A Longitudinal Study to Establish the Normative Value and to Evaluate Perinatal Factors Affecting Intraocular Pressure in Preterm Infants

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PURPOSE. To establish a normative range of intraocular pressure (IOP) in preterm infants and to identify important perinatal factors that could affect the IOP during the early weeks of neonatal life.

METHODS. The IOP of 104 preterm infants, with a median (interquartile range) gestational age of 29.8 (28.7–30.9) weeks and birth weight of 1208 (1049–1370) g, were assessed in a university-affiliated tertiary neonatal center. These infants had IOP measured by a handheld tonometer at 1, 4, 6, 8, and 10 weeks of postnatal age. The mixed-effects models were used to evaluate the longitudinal IOP measurements and to identify critical perinatal factors that would significantly affect the ocular pressure.

RESULTS. A percentile chart of IOP in preterm infants was constructed, and the median (10th–90th percentile) IOP ranged from 16.9 (12.3–21.5) to 14.6 (10.1–19.2) mm Hg at 26.1 and 46.4 weeks of postconceptional age, respectively. The IOP was significantly and negatively associated with postconceptional age (P < 0.001), mean blood pressure (P = 0.01), Apgar score at 1 minute (P = 0.04), and use of inhaled corticosteroids (P = 0.05), but was positively correlated with the commencement of high-frequency oscillatory ventilation (P = 0.01).

CONCLUSIONS. A quantitative statistical model has been developed and a percentile chart of IOP constructed for preterm infants that could be used for future reference. Pediatric ophthalmologists and neonatal clinicians can compare the IOP of preterm infants against this chart and make relevant quantitative adjustments for critical perinatal factors so that the IOP may be properly evaluated, both in healthy and ill infants.

Preterm, very-low-birth weight (VLBW; 1500 g) infants are frequently exposed to high concentrations of oxygen and are at risk of development of retinopathy of prematurity (ROP).^1^3 Regular screening for ROP is necessary for these vulnerable, high-risk infants after birth, and intraocular pressure (IOP) can be easily measured by a handheld instrument during routine ophthalmic examination. An understanding of the natural maturation process of the visual system, establishment of a normative range of values, and identification of important intrinsic or extrinsic factors that may affect various ocular measurements, including IOP, are essential in assisting clinicians in assessing developmental abnormalities and congenital diseases involving the eyes. To date, relatively few studies have reported IOP in preterm infants. Of these studies, most obtained the IOP measurements in a cross-sectional manner. In only one small trial involving 20 preterm infants was IOP measured weekly during the first month of life. Although investigators performing earlier studies have been meticulous in their examination techniques and in the measurement of ocular pressure, relatively little clinical information concerning the characteristics and outcomes of patients was described. Important information included the mode of mechanical ventilation, presence or absence of intracranial complications, and interventions or drugs that may influence the IOP. However, the interrelationship and complexity of different factors affecting the IOP renders normative data difficult to determine. Thus, the objectives of this study were (1) to determine a normative range of IOP by longitudinally measuring the ocular pressure at standardized time intervals (1, 4, 6, 8, and 10 weeks) after birth and (2) to determine important perinatal factors, both physiologic and environmental, that may affect the IOP during the early weeks of neonatal life. A percentile chart of IOP in preterm infants will provide neonatal clinicians and pediatric ophthalmologists with the ability to compare ocular pressures between well and sick infants and to monitor infants who receive specific medications, such as systemic corticosteroids, or undergo eye surgery and/or laser photocoagulation treatment.

