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Original Article

CORRELATION BETWEEN INTRAOCULAR PRESSURE MEASUREMENTS USING APPLANATION TONOMETRY AND OCULAR RESPONSE ANALYZER (ORA) IN PRIMARY CONGENITAL GLAUCOMA (PCG) PATIENTS

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Abstract

Objective: *This study aims to assess the degree of agreement between IOP measured using Perkins and Goldmann applanation tonometers, and both Goldmann correlated intraocular pressure (IOPg) and corneal compensated intraocular pressure (IOPcc) measured using ORA in PCG patients.* ***Study Design:*** *a prospective, single-center, observational study.* ***Patients and Methods:*** *All patients with PCG and fulfilling the inclusion criteria of the study underwent full ophthalmological examination and CCT measurement using ultrasound pachymetry. Applanation tonometer was used to measure the IOP. ORA was used to detect CH, CRF, IOPcc, and IOPg. Agreement between IOP measured using applanation tonometers, and both IOPg and IOPcc was tested using interclass correlation (ICC).* ***Results:*** *Forty three eyes of 28 patients were included. Twenty two were males. The mean patients age was 9.14 years. The mean IOP measured using applanation tonometry was 16.07 mmHg. The mean IOPg was 21.857 mmHg. The mean IOPcc was 24.17 mmHg. The mean difference of IOP measured by applanation and both IOPg and IOPcc was 5.78 mmHg and 8.1mmHg respectively with higher measurements by ORA. These differences were statistically significant (p =0.00). IOPg error % was statistically significantly positively correlated with CCT (p=0.009) and CRF (p=0.00) with correlation coefficient of 0.399 and 0.504 respectively. IOPcc error % was statistically significantly negatively correlated with CH (p=0.034) with correlation coefficient of - 0.324.* ***Conclusion:*** *In the current study, a statistically significant difference between the IOP measured using applanation tonometry and ORA obtained IOP namely IOPg and IOPcc was detected with higher ORA measurements.*

Keywords: *PCG, Applanation tonometry, ORA.*

1. Introduction

Although being a rare disease, Primary congenital glaucoma (PCG) whether of neonatal or juvenile onset has a dangerous effect on the child's vision [1]. Proper control of the intraocular pressure (IOP) is the target of the ophthalmologists to prevent this visual disability. Goldmann applanation tonometer is considered the standard reference for measuring IOP. Since it needs the patient to be in upright position and highly cooperative, the handheld Perkins applanation tonometer (PAT) is highly

recommended to be used instead of GAT in pediatric age group as it allows for IOP measurement of the infants and young children in the supine position and allows for free movement of the examiner with the examined child [2]. The corneal thickness was introduced as a factor which can influence the IOP measurement using applanation tonometer and it can predict the progression of glaucoma [3], ever since the concept of corneal biomechanics and their effects on the accurate IOP measurement became into focus. The Ocular Response Analyzer (ORA) is a non-contact non- invasive instrument developed since 2005 to measure corneal biomechanical properties [4] and it is considered as an air puff tonometer that corrects for corneal biomechanics [5]. Since multiple studies detected decrease in the corneal biomechanics in patients with PCG [6,7], this decrease can affect the IOP measurement adding to the challenge of accurate IOP monitoring. The aim of this study is to detect the feasibility of using ORA in pediatric cases of PCG and to assess the degree of agreement between the IOP measured using Perkins and Goldmann applanation tonometers, and both Goldmann correlated intraocular pressure (IOPg) and corneal compensated intraocular pressure (IOPcc) measured using ORA in those patients

2. Patients and Methods

This was a prospective, analytical, observational, single-center study applied on 43 eyes of 28 patients presented to Abo Elreesh glaucoma subspecialty clinic, Cairo University. All guardians of selected patients received an explanation of the study aims and design. An informed oral consent (since it is a non-interventional procedure) was obtained from all guardians of the patients. All procedures performed in the study followed the 1964 Helsinki declaration and its later amendments.

2.1. *Study population*

2.1.1. Inclusion criteria

Based on the guidelines of the Childhood Glaucoma Research Network (CGRN), all patients meeting the diagnostic criteria for PCG, including elevated IOP, enlarged corneal diameter, corneal edema and glaucomatous cupping of the optic nerve, in the absence of any associated ocular anomalies were included [1].

