bias in paired IOP measurements was +0.43 mm Hg higher with the CATS prism, which was not statistically significant (p=0.19).
Modified (CATS) prism's concave-convex applanation surface is a modelled iterative parametric solution to simultaneously minimise all four sources of error.\textsuperscript{12}

Both CCT and CH are recognised corneal biomechanical metrics associated with error in GAT IOP measurement.\textsuperscript{13–12,12,23} Corneal hysteresis (CH) is a dynamic measurement of corneal energy absorption from an impulse force which has an indirect relationship to global corneal elasticity produced by CCT and the cornea’s modulus of elasticity.\textsuperscript{24} The present study demonstrates a decreased sensitivity to variations in CH with the modified CATS compared with the GAT, which is likely reflective of CATS design minimising errors due to corneal biomechanical variability. Many studies have demonstrated in vitro and in vivo the correlation between CCT and CH to Goldmann IOP measurement error.\textsuperscript{11,12,17,21,24} With respect to CCT, studies have produced GAT CCT correction algorithms which produce a more accurate GAT IOP when compared with true intracamer-eral pressure.\textsuperscript{11,12,17,21} However, these CCT corrections have not demonstrated a more accurate predictive clinical model for primary open-angle glaucoma.\textsuperscript{13,14} Presently, clinical evidence only indicates that low CCT and low CH values are risk factors for glaucoma progression.\textsuperscript{13,14,24,25} CCT is only one source of error and its correction alone is likely insufficient to correct GAT IOP producing a clinically effective predictive model for glaucoma.\textsuperscript{24,26}

The present study presents evidence that a simple modified (CATS) replacement prism on any Goldmann-type tonometer may significantly improve the IOP measurement accuracy of a Goldmann tonometer. This advancement in Goldmann technology may further its use as the standard of care in the diagnosis and treatment of pressure-related diseases.

Future studies will examine the modified (CATS) prism and standard GAT prism IOP measurements in problematic patient populations. For the same reasons that the modified (CATS) prism demonstrates decreased corneal biomechanical sensitivity, it will likely afford improved IOP accuracy in both paediatric and post-refractive surgery patients. Planned studies will be conducted on patients before and after LASIK refractive procedures as well as on paediatric patients comparing with intracamer-eral pressure. These two populations comprise nearly 30% of the population.\textsuperscript{4,23} Additional studies are underway examining the difference in CATS and GAT IOP measurement differences in patients with keratoconus before and after corneal cross-linking as well as examining paired IOP differences with the introduction of topical prostaglandin analogues for glaucoma. Changes in the difference in CATS and GAT IOP measurements may reflect changes in overall corneal elasticity.\textsuperscript{20}

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Contributors
SJM: design, drafting, data acquisition, analysis and interpretation.
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Competing interests  The submitted manuscript was completed by referencing studies funded by an NIH/NEI SBIR grant, 1R43 EY026821-01. Requirements of this grant are commercialisation of potentially beneficial ophthalmic/optometric medical devices/products. The commercialisation necessitates intellectual property and a company to produce the product. Commonly in new technology start-up companies, the corresponding author is also part owner in the intellectual property and the associated company (Intuo Technologies) producing the medical device. This is a conflict of interest. However, the authors attest to the stringent efforts made to provide unbiased information provided in this manuscript. We believe, as does the NIH and ASCRS, that the tonometer device has a potential to bring considerable value to the ophthalmic medical community and their patients.

Patient consent for publication  Not required.

Ethics approval  This clinical study was conducted in accordance with the ethical principles contained within Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56) and Obligations of Clinical Investigators (21 CFR 812).

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