

Improved Efficacy of Topical Latanoprost 0.005% Demonstrated by Corneal Biomechanical Correcting Modified Goldmann Prism

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Purpose: To evaluate intraocular pressure (IOP) reduction measured by a Goldmann applanation tonometer (GAT) prism and a modified surface Goldmann (CATS) prism with the institution of a topical prostaglandin analog (PGA) or alternatively a topical beta blocker.

Design: Prospective, open-label, randomized, controlled, and reference device comparison.

Methods: Thirty-six (36) treatment naïve glaucoma patients (72 eyes) were randomized equally to treatment with latanoprost 0.005% or timolol maleate 0.5%. Each patient underwent IOP measurement with standard GAT and CATS prisms before and at 1, 3, and 6 months of treatment. Central corneal thickness (CCT) and corneal hysteresis (CH) were also measured. Medication response was defined as a 20% reduction in IOP from baseline.

Results: The CATS prism demonstrated the IOP reduction with topical latanoprost at a mean of 1.9 mmHg lower than the IOP measured with GAT ($p=0.01$). The CATS and GAT prisms detected no difference in IOP reduction with timolol ($p=0.23$). The number of latanoprost treatment non-responders was reduced from 36.1% measured with GAT to 13.8% when measured with the CATS prism ($p=0.005$). Timolol indicated no difference in the treatment non-response rate at 22.2% ($p=0.999$). CH increased significantly with latanoprost treatment by an average of 0.55 mmHg ($p=0.014$) and remained unchanged with timolol at -0.014 mmHg ($p=0.68$).

Discussion: IOP reduction and responder rates were increased when measured with a CATS prism in patients using latanoprost and not with timolol use. Latanoprost-induced alterations in corneal biomechanics may dampen the actual IOP reduction measured with a standard GAT prism.

Clinical Trial Registration: ClinicalTrials.gov NCT04178863.

Keywords: glaucoma, prostaglandins, IOP, tonometer, corneal biomechanics, timolol, latanoprost

Plain Language Summary

Latanoprost 0.005% drops for glaucoma may be more effective at lowering eye pressure by measurement with an improved accuracy tonometer device when compared to the historical standard tonometer device.

Synopsis

Latanoprost 0.005% reduction in IOP measured using a corneal biomechanical correcting Goldmann prism indicates 1.9 mmHg lower IOP compared to that measured by a standard Goldmann prism, which is not seen with use of timolol 0.5%.

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Introduction

Intraocular pressure (IOP) is the most important risk factor for glaucoma and glaucoma progression.¹ It remains the only leading indicator of glaucoma progression and the primary modifiable parameter in the treatment of glaucoma.² Goldmann Applanation Tonometry (GAT) remains the standard of care for IOP measurement.³ Variability in a patient's central corneal thickness (CCT), modulus of elasticity, corneal curvature, and tear film produces significant errors in GAT IOP measurement.⁴⁻⁶

The corneal biomechanical measurements of corneal hysteresis (CH) and CCT have been shown as independent risk factors for the diagnosis and progression of glaucoma. Thin CCT is associated with glaucomatous progression demonstrated by field loss despite equal pressures to those patient's with normal CCTs.⁷⁻¹⁰ Low corneal hysteresis is also associated with optic nerve and visual field damage in glaucoma.¹¹⁻¹³ Although both CCT and CH are seen as independent factors for glaucoma, their association with inaccurate IOP measurement likely contributes to the increased risk of progression.^{11,14,15}