2.1.2. Exclusion criteria

Exclusion criteria included patients with associated non acquired ocular or systemic anomalies (e.g. iridocorneal endothelial dystrophies, Sturge–Weber syndrome, and neurofibromatosis), acquired ocular diseases (e.g. uveitis, ocular malignancies or ocular traumas) and glaucoma following cataract surgery (GFCS). All uncooperative patients, patients less than 4 years of age and cases with poor fixation were also excluded.

2.2. *Data collection*

History (including; personal history, present history, history of systemic diseases, history of ocular diseases, history of ocular treatments or previous surgeries) was taken from all guardians of the patients. All patients underwent a full ophthalmological examination in the form of best corrected visual acuity (BCVA) using Snellen’s chart (whenever feasible), slit lamp examination, fundus examination by indirect ophthalmoscopy when the clarity of the cornea allowed, otherwise ultrasonography was done. Horizontal corneal diameter (HCD) measurement using calipers was done under general anesthesia with the examiner standing at the head of the patient. white-to-white HCD was measured from 3 o'clock limbus to 9 o'clock limbus.

IOP measurement by Perkins or Goldmann tonometer was done. IOP measurement for cooperative and older children was done in the outpatient clinic after instillation of anesthetic eye drops, benoxinate hydrochloride 0.4 mg and fluorescein eye drops. GAT was used to measure IOP for older cooperative children while PAT was used for younger and uncooperative patients. Measurement of IOP was done under general anesthesia using PAT for uncooperative children. The measurement was done during induction of anesthesia to avoid the IOP lowering effect of inhalation anesthesia. Areas of corneal scaring must be avoided during measuring of IOP (this was not encountered during this study since these patients were excluded from the study). To avoid the diurnal variation of IOP, IOP was measured in the morning. Hand held pachymeter (Pachmate2, DGH technology, Inc, Exton, PA, USA®) was used to measure Central corneal thickness (CCT). Measurement of corneal biomechanics using ORA (Reichert Ophthalmic Instruments, Buffalo, NY, USA) was done. Each patient was instructed about the machine and the jet of the air puff which will be felt. The patient was instructed to focus on the red light and then the machine was activated. Three readings for each patient were taken. The reading which could be reliably taken was the one with the highest waveform score. Readings with waveform scores of less than 3.5 were discarded.

2.3. *Outcome measures*

1) Detection of biomechanical properties of cornea in eyes with PCG through detection of corneal hysteresis (CH), corneal resistance factor (CRF), IOPg and IOPcc. **2)** Detection of the degree of agreement between IOP measured using Perkins or Goldmann applanation tonometers, and both IOPg and IOPcc measured using ORA. **3)** Detection of the difference between the measurements of IOP using Perkins or Goldmann applanation tonometers and Goldmann correlated IOP (ie: IOPg error) and the percentage of this error (ie: IOPg error %). **4)** Detection of the difference between the measurements of IOP using Perkins or Goldmann applanation tonometers and corneal compensated IOP (ie: IOPcc error) and the percentage of this error (ie: IOPcc error %). **5)** Detection of Correlation between age, CH, CRF, CCT, corneal diameter and IOPg error and between them and IOPcc error

2.4. *Statistical analysis*

Data were presented in forms of mean ± standard deviation (± SD), range, percentages and frequencies. Comparison between the different techniques of measuring IOP was done using paired *t* test. Pearson and Spearman correlation equations were used for Correlation between various variables. *p* values less than 0.05 was considered statistically significant. Agreement was tested using interclass correlation (ICC) statistics. Computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) was used for statistical calculations.

3. Results

Forty three eyes of 28 patients were included in the study. Twenty two (78.6%) were males. The mean patients age was 9.14± 3.385 years. The mean corneal diameter was 14.07± 1.172 mm. The mean central corneal thickness was 541.67± 72.26 um, tab. (1). CH, CRF, IOP measurements using Perkins or Goldman applanation tonometers, IOPg, IOPg error, IOPg error %, IOPcc, IOPcc error and IOPcc error % are presented in tab. (2).

