INTRODUCTION

Primary congenital glaucoma (PCG) is responsible for approximately 5% of childhood blindness. PCG is diagnosed clinically in a neonate or infant by detecting the typical sign and symptoms of photophobia, epiphora, globe enlargement, corneal edema and opacification, and ruptures of Descemet's membrane (Haab’s striae). All corneal changes as well as globe enlargement and optic disc cupping result from elevated intraocular pressure (IOP). Clinical optic nerve head evaluation, gonioscopy, computerized perimetry, and other ophthalmic examinations are difficult to perform in children. Additionally, IOP reduction is the only method of glaucoma treatment for which there is extensive evidence. Therefore, accurate IOP measurement represents a key factor to proper diagnosis, treatment and follow-up in PCG patients.

Different devices and methods for IOP measurement have been developed. Since its introduction, Goldmann...
Four We used the 1 As PCG patients have characteristic corneal pathology (corneal edema, corneal scar, or band shape keratopathy), secondary glaucoma, and congenital optic neuropathies were excluded. The participants had undergone trabeculotomy as the first surgical procedure for glaucoma. Those with uncontrolled IOP following initial surgery were on medications or had received shunt surgery.

All patients underwent a full eye examination, including slit lamp biomicroscopy, gonioscopy using a Sussman goniolens (for uncooperative patients, we used their gonioscopy records during surgical procedures or examinations under anesthesia), and fundus slit lamp biomicroscopy using a Volk Superfield lens.

The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents/guardians of all participants.

IOP Measurements
To minimize the potential confounding effects of diurnal IOP variation, all study measurements were taken between 9:00-11:00 AM. Measurements were taken randomly to compensate for any variation in IOP caused by corneal applanation. The time interval between the tests was approximately 15 min and all cases were examined in sitting position. IOP measurements were carried out by 3 qualified examiners, each using one tonometer device, while being masked to the results obtained by the other devices. The manufacturer’s instructions were followed by the equipment operators.8,14,15 We used the exact value measured by each device, and did not make any correction based on CCT.

Two GAT measurements were obtained by an experienced glaucoma specialist (MRR) using a calibrated GAT (Haag-Streit, Köniz, Switzerland), averaged and noted as the GAT-IOP. The average of 3 consecutive measurements obtained by an NCT (CT80; Topcon Co., Tokyo, Japan) was regarded as the NCT result.9 Four to five measurements were taken by an ORA tonometer and the results with the highest waveform score were used for recording CH, CRF, IOPcc, and IOPg values.14

CCT and Corneal Curvature Measurements
All pachymetries were performed on the central cornea using an ultrasound pachymeter (Paxis, Biovision Inc., Clermont-Ferrand, France). Ten measurements were taken at the center of the cornea and after excluding the outliers, the average value was regarded as CCT.16 An autokerato-refractometer (KR-8900; Topcon Co., Tokyo, Japan) was employed to determine corneal curvature. Average values of k1 and k2 were regarded as the Mean keratometry (MK).

Statistical Analysis
Statistical analysis was performed using SPSS version 17 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to confirm normal distribution for all collected data. IOPs obtained by 3 devices were compared using repeated-measures analysis of variance (RM-ANOVA) with Bonferroni adjustment for multiple-comparisons. Pearson’s correlation coefficient was used to evaluate the correlation between each pair of measurements. Because of the rarity of the condition,
we included both eyes of patients, if eligible. As a result, the final dataset contained measurements from both eyes of the same subject in 12 PCG patients. Therefore, we performed a clustered analysis in which each participant was considered as a cluster to adjust for the dependency of measurements in the fellow eye.

Bland-Altman plots with 95% limits of agreement (LoAs; calculated as the mean difference of 2 methods ± 1.96 SD) were used to evaluate the difference between individual measurements for each subject. The GAT was regarded as the gold-standard procedure for IOP measurement, and agreements between other devices with the results obtained by GAT were assessed. Linear regression analysis was applied to evaluate the associations between average IOP, CCT, CH, CRF, or corneal curvature and differences in IOP readings between methods. All reported P values are two-tailed and deemed significant if < 0.05. A difference of more than 1.5 mmHg in IOP was considered as clinically relevant, and the data were interpreted accordingly. With the power of 0.9, and at two-tailed significance level (alpha) of 0.05, the required sample size to evaluate the clinically significant difference between measurements was calculated as 13. We enrolled more eyes in order to compensate for inclusion of both eyes in some patients and to increase the precision of Bland-Altman plots.