Topical prostaglandin analog (PGA) medications are among the most commonly used glaucoma drops and are highly effective at reducing IOP.¹⁶ Prostaglandins have been shown to significantly affect the biomechanical properties of tendinous collagenous tissue.¹⁷ Several studies have shown an increase in CH and Corneal Resistance Factor (CRF) with the use of PGAs.^{16,18,19} One study indicated possibly an opposite response with an increase in CH and CRF upon cessation of PGAs.²⁰ The Corvis ST corneal response was shown to have a possible decrease in corneal stiffness with PGA use but the results were without a definitive indication as to the global change in corneal biomechanics.²¹ Although the question of whether PGA medications cause global corneal softening may be a significant oversimplification of the process particularly as a predictor of its effect on tonometry. There is growing evidence that corneal deformation is affected by a redistributed "buckling stress" and its behavior during applanation is more complex and highly non-linear.²²⁻²⁴ Topical timolol maleate drops have not been shown to have an effect on corneal biomechanical properties.²¹ Changes in IOP have been shown to change the cornea's modulus of elasticity and CCT which would affect tonometric IOP accuracy.^{4,6,22}

A modified Goldmann prism (CATS) was recently cleared for use by the United States Food and Drug

Administration (US FDA) to measure IOP. The modified prism incorporates a correcting applanation tonometry surface (CATS) to the GAT prism and can replace the GAT prism on any Goldmann type tonometer. (Figure 1) Several studies, including intracameral pressure comparisons, have shown the CATS prism to have significantly decreased sensitivity to variations in corneal biomechanical properties when compared to the GAT prism.^{22,25-29} The design differences were described in detail previously.²² Differences in IOP between the CATS and GAT measurements were strongly correlated with variations in corneal biomechanical properties such as CCT and CH.^{22,25,27-29} The CATS prism demonstrates a more accurate IOP as it negates much of the tonometer force due to corneal biomechanical deformation measuring predominantly the IOP when compared to the GAT prism. Furthermore, there was no overall IOP bias demonstrated between the two prisms over a large standard population.^{22,25-29} Since both prisms measure the same pressure for a cornea with nominal biomechanical properties, it is likely that the difference in CATS and GAT IOP is a direct measurement (in mm Hg) of those combined corneal biomechanical properties affecting its deformation.^{25,26}

The present study was completed to evaluate the effect of PGAs on IOP measurement accuracy and measure changes in corneal biomechanical properties. In addition, the study participants were equally randomized to timolol maleate treatment to delineate the effects of lowering IOP on the corneal biomechanics and IOP differences. Study design complies with the International Standards Organization (ISO) 8612:2009.



Figure 1 Applanating surface of the centrally concave and circumferentially convex (CATS) prism.

Methods

Enrollment included treatment naïve glaucoma patients. Upon enrollment, subjects underwent a series of IOP measurements with the modified (CATS) and standard GAT tonometer prisms. The design was a randomized, controlled, prospective, open-labeled, device comparison. The study was registered prospectively on clinicaltrials.gov (NCT04178863) and IRB approved by Chesapeake. Eligible subjects were screened, enrolled, and evaluated according to the study protocol and were recruited from 2 sites. Participation in the study included subjects 18 years or older, meeting the protocol criteria, who provided written informed consent.

The clinical study was conducted within the ethical principles contained in Declaration of Helsinki, Code of Federal Regulations (CRF), Protection of Human Volunteers (21 CFR 50), Obligations of Clinical Investigators (21 CFR 812), and Institutional Review Boards (21 CFR 56)

Description of Study Population

Naïve glaucoma patients were enrolled into the study to include thin ($<600\mu\text{m}$) and normal corneas ($600\mu\text{m}>\text{CCT}>500\mu\text{m}$). The 72 eye sample size was calculated using the difference between two paired means with an $\alpha=0.05$ (2-tailed), $\beta=0.2$, power=0.85 and the mean differences and standard deviations from previous studies.^{20,22,25}

The following exclusionary conditions were prevented from study participation: corneal scarring, lid, corneal, or ocular conditions, disease, disorders, or infection that potentially affect corneal biomechanics and may have confounded the study results. Also excluded from the study were high myopes (>6 diopters) and high astigmatism (>3 diopters). Pregnant or nursing women and contact lens wearers were also excluded as well as any prior ocular surgery.