METHODS

Patients

Preterm infants admitted consecutively into the neonatal intensive care unit (NICU), at the Prince of Wales Hospital, Hong Kong, who met the screening criteria for ROP were prospectively enrolled over a period of 32 months. The inclusion criteria were: (1) all infants <32 weeks of gestational age or birth weight <1500 g, (2) moderately preterm infants (32–36 weeks gestational age) receiving supplemental oxygen >7 days, and (3) parental consent to participate in the study. Infants were excluded if they had undetermined gestational age; multiorgan dysfunction and were expected to die imminently; chromosomal abnormalities and dysmorphic syndromes; or congenital ocular abnormalities, such as corneal clouding or cataract. Patients who received postnatal systemic (i.e., oral or intravenous) corticosteroids treatment were investigated separately, as previous trials in older children and adults have found that the use of systemic corticosteroids as well as topical steroids applied locally to the eye are important factors associated with the development of ocular hypertension. Further, we
monitored the latter group of infants differently, with IOP checked according to the dose regimen of the dexamethasone course received by the patient.

**Methods**

**Gestational and Postconceptional Ages.** The gestational age of an infant was obtained on the basis of maternal obstetric history or early perinatal ultrasound, and was subsequently confirmed after birth by the New Ballard score. The postconceptional age was calculated by adding the postnatal age of the infant at the time of ophthalmic examination to the gestational age.

**Measurement of IOP.** The IOP of preterm infants was longitudinally measured at standard time intervals at 1, 4, 6, 8, and 10 weeks after birth. The first eye examination at week 1 was voluntary and the other four measurements coincided exactly with the timing of routineROP examinations provided by the NICU for at-risk infants. A single ophthalmologist (BSMT) performed the ocular examination in all studied infants. In each examination, 1 drop of 1% preservative-free amethocaine hydrochloride (Chauvin Pharmaceuticals Ltd., Surrey, UK) was instilled before the eyelids were opened with a Cook’s infant speculum. The infant was then held supine by an experienced neonatal nurse. It usually took the patient 30 to 90 seconds become accustomed to the speculum and settle down. IOP was always measured before the dilatation of pupils and indirect ophthalmic examination for ROP and never in irritable or crying infants. None of the patients received sedative drugs or muscle relaxants just before or during the eye examination. IOP was measured with a handheld applanation tonometer (Tonopen II; Oculab, La Jolla, CA). Other methods of IOP measurement such as Goldmann applanation tonometry and noncontact (Tonopen II; Oculab, La Jolla, CA). Other methods of IOP measurement such as Goldmann applanation tonometry and noncontact tonometry are impossible to perform at the bedside in preterm newborns, and Perkin’s tonometry is also not suitable because of the relatively large contact area on the cornea. Previous studies have reported good agreement in IOP measurement between the Tonopen and Goldmann applanation tonometers, in addition, applanation tonometry was chosen over indentation tonometry because the latter method is substantially affected by scleral rigidity. Thus, the handheld Tonopen represents the most accessible tool that can be reliably used for IOP assessment in this age group of patients. The reported IOP in each eye represented an average value of three consecutive measurements. Triplicate measurements with discrepancy greater than 10% were considered unreliable and the outlier readings were excluded from the study.

**Data Collection.** During each IOP assessment, detailed information was recorded regarding the health status of the subject. The information included postconceptional and postnatal ages; anthropometric parameters such as body weight, body length, and head circumference; systolic, mean, and diastolic blood pressures; respiratory data comprising the mode of mechanical ventilation at the time of IOP measurement; high-frequency oscillatory ventilation (HFOV) model 3100A; Sensormedics Co., Yorba Linda, CA), intermittent positive-pressure ventilation (IPPV; Infant Star; Infrasonics Inc., San Diego, CA), continuous positive airway pressure (CPAP; Infant Flow System MDE/ Mc72B; Electro Medical Equipment Ltd., Brighton, UK), and the maximum mean airway pressure (MAPmax) and maximum oxygen concentration (FiO2max) during the assessment period; medications, especially inhaled corticosteroids (fluticasone propionate; Flotrolide; GlaxoSmithKline Ltd., Brentford, UK) 100 μg administer ed every 12 hours via a holding chamber (MV15s Aerochamber; Trudell Medical International, London, ON, Canada); diuretics (hydrochlorothiazide; Apotex Inc., Weston, ON, Canada, 1 mg/kg administered every 12 hours or spironolactone; Pharmacila Ltd., New York, NY, 1 mg/kg administered every 12 hours); and serious complications associated with prematurity—in particular, adverse intracranial events such as intraventricular hemorrhage, periventricular leukomalacia, and cerebral atrophy; stages of ROP; bronchopulmonary dysplasia; and clinical sepsis.