RESULTS

Demographics, baseline, and corneal characteristics of patients are summarized in Tables 1 and 2. Mean IOP (±SD) was 15.3 ± 2.8 mmHg for GAT, 15.5 ± 6.0 mmHg for NCT, 19.2 ± 7.0 mmHg for IOPg, and 21.1 ± 7.9 mmHg for IOPcc (P = 0.001, RM-ANOVA). Figure 1 shows the distribution of the IOP measurements with the three tonometers.

Table 1. Baseline characteristics of the study population

| Characteristic                  | Mean±SD     | Minimum | Maximum |
|---------------------------------|-------------|---------|---------|
| Age (mean±SD) Y/O               | 12±3 (8-15) |         |         |
| Gender (male/female)            | 12/5        |         |         |
| Cup-disc ratio (mean±SD)        | 0.62±0.15   |         |         |
| SE (mean±SD) (diopter)          | −0.8±1.9    |         |         |
| Number of eyes on glaucoma medications* | 2          |         |         |
| Prostaglandin analogues         | 2           |         |         |
| β-Blockers                      | 20          |         |         |
| α2-Adrenergic agonists          | 5           |         |         |
| Topical CAIs                    | 20          |         |         |

*8 eyes were under treatment with one drug, and 21 eyes were under treatment with 2 or more drugs. Y/O, years old; SD, standard deviation; SE, spherical equivalent refraction

Table 2. Corneal characteristics of the study population

| Characteristic                  | Mean±SD     | Minimum | Maximum |
|---------------------------------|-------------|---------|---------|
| CCT (µm)                        | 577±55      | 443     | 704     |
| CH (mmHg)                       | 8.6±3.0     | 2.3     | 13.8    |
| CRF (mmHg)                      | 10.0±2.5    | 5.5     | 15.5    |
| Mean keratometry (D)            | 41.1±1.5    | 36.5    | 43.8    |

CCT, central corneal thickness; CH, corneal hysteresis; CRF, corneal resistance factor; SD, standard deviation

Figure 1. Box and whisker plot showing the distribution of intraocular pressure (IOP) measurements by non-contact tonometer (NCT), Goldmann applanation tonometer (GAT), Goldmann-correlated IOP (IOPg), and corneal compensated IOP (IOPcc).

The scatter plots [Figure 2] suggested an association between the magnitude of the average of paired measurements (horizontal axis in the Bland-Altman plot) and the difference in paired measurements (the vertical axis), a subgroup analysis (stratified by the average of paired measurements) was performed to evaluate 95% LoAs for IOPs greater than 15.8 mmHg vs. IOPs less than 15.8 mmHg [Figure 3]. The figure 15.8 mmHg was retrieved by averaging the medians of the horizontal axis values of the 3 plots [Figure 2], resulting in approximately an equal number of eyes in each subgroup, while still allowing comparison between different plots [Figure 3].
In a linear regression model, we evaluated the association between independent variables (average IOP, CCT, CH, CRF, and MK) and the difference in IOP measurement for each pair of methods as the dependent variable. For the NCT vs. the GAT, only average IOP value showed a significant association ($r = 0.715, P = 0.001$). For IOPg vs. GAT, average IOP ($r = 0.802, P < 0.001$) and CH ($r = 0.539, P = 0.026$) both showed a significant association with the difference in IOP measurement. In stepwise multiple regression analysis, however, only average IOP value remained as an independent predictor ($P < 0.001$). For IOPcc vs. GAT,