Protocol

Enrolled subjects received an ophthalmic exam from one of the investigators which included a new diagnosis of primary open-angle glaucoma by at least one of the following criteria: (1) visual field progression in at least one eye; (2) optic disc progression in at least one eye by OCT; (3) optic disc hemorrhages in at least 1 eye.³⁰ Subjects were randomized by (a) random number generator to topical drop treatment with latanoprost 0.005% once daily or timolol maleate 0.5% twice daily. An Ocular Response Analyzer (ORA) was used to measure corneal hysteresis (CH) and IOP (Reichert, Inc,

Depew, NY), by an assistant investigator. Central corneal thickness (CCT) was measured with a Zeiss HD-OCT-5000 spectral domain ocular coherence tomographer (Zeiss, Jena, Germany), by an assistant investigator.

Two Investigators measuring IOP were masked to the results of the assistant investigator's tests. Randomized initial use of the CATS and GAT prism devices was chosen by random number generator. Topical anesthetic drops with Fluorescein (fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.25%/0.4%, Bausch & Lomb, Tampa, FL) were used before each measurement. A calibrated Haag-Streit model 900 applanation tonometer (Mason, OH) was used to measure IOP with an alternated Haag-Streit GAT prisms and a CATS prism. Pressure measurements spaced by 5 minutes were made two (2) times with each a CATS and GAT prism (consisting of averaged measurements at 180 and 90 degrees to correct for astigmatism).²⁶ Measurements were completed before treatment and at 1, 3, and 6 months following the institution of topical medication.

Endpoints

The primary endpoint was an IOP measurement comparison between modified (CATS) and GAT prisms with the use of latanoprost and timolol topical treatment for glaucoma. Also examining the difference between CATS and GAT IOP measurements' correlation to the known corneal biomechanical parameters of CCT and CH with the use of latanoprost and the use of timolol as a pressure lowering control. Non-response rates to the topical medications were defined as failure to lower the pressure by 20% from baseline IOP at 6 months and were calculated for both CATS and GAT prism use each with latanoprost and timolol. Validating analyses were completed on the changes seen in CCT and CH with the use of latanoprost and timolol.

Statistical Methods

The Full Analysis Set (FAS) was used to analyze the primary and secondary endpoints. The FAS included all eligible eyes.

Continuous variables were used for descriptive statistics including mean, standard deviation, median, and range. The primary endpoint was analyzed using a homoscedastic or paired, 2-tailed *t*-test ($\alpha = 0.05$). A linear regression analysis of the difference in paired GAT and CATS IOP measurements was correlated to CCT and CH. A multiple linear regression analysis was

Table 1 Table of Unique Patient and Eye Demographics in Test and Control Arms

Indiv. Measurements	Total	Latanoprost 0.005%	Timolol 0.5%
Unique eyes	36 pts./72 eyes	36 eyes from 18 pts.	36 eyes from 18 pts.
Male,Female	8,28	3,15	5,13
Age $\pm$ S.D.	61 $\pm$ 14	60 $\pm$ 15	63 $\pm$ 15
Initial CCT (μ m) $\pm$ S.D.	540 $\pm$ 34	540 $\pm$ 36	541 $\pm$ 33
Initial CH (mmHg) $\pm$ S.D.	9.7 $\pm$ 1.3	9.6 $\pm$ 1.5	9.8 $\pm$ 0.95
Initial GAT IOP (mmHg) $\pm$ S.D.	20.7 $\pm$ 7.0	20.6 $\pm$ 7.9	20.8 $\pm$ 6.2
% by GAT/CATS initially below 21mmHg	61.1/38.9	63.9/33.3	58.3/44.0

completed on the FAS using a general linear mixed effects model examining CH, CCT, IOP, age, and gender.

control arm. CCT, CH, Initial IOP, and percent of eyes below 21mmHg were closely matched between cohorts (Table 1)

Results

Seventy-two (72) eyes were measured from 36 patients. There were thirty-six (36) eyes enrolled from 18 patients with the use of latanoprost and thirty-six (36) eyes from 18 patients with the use of timolol. Four (4) eyes (2 patients) in the latanoprost group and six (6) eyes (3 patients) in the timolol group did not complete all measurements and were included in the FAS to the degree which they were completed. There were 3 (17%) males and 15 (83%) females with an average age of 60 $\pm$ 15 years who were enrolled in the latanoprost arm. There were 5 (27%) males and 13 (73%) females with an average age of 63 $\pm$ 15 years who were enrolled in the timolol

CATS and GAT IOP Reduction Analysis

The IOP reduction with both CATS and GAT measurements in each cohort is demonstrated before and at pre-scribed follow-up times in Figure 2 and Table 2.