3.1. *The degree of agreement between the measurements of IOP using Perkins or Goldman applanation tonometers and IOPg*

A good agreement between the measurements of IOP using Perkins or Goldman applanation tonometers and IOPg was detected (P =0.00) with intraclass correlation coefficient = 0.705, fig. (1). Using the multivariate linear regression analysis, none of age, gender, IOP measurement, CH, CRF, CCT and corneal diameter were with significant effect on the difference between the measurements of IOP using Perkins or Goldman applanation tonometers and IOPg (P = 0.638, 0.781, 0.347, 0.205, 0.166, 0.817 and 0.993 respectively). Despite this good agreement, the difference between the measurements of IOP using Perkins or Goldman applanation tonometers and IOPg were statistically significant (p=0.00). The mean IOPg error was 5.786 mmHg with higher readings of IOPg obtained with ORA. Also the mean percentage of this error was statistically significant (p=0.00) and it was equal to 38.74%.

Table 1: Age, CCT and corneal diameter of all patients.

	Mean	SD	Minimum	Maximum	Median
Age (years)	9.14	3.385	4.00	15.00	9.50
CCT (µm)	541.67	72.26	423.00	703.00	540.00
Corneal diameter (mm)	14.07	1.172	12.00	16.00	14.00

***CCT**: central corneal thickness, **µm**: micrometer, **mm**: millimeter, **SD**: standard deviation.*

Table (2): CH, CRF ,IOP (GAT), IOPg ,IOPg error ,IOPg error %, IOPcc ,IOPcc error and IOPcc error % of all patients

	Mean	SD	Minimum	Maximum	Median
CH (mmHg)	7.90	2.39	3.90	13.70	7.80
CRF (mmHg)	10.19	3.78	3.40	19.00	9.55
IOP (GAT) (mmHg)	16.07	8.49	6.00	42.00	12.50
IOPg (mmHg)	21.86	12.98	7.70	55.40	17.50
IOPg error (mmHg)	5.786	7.832	-6.40	25.40	4.450
IOPg error %	38.74	50.206	-36.00	166.00	32.05
IOPcc (mmHg)	24.171	12.244	10.60	54.70	19.250
IOPcc error (mmHg)	8.100	7.097	-7.40	24.60	6.800
IOPcc error%	58.33	52.487	-41.00	197.00	50.42

***CH**: corneal hysteresis , **CRF**: corneal resistance factor, **IOPcc**: corneal compensated intraocular pressure, **IOPg**: Goldman correlated intraocular pressure, **IOP (GAT)**: Goldman applanation tonometer, **mmHg**: millimeter mercury, **SD**: standard deviation*

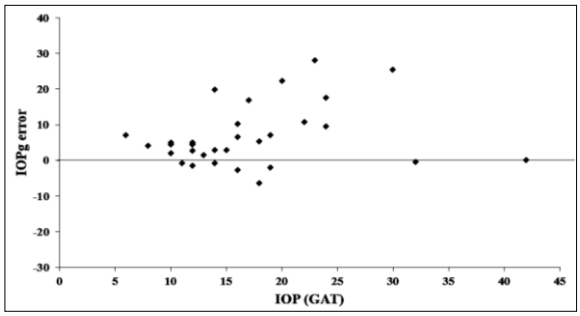

Figure 1: Bland Altman plots of the degree of agreement between the measurements of IOP using Perkins or Goldmann applanation tonometers and Goldmann correlated IOP using ORA (IOPg)

3.2. *Correlation between IOPg error, IOPg error % and age, CH, CRF, CCT, and corneal diameter*

Using Pearson and Spearman correlation equations to detect the correlation between IOPg error and age, CH, CRF, CCT, and corneal diameter, IOPg error was found

to be statistically significantly positively correlated with CCT (p= 0.012) and CRF (p=0.00) with correlation coefficient of 0.386 and 0.729 respectively. In addition, IOPg error % was statistically significantly positively correlated with CCT (p=0.009) and CRF (p= 0.00) with correlation coefficient of 0.399 and 0.504 respectively.