**Statistical Analysis.** The descriptive statistics on demographic data and outcomes are expressed as median (interquartile range) or number (%). As multiple measurements were obtained for each infant, mixed-effects models were used to assess the association between IOP and gestational/postconceptional/postnatal ages, anthropometric parameters, and the important physiologic or environmental factors listed in Tables 1 and 2 that may affect the ocular pressure. The mixed-effects models were used to adjust for longitudinal and cross-sectional (i.e., left-and-right eye correlation) random factors, and the covariates were chosen by a stepwise selection method consisting of a forward addition step and a backward elimination step. The forward addition step started with the null model, which included the intercept term and the random individual effect only. The most significant covariate is then added in a stepwise fashion into the model until all covariates that are not selected have $P > 0.05$. Thereafter, the backward elimination step removes the most nonsignificant covariate from the model until all covariates remaining have $P < 0.05$. In this exercise, the first forward step indicated that postconceptional age, postnatal age, and body length were the most significant covariate factors. As these factors were highly intercorrelated and the postconceptional age was considered most important and clinically meaningful among them, the forward addition procedure, therefore, started from the model that included the intercept and postconceptional age as the fixed effects. The random effect was always included to explain the individual variation. All tests were performed with commercial software (Windows version of S-Plus 2000; MathSoft Inc., Seattle, WA). The mixed-effects models were fitted using the function LME in the software. All comparisons were two-tailed, and the level of significance was set at 5%.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>$n = 104$</th>
</tr>
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<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>29.8 (28.7–30.9)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1208 (1049–1370)</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>37.6 (36.5–39.0)</td>
</tr>
<tr>
<td>OFC (cm)</td>
<td>26.5 (25.8–27.7)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male (n) = 52 (50%)</td>
</tr>
<tr>
<td></td>
<td>Female (n) = 52 (50%)</td>
</tr>
<tr>
<td>Apgar scores</td>
<td>1 min = 7 (6–9)</td>
</tr>
<tr>
<td></td>
<td>5 min = 9 (8–10)</td>
</tr>
<tr>
<td>Arterial cord blood</td>
<td>pH = 7.30 (7.23–7.34)</td>
</tr>
<tr>
<td></td>
<td>Base excess (mmol/L) = −4.0 (−7.2–−2.2)</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>No ventilatory support = 43 (41%)</td>
</tr>
<tr>
<td></td>
<td>&gt;Stage 2 = 44 (43%)</td>
</tr>
<tr>
<td></td>
<td>HFOV = 11 (11%)</td>
</tr>
<tr>
<td></td>
<td>IPPV = 5 (5%)</td>
</tr>
<tr>
<td></td>
<td>CPAP = 45 (43%)</td>
</tr>
<tr>
<td></td>
<td>No ventilatory support = 43 (41%)</td>
</tr>
<tr>
<td></td>
<td>Use of surfactant (n) = 86 (83%)</td>
</tr>
<tr>
<td></td>
<td>Duration of mechanical ventilation (days) = 3.8 (2–6)</td>
</tr>
<tr>
<td></td>
<td>Duration of O2 requirement (days) = 17 (5–54)</td>
</tr>
<tr>
<td></td>
<td>FiO2max = 0.30 (0.23–0.40)</td>
</tr>
<tr>
<td></td>
<td>Mean airway pressuremax (cmH2O) = 9 (8–11)</td>
</tr>
</tbody>
</table>