Table 2 illustrates the differential IOP means. Initial paired CAT minus GAT IOP differences indicated an average of 1.95 $\pm$ 2.23 mm Hg higher IOP with the CATS prism compared to the GAT prism. Twenty-two percent (22%) of the patients initially classified as normal tension glaucoma by GAT IOP measurement less than 21 mmHg would have been reclassified as primary open angle glaucoma by the higher CATS IOP measurements at 6 months, a representative

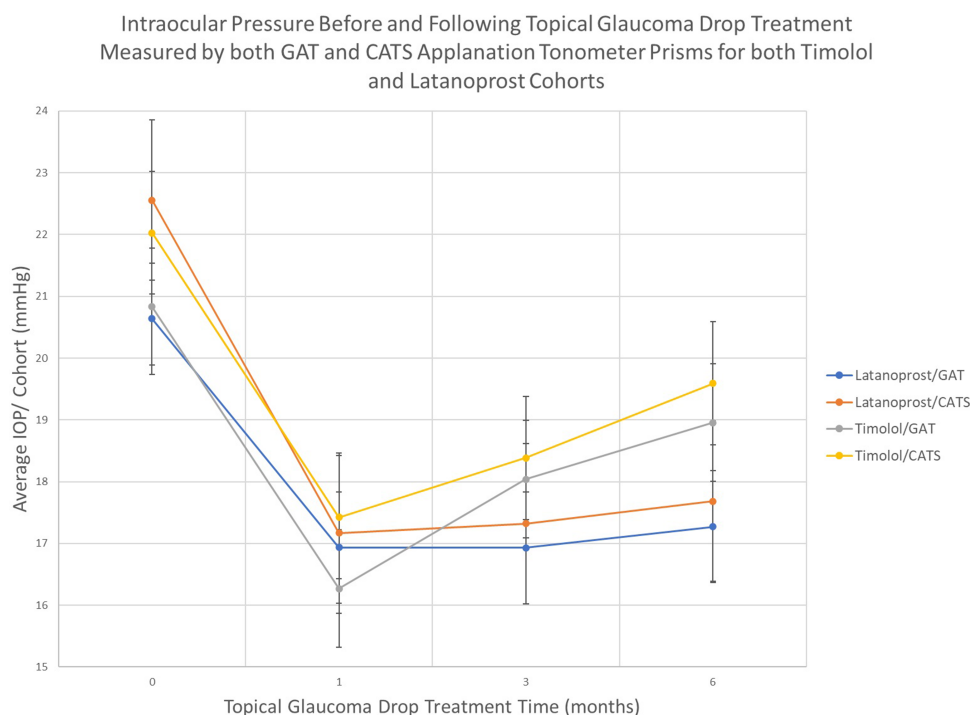


Figure 2 Timolol and latanoprost cohort IOP measurements at treatment times.

Table 2 Timolol and Latanoprost Cohort Mean IOP Measurements and Standard Deviation at Treatment Examination Times

	Pre-Treatment	1 Month	3 Months	6 Months
Latanoprost cohort				
Mean GAT	20.64	16.93	16.93	17.27
S.D.	2.57	1.12	1.13	1.31
Mean CATS	22.56	17.17	17.32	17.68
S.D.	2.65	1.21	1.09	1.32
CATS-GAT	2.02	0.23	0.39	0.41
Paired Difference				
S.D.	2.30	1.41	1.14	1.85
Timolol cohort				
Mean GAT	20.83	16.27	18.04	18.95
S.D.	2.03	1.37	1.64	1.90
Mean CATS	22.03	17.42	18.38	19.59
S.D.	2.11	1.27	1.49	1.69
CATS-GAT Paired	1.91	1.07	0.34	0.5
Difference				
S.D.	2.02	1.77	1.54	1.5