3.3. *The degree of agreement between the measurements of IOP using Perkins or Goldman applanation tonometers and IOPcc*

There was a good agreement between the measurements of IOP using Perkins or Goldman applanation tonometers and IOPcc (p=0.00) with intraclass correlation coefficient = 0.728, fig. (2). Using the multivariate linear regression analysis, none of age, gender, IOP measurement, CH, CRF, CCT and corneal diameter were with significant effect on the difference between the measurements of IOP using Perkins or Goldman applanation tonometers and corneal compensated IOP (IOPcc) (P=0.640, 0.911, 0.348, 0.139, 0.245, 0.815 and 0.987 respectively) Despite this good agreement, the difference between the measurements of IOP using Perkins or Goldman applanation tonometers and corneal compensated IOP (IOPcc) was statistically significant (p=0.00). The mean IOPcc error was 8.10 mmHg with higher reading of IOPcc obtained with ORA. Also the mean percentage of this error was statistically significant (p=0.00) and it was equal to 52.48%.

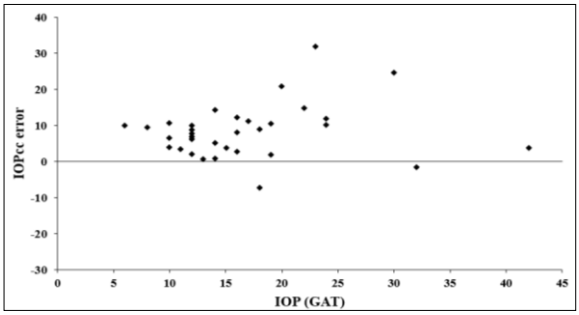

Figure 2: Bland Altman plots of the degree of agreement between the measurements of IOP using Perkins or Goldmann applanation tonometers and corneal compensated IOP using ORA (IOPcc)

3.4. *Correlation between IOPcc error, IOPcc error % and age, CH, CRF, CCT, and corneal diameter*

Using Pearson and Spearman correlation equations to correlate between IOPcc error and age, CH, CRF, CCT and corneal diameter, IOPcc error was found to be statistically significantly negatively correlated with CH (p=0.008) with correlation coefficient of - 0.397 while it was statistically significantly positively correlated with CRF (p=0.002) and CCT (p=0.024) with correlation coefficient of 0.459 and 0.348 respectively. IOPcc error % was statistically significantly negatively correlated with CH (p=0.034) with correlation coefficient of - 0.324.

4. Discussion

The meticulous measurement of IOP in cases with PCG is the most important step in the diagnosis, follow up and in the prevention of the progression of the disease process. Many parameters were introduced as factors which can affect the IOP measurement in glaucoma like gender, axial length and refractive error [8]. Cornea also has an important effect on the IOP measurement either through its structural properties (namely thickness, curvature and topography) or its biomechanical properties. Underestimation of the IOP was observed in cases with thin corneas with subsequent progression of glaucoma and overestimation of the IOP in cases with thick corneas [5]. Only thick corneas due to corneal edema lead to underesti-