Table 3. Mean difference, Pearson correlation, and 95% limits of agreement for intraocular pressure measurements obtained with Goldmann applanation tonometer, non-contact tonometer, and ORA (IOPg and IOPcc) in patients with primary congenital glaucoma

| Measurements   | Mean difference±SD (mmHg) | 95% CI | Pearson correlation | 95% LoA (mmHg) |
|----------------|---------------------------|--------|---------------------|----------------|
| NCT versus GAT| 0.22±4.80                 | 1.0    | −3.3 to 3.7         | −10.24 to 10.34|
| IOPg versus GAT| 3.85±5.57                 | 0.069  | −0.2 to 7.9         | 0.647          |
| IOPcc versus GAT| 5.73±6.99               | 0.023  | 0.6 to 10.8         | 0.471          |
| NCT versus IOPg| −3.63±4.94               | 0.047  | −7.2 to 0.3         | 0.719          |
| NCT versus IOPcc| −5.51±6.31              | 0.014  | −10.1 to −0.9       | 0.613          |
| IOPcc versus IOPg| 1.88±2.94              | 0.107  | −0.3 to 4.0         | 0.928          |

*Tested by repeated-measures ANOVA and multiple comparison with Bonferroni correction; $P<0.05$ considered statistically significant. $P<0.05$ considered statistically significant. CI, confidence interval; GAT, goldmann applanation tonometer; IOPcc, corneal compensated intraocular pressure; IOPg, goldmann-correlated intraocular pressure; LoA, limits of agreement; NCT, non-contact tonometer; SD, standard deviation; ANOVA, analysis of variance; ORA, ocular response analyzer.

Figure 2. Bland-Altman plots for different measurements compared with Goldmann applanation tonometer. The differences between the two methods are plotted against the mean value of both. The upper and lower lines represent the 95% limits of agreement. Non-contact tonometer (NCT), Goldmann applanation tonometer (GAT), Goldmann correlated IOP (IOPg), corneal compensated IOP (IOPcc).

Figure 3. Bland-Altman plots with subgroup analysis. The eyes with an average intraocular pressure (IOP) of >15.8 mmHg are compared to those with an average IOP of <15.8 mmHg. The differences between the two devices are plotted against the mean value of both for each subgroup. The upper and lower lines represent the 95% limits of agreement. Non-contact tonometer (NCT), Goldmann applanation tonometer (GAT), Goldmann correlated IOP (IOPg), corneal compensated IOP (IOPcc).
average IOP ($r = 0.806, P < 0.001$) and CH ($r = 0.830, P < 0.001$) showed a significant association. In stepwise multiple regression analysis, both parameters remained significant and served as independent predictors for the difference in IOP measurement ($P = 0.002$ and $P = 0.001$, for average IOP and CH, respectively).

**DISCUSSION**

The present study compared IOP values obtained by 3 different tonometers in a group of PCG patients. The mean ($\pm$SD) difference in IOP measured by NCT and GAT was only $0.2 \pm 4.8$ mmHg which was neither clinically nor statistically significant. Both IOPg and IOPcc methods significantly overestimated mean IOP as compared to GAT. The IOPcc vs. GAT values were not correlated, whereas NCT and IOPg measurements showed a significant correlation with GAT readings. The corneal compensation used in IOPcc calculation may be a factor to reduce the correlation between IOPcc values with that of GAT readings. Compared with the standard GAT, the best 95% LoA was found for NCT measurements. However, NCT may measure IOP up to $\pm 10$ mmHg different from GAT measurements which is far greater than the predetermined threshold used in the present study, and therefore, the methods mentioned herein cannot be used interchangeably for measuring IOP in PCG patients.

Figure 3 demonstrates that agreements between NCT or IOPg values and GAT are about twice better for mean IOP less than 15.8 mmHg as compared to mean IOP of greater than 15.8 mmHg. Thus, considering the convenience of methods of NCT and IOPg, they may be acceptable alternatives for IOP measurement in a subgroup of PCG with lower pressures. For example, in a PCG patient with controlled glaucoma and IOP of 12 mmHg, NCT-IOP measurements may not need to be rechecked with a GAT while in a patient with IOP of 20 mmHg this may not hold true.