analysis of the differential IOP between paired GAT and CATS measurement is presented. The differential IOP at both the one and three month examination times is similar as shown in Figure 2 and Table 2. The IOP reduction with the CATS prism in patients using topical latanoprost 0.005% was normally distributed with an average of 6.5 ± 5.9 mmHg lower from baseline IOP at 6 months. The IOP reduction with the GAT prism in patients using latanoprost averaged 4.6 ± 5.2 mmHg lower from baseline at 6 months. The CATS prism IOP measurements were 1.9 mmHg lower than the paired IOP measured with the GAT prism ($p=0.01$). (Table 3)

CATS IOP reduction with timolol maleate 0.5% was 2.8 ± 6.7 mmHg compared to 3.3 ± 6.7 mmHg in the paired timolol control arm. The IOP measurements between CATS and GAT prisms did not demonstrate a significant difference with timolol ($p=0.23$). The GAT IOP reduction seen with latanoprost approached significantly lower than timolol in this sample size ($p=0.08$). However, the IOP reduction of latanoprost compared to timolol was significantly lower when the IOP was measured with the CATS prism ($p=0.008$). (Table 3)

CATS and GAT Non-Response Rate Analysis

Topical treatment non-response was defined as a failure of the medication to lower the IOP by 20% from baseline at 6

Table 3 CATS and GAT IOP Reduction in Latanoprost 0.005% Test and Timolol 0.5% Control Arms at 6 Months

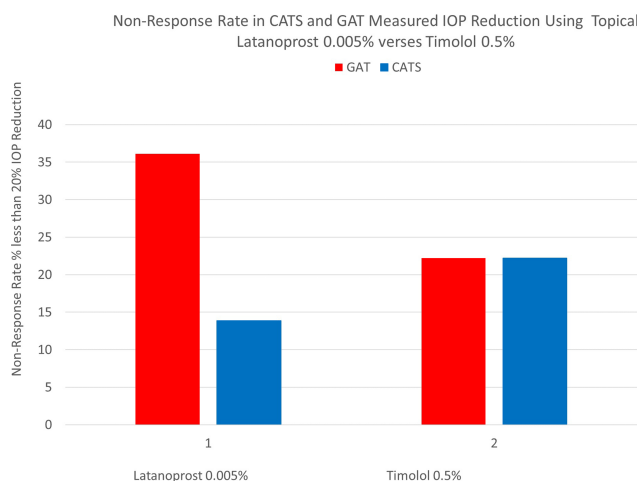
Prism	Latanoprost 0.005% mmHg	Timolol 0.5% mmHg	Difference (Lat-Tim) mmHg (p =homoscadastic)
CATS mmHg $\pm$ S.D.	6.5 ± 5.9	2.8 ± 6.7	3.7 ($p=0.008$)
GAT mmHg $\pm$ S.D.	4.6 ± 5.2	3.3 ± 6.7	1.5 ($p=0.08$)
IOP drop (Pre-6 mos.) mmHg (p =paired)	1.9 ($p=0.01$)	-0.5 ($p=0.23$)	

months. The number of latanoprost treatment non-responders was reduced from 36.1% measured with the standard GAT prism to 13.8% when measured with the CATS prism ($p=0.005$). Timolol indicated no difference in the treatment non-response rate at 22.2% ($p=0.999$). (Figure 3)

Corneal Hysteresis and CCT Validation

Corneal hysteresis (CH) increased significantly with latanoprost treatment by an average of 0.55 mmHg ($p=0.014$) and remained unchanged with timolol at -0.014 mmHg ($p=0.68$). The subject's average CH was 9.6 ± 1.5 mmHg in the latanoprost arm and 9.8 ± 0.95 mmHg in the timolol control arm, before treatment.