mation of IOP [9]. The Ocular Response Analyzer (ORA) developed since 2005 is a non-contact instrument which measures in vivo corneal biomechnical properties [8] and it is considered as an air puff tonometer that corrects for corneal biomechanics [5]. Corneal hysteresis (CH), measured as the difference of the two recorded pressure values (P1 and P2), gives an impression about corneal viscoelastic properties. The overall elastic resistance and viscosity of the cornea is determined through corneal resistance factor (CRF) which is significantly correlated with Goldmann applanation tonometry and central corneal thickness. IOPg which is the average of the two pressure values is comparable to GAT [4]. IOPcc is not correlated with the CCT and it does not depend on corneal properties but it is correlated with CH [10]. The current study aims to detect the feasibility of using ORA in pediatric cases of PCG. In addition, the aim was to detect the degree of agreement between IOP measurements using Perkins and Goldmann applanation tonometers, and both IOPg and IOPcc measured using ORA in those patients. In the current study, the mean CCT was 541.67 ± 72.26 µm and ranged from 423 µm to 703 µm. CCT was found in some studies to be decreased in cases with PCG as in the study of Lopes and his associates who detected thinner corneas in PCG cases compared to controls (543.3 ± 66.9 µm vs. 555.6 ± 38.4 µm, respectively) [11] and in the study of Henriques, et al (525.4 ± 53.3 µm in PCG patients compared to 556.7 ± 26.7 µm in control subjects; p = 0.01) [12]. Other studies detected increase in the CCT in cases with PCG as in the study of Zareei, et al (594.5 ± 64.3 µm in cases of PCG compared to 536.5 ± 33.16 µm in the control group, $p < 0.0001$) [6] and in the study of Amini and his colleagues who reported thicker corneas in PCG cases with CCT of 589.42 ± 53.44 µm compared to 556.14 ± 30.51 µm in the control group. Increased CCT in PCG patients can be attributed to corneal edema or genetic and racial factors [9]. On the other hand, Doozandeh, et al documented no statistically significant difference in CCT between the affected eye of PCG patients, their normal fellow eye and the controls (CCT were 588.36 ± 60.94, 605.64 ±42.99 and 551.78 ± 33.84 respectively) [13]. The mean CH was 7.9 ±2.39 mmHg and the mean CRF was 10.168 ± 3.78 mmHg. This was comparable to study of Perucho-González, et al in which the mean CH was 8.51 ± 2.25 mmHg and the mean CRF was 9.85 ± 3.03 [7]. In a number of studies which were comparative studies between PCG patients and normal age matched groups, a decrease of CH and CRF in PCG patients was found as in study of Zareei, et al (CH was 8.68 ± 3.2mmHg compared to 11.87 ±2.05 mmHg in the control group with $p < 0.0001$ and CRF was 10.28 ± 3.3 while it was 12.90 ± 2.13 mmHg in control group with $p < 0.0001$) [6], Gatzioufas and his associates (CH was 9.1±1.6 mmHg in PCG patients compared to 11.4±1.2 mmHg in the normal control, p=0.01 and CRF was 7.9±1.1mmHg compared to 10.4± 1.5 mmHg in normal group, p =0.02) [14], and the study of Morales-Fernandez, et al (CH was 8.02 ±11.35 mmHg in PCG patients vs 11.35 ± 1.42 mmHg in normal control, $p < 0.001$ and CRF was 9.48 ± 2.83mmHg in PCG cases vs 10.77 ±1.34 mmHg in the normal control, $p < 0.001$) [15]. In glaucoma patients including PCG patients, applanation tonometry is the standard tonometer to measure IOP. In this study, the difference between the mean IOP obtained using applanation tonometry and IOPg was statistically significant with higher readings of IOPg. The mean IOP measured using applanation tonometer was 16.07 ± 8.494 mmHg, while the mean IOPg was 21.857± 12.893 mmHg. In addition, the difference between the mean IOP obtained using applanation tonometry and IOPcc was statistically significant with higher readings of IOPcc. The mean IOPcc was 24.17± 12.244 mmHg. This was in agreement with the studies of Zareei, et al

[16] (GAT- IOP was 15.3 ± 2.8 mmHg, IOPg was 19.2 ± 7.0 and IOPcc was 21.1 ± 7.9; $P = 0.001$), Doozandeh, et al in which GAT-IOP, IOPg, and IOPcc were 16.4 mmHg, 19.68± 6.25 mmHg and 21.75± 6.38 mmHg respectively in the glaucomatous eye while they were 12.1 mmHg, 15.99± 2.45mmHg and 14.88 ±2.61mmHg respecttively in the normal control[(13)] and in the study of Zareei and his colleagues in which GAT-IOP, IOPg, and IOPcc were 17.05 ± 3.9 mmHg, 19.96 ± 7.2 mmHg and 21.68 ± 7.5mmHg respectively in PCG patients while they were 16.17 ± 0.97 mmHg, 19.59±2.82 mmHg and17.92 ± 2.84 mmHg respectively in the normal control [6].

5. Conclusion

in the current study, the use of ORA in the measurement of IOP in cases of PCG was feasible and easy being a non-contact method which overcame the difficulties encountered during IOP measurement using applanation tonometry. A statistically significant difference between the IOP measured using applanation tonometry and ORA obtained IOP namely IOPg and IOPcc was detected with higher ORA measurements. This statistically significant difference and the fact that IOPcc is not correlated with the CCT and it does not depend on corneal properties [(9)] may explain in part the progression of glaucoma in patients who may show normal IOP values when measured by any of the applanation devices, which seem to underestimate the IOP in these cases. Studies with larger sample size and long follow up periods are needed to correlate between the IOP measurements using different types of tonometers and the progression of glaucoma aiming at detection of the most accurate devices.

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