Results are median (interquartile range) or number (%). * Data were available in 82 infants.
Use of inhaled corticosteroids (n) 40 (38.8%)
Use of diuretics (n) 42 (40.0%)
Clinical sepsis (n) 31 (30.0%)
ROP (left eye) P < 0.001; Fig. 1; (2) increased by 1.86 (0.68) mm Hg in infants on HFOV compared with those who were breathing spontaneously without assisted ventilation (P = 0.01; Fig. 1). There was, however, no significant influence of conventional IPPV (P = 0.63) or CPAP (P = 0.35) on IOP; (3) decreased by -0.05 (0.02) mm Hg for each 1-mm Hg increment in mean blood pressure (P = 0.01); (4) decreased by -0.70 (0.32) mm Hg after beginning of treatment with inhaled corticosteroids (P = 0.03; Fig. 1). In addition, in 40 infants treated with inhaled fluticasone propionate, the IOP before and after treatment was 16.7 (14.9–19.8) mm Hg (median [interquartile range]) and 15.0 (13.5–18.0) mm Hg; respectively (P < 0.05); and (5) decreased by -0.25 (0.11) mm Hg for each unit increase in Apgar score at 1 minute (P = 0.04). In the third stage with the backward elimination step, all nonsignificant parameters were successfully eliminated, whereas factors (1) through (5) were retained in the statistical models.

The median (interquartile range) IOP ranged from 16.9 (14.5–19.3) to 14.6 (12.2–17.1) mm Hg at 26.1 and 46.4 weeks of postconceptional age, respectively. Figure 1 summarizes the 10th, 50th, and 90th percentile distribution of the normative IOP after adjustment for the significant perinatal factors.

**Discussion**

We designed this study to establish a normative range of IOP in preterm infants and to monitor longitudinal changes of ocular pressure during this vulnerable period of eye development. We also determined critical perinatal factors, both physiologic and environmental, that may affect IOP during the early weeks of postnatal life. This study, however, was not designed to identify the underlying mechanisms of action of these influential perinatal factors. The latter investigation is beyond the scope of the present study and should be performed after such factors have been identified. As far as we are aware, this is the first large-scale longitudinal study of IOP in preterm newborns that has taken into account the clinical factors and outcomes that may affect the ocular pressure. The most significant and consistent finding was that the IOP of preterm infants decreases with increasing postconceptional age. The IOP was also negatively associated with the mean blood pressure, Apgar score at 1 minute, and use of inhaled corticosteroids, but correlated positively with HFOV. In addition, the study provides a range of normative IOP after adjustment for influential perinatal factors (Figs. 1). There is, however, no significant association between IOP and stages of ROP. Pediatric ophthalmologists and neonatal clinicians equipped with such information may now compare their clinical measurements against the percentile chart (Fig. 1) and make appropriate adjustments for perinatal factors so that the IOP of these vulnerable infants can be properly assessed. Thus far, neonatal clinicians have not been routinely monitoring IOP in serious neonatal conditions with intracranial complication or the effects of drug treatments, in particular, systemic corticosteroids usage. The percentile chart should therefore be useful in assisting surveillance and revealing clinical conditions or therapeutic agents that may result in ocular hypertension and adversely affect vision.

To our knowledge, there has been no normative range of IOP established in preterm newborns in the literature. In the present study, none of our subjects was sedated or given muscle relaxants during the examination, as these medications could have interfered with the results by artificially lowering the IOP. Thus, our measurements are intended to reflect the IOP of calm and resting preterm infants in the normal arousal state. Two previous cross-sectional studies in 1950s suggested...
that the IOP in preterm infants ranged between an average of 24.5 mm Hg (range: 6.5–33.0 mm Hg) and 35.0 mm Hg. These results are much higher than the IOP of 16.9 (14.5–19.3) and 14.6 (12.2–17.1) mm Hg obtained at 26.1 and 46.4 postconceptional weeks in our present study (Fig. 1). In contrast, our measurements are in good agreement and correspond closely with values obtained from more recent studies. The latter clinical trials recorded IOP levels ranging between (