Central corneal thickness (CCT) increased from baseline but not significantly by 0.5% ($p=0.27$) in the latanoprost group and decreased by 0.9% in the timolol group ($p=0.10$). However, the difference in CCT change between the latanoprost test and timolol control groups was statistically increased in the latanoprost group by 1.4% ($p=0.005$).

**Figure 3** Non-response rates less than 20% reduction from baseline IOP in CATS and GAT measured IOP reduction using topical latanoprost 0.005% or alternatively timolol 0.5%.

The general linear mixed effects (GLME) model indicated significant and nearly significant correlations between the difference in CATS and GAT IOP measurements to CCT and CH ($p=0.010$, $p=0.065$). Age also correlated to the difference in CATS and GAT IOP measurements to CCT and CH ($p=0.025$, $p=0.016$). No significant correlation was seen in either group or combined groups between the difference in CATS and GAT IOP measurements nor CH to IOP.

Conclusions

Significantly greater IOP reduction was demonstrated using a PGA, latanoprost 0.005%, by IOP measurement with a corneal biomechanical correcting modified Goldmann (CATS) prism. No additional timolol 0.5% IOP reduction was seen using the CATS prism with when compared to the standard flat applanation surface GAT prism. These results were demonstrated at 1.3, and 6 months. The GAT measured IOP reduction approached statistically lower with latanoprost compared to timolol cohorts. However, modified CATS IOP measurement shows the latanoprost group demonstrates significantly greater IOP reduction than the timolol group.

The modified CATS prism is reading a greater pressure reduction than has been previously demonstrated with PGAs measured by GAT. It is unlikely that these results indicate a global change in corneal rigidity with PGAs. The authors see evidence the study findings are consistent with the PGA inducing a stress redistribution within the stromal lamellae. The corneal response to applanation and the changes due to PGAs appear more complex than a simplified global metric of increased or decreased corneal stiffness is able to predict. Modeling used to design the modified applanating surface of the CATS prism indicated that the pressure across the applanation surface is not constant as it has been presumed.²² The local pressure force at the center of the applanation diameter approaches zero using a flat surfaced Goldmann prism and the cornea actually buckles or dimples centrally.^{15,22} This corneal buckling is supported by other studies.^{23,24} The modified CATS prism surface equalizes this pressure distribution across the applanation surface and demonstrates a significantly decreased sensitivity to alterations in the major sources of corneal biomechanical error.^{22,25-29}

Decreased non-responder rates were also demonstrated with a modified Goldmann (CATS) prism in patients using the PGA latanoprost and not with timolol use. Part of the latanoprost non-response may be latanoprost induced

alterations in corneal biomechanics which dampen the actual IOP reduction measured with a standard GAT prism.

Corneal hysteresis was shown to increase in the PGA latanoprost group and not in the timolol group. Hysteresis and corneal rigidity are parameters that tend to follow each other as they are related under specific narrow assumptions. However, CH is a dynamic global corneal dampening coefficient and not a static spring constant measuring global corneal stiffness or rigidity. The difference in CATS and GAT IOP differs from CH in that it is likely a measure of the static spring constant or average corneal rigidity at full applanation. The study findings corroborate well with previous studies and likely validate the effect of corneal stress redistribution and buckling previously discussed.^{16,18,19,23,24}

CATS tonometer prism IOP measurements have been shown substantially equivalent to flat surfaced GAT prism IOP measurements in patients without disease such as glaucoma and having nominal CCTs between 500 and 600 microns.^{26,27} Initial differential CATS minus GAT IOP measurements indicated an average of 1.95 ± 2.23 mm Hg higher IOP with the CATS prism compared to the GAT prism. Additionally, 22% of the patients would be reclassified as primary open-angle glaucoma from normal tension glaucoma based upon the higher IOP measurement with the CATS prism. The obvious difference accounting for the pre-treatment higher IOP bias with CATS is that these are patients with glaucoma and about half are normal tension glaucoma. The CATS prism has been shown to correct for corneal biomechanical errors in IOP and the difference between CATS and GAT is likely a measure of relative corneal biomechanical properties as demonstrated by its correlation to CCT and CH.^{22,23,26-29} Similar measures of corneal biomechanical properties such as low CH have been shown to have a significant predictive value for glaucoma progression and higher prevalence in glaucoma patients including NTG patients.^{13,16} Similarly, this glaucoma pre-treatment bias suggests there may be higher predictive value for the diagnosis or progression of glaucoma with CATS IOP measurements using historical benchmarks such as 21 mm Hg when compared to GAT prism IOP. A longitudinal study examining glaucoma diagnosis and progression would be required to confirm this hypothesis.