Several studies have evaluated the agreement between ORA-IOP and GAT-IOP. The 95% LoAs for the IOPcc vs. GAT were $-3.4-7.4$ mmHg in the study by Kotecha et al$^{[10]}$ (100 subjects, mixed glaucoma and normal adults), 0.4-16.1 mmHg as reported by Martinez-de-la-Casa et al$^{[11]}$ (48 cases, glaucomatous adults), $-2.4-8.0$ mmHg in the report by Bayoumi et al$^{[12]}$ (56 normal adults), and $-3.6-8.5$ mmHg as described by Renier et al$^{[13]}$ (102 subjects, mixed glaucoma and normal adults). The 95% LoAs for IOPg vs. GAT were $0.3-14.2$ mmHg$^{[14]}$, $-3.3-6.0$ mmHg$^{[15]}$, and $-3.8-6.9$ mmHg$^{[16]}$ in the last three studies, respectively. In other words, these studies suggested that IOPg or IOPcc values could not be used interchangeably with GAT in normal nor glaucomatous adults. The results of our study are in line with the aforementioned studies; IOPg or IOPcc values generally overestimated IOP measurements as compared to GAT. However, the range of agreement found in the present study (approximately 23 mmHg for IOPg vs. GAT, and 27 mmHg for IOPcc vs. GAT) was considerably higher than those reported in the above-mentioned studies ($9.3$ mmHg for IOPg vs. GAT in Bayoumi et al$^{[12]}$ and $15.7$ mmHg for IOPcc vs. GAT in Martinez-de-la-Casa et al$^{[11]}$). This finding is probably due to higher IOP and/or characteristic corneal structure and biomechanical properties in PCG patients. Kaushik et al$^{[19]}$ also reported that the agreement between IOPg and GAT was weaker for adults with high IOP as compared to those with normal IOP.

Ogbuehi$^{[8]}$ reported no statistically significant difference between average IOP measured with NCT vs. GAT (mean difference, $0.2$ mmHg; 95% LoA, $-3.1-2.7$ mmHg). Our results also revealed no significant difference in the average measurements by the two devices, but with considerably weaker agreement (95% LoA, approximately $\pm 10$ mmHg).

Corneal hysteresis in healthy children has been reported to be similar to that of adults$^{[8]}$. In PCG patients, however, CH and CRF are reduced significantly. Kirwan et al$^{[40]}$ reported that mean CH was $12.5$ mmHg in healthy children, while mean CH was $6.3$ mmHg in a subset of patients with PCG. In the study by Gatziofhas et al$^{[41]}$, mean CH was $11.4$ in healthy children (mean CCT = $566 \mu$m) and $9.1$ mmHg in PCG subjects (mean CCT = $519 \mu$m). In line with these studies, mean CH in our study was $8.6$ mmHg, further confirming lower CH values in PCG patients.

Mean CCT in our cohort was $577 \mu$m. Published reports on CCT in PCG have revealed mixed results with both thicker$^{[25,26]}$ and thinner$^{[24,27]}$ corneas as compared to normal controls. Thinner corneas could be due to corneal stretching but thicker corneas may be secondary to corneal structural changes, scarring or subclinical edema$^{[25]}$. Racial and genetic factors may also be important. In a report by Amini et al$^{[28]}$ from the same region as our study, mean CCT in a group of patients with PCG was $589$ mmHg compared with $556$ mmHg in normal controls, which is in agreement with our study.

Our study did not evaluate and cannot comment on which device is more accurate; we only compared IOP values and determined the agreement of two NCTs devices with that of GAT. This study is limited by the relatively small sample size, which precludes appropriate extrapolation of findings to all PCG patients. However, PCG is not a common type of glaucoma, and considering the strict eligibility criteria used in our study the sample size seems to be reasonable.

In conclusion, our results suggest that mean IOP obtained by NCT was not significantly different from that of GAT, while mean ORA-IOPs (IOPg and IOPcc) were $3.9$ and $5.7$ mmHg higher than GAT, respectively. The limits of agreement between GAT values and all of the mentioned methods were far beyond the clinically...
acceptable range and therefore, these methods cannot be used interchangeably for measuring IOP in PCG. The results of the present study should not be extrapolated to PCG patients with corneal disorders (including edema and scar) and patients with other types of glaucoma.

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