It is possible that latanoprost increased CH more than timolol because latanoprost is more effective at lowering IOP, particularly as it has been shown over the entire 24-hour window.³¹ That selective laser trabeculoplasty (SLT)

also increases CH in a manner similar to latanoprost, suggests that IOP lowering may itself elevate CH.³² However no change in CH or CATS-GAT IOP difference was noted with IOP reduction in the Timolol group. Differential tonometry (using two different tonometers) has been described and used in several studies to measure changes in corneal rigidity.³³ The differential tonometry between CATS and GAT IOP has an advantage in that the CATS prism was designed to have zero overall bias when compared to GAT.²⁶ However, whether latanoprost directly alters the corneal biomechanics or whether it elevates CH through its action on IOP, the magnitude of IOP lowering as measured by GAT measurements may remain underestimated.

Additional results include a statistically significant correlation between the CATS and GAT IOP measurement differences to CCT and nearly to CH. This finding validates previous results demonstrating a decreased sensitivity in CATS IOP measurements to the corneal biomechanical parameters of CCT and CH.^{22,25-29} The modified (CATS) and GAT prisms showed no differences in measurement based upon gender, or IOP, but indicated a statistically significant correlation with age. The age-related increase in CATS-GAT IOP differences and related decrease in CH corroborate prior studies.^{9,15}

Studies measuring IOP as a primary endpoint, such as glaucoma medication clinical trials, should include some correction for corneal biomechanical differences or alterations which create significant error in GAT. Even surgical studies that appear remote to the cornea can have a significant effect on corneal biomechanics and induce significant GAT error.^{34,35} Future studies include examining the difference in CATS-GAT IOP measurement differences before and after LASIK and corneal cross-linking as well as examining paired IOP differences pediatric populations.

Abbreviations

ANSI, American National Standards Institute; CATS, correcting applanation tonometry surface; CCT, Central Corneal Thickness; CH, corneal hysteresis; CFR, Code of Federal Regulations; CRF, corneal resistance factor; FDA, Food and Drug Administration; GAT, Goldmann applanation tonometer; IOP, intraocular pressure; IRB, Independent Review Board; ISO, International Standards Organization; NTG, normal tension glaucoma; ORA, Ocular Response Analyzer; PGA, prostaglandin analog; SLT, selective laser trabeculoplasty.

Ethics and Consent to Participate

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). Deidentified data will be made available upon request to the corresponding author for a period of three years.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Sean McCafferty has an interest in Intuor Technologies (Tucson, AZ) which owns the technology being examined in this clinical trial. Additional grant support unrelated to this study has been provided by Abbott Medical Optics (Santa Ana, CA), and Alcon, Inc. (Ft. Worth, TX). He also reports grants from NIH/NEI, during the conduct of the study; non-financial support from Reichert, outside the submitted work. Sean McCafferty has a patent on prism owned by CATS Tonometer issued. Jason Levine has unrelated study grant support from Innfocus, Inc. John Berdahl is a consultant to and reports personal fees from Intuor. Justin Schweitzer reports personal fees from Reichert, during the conduct of the study. Mitchel Ibach reports personal fees from Aerie pharmaceuticals, outside the submitted work. Nathan Radcliffe reports personal fees from Reichert, CATS, LLC, Allergan, Alcon, Novartis, Glaukos, Ivantis, New World Medical, Bausch & Lomb, Omeros, Lumenis, and Ellex, outside the submitted work. The authors report no other conflicts of interest in this work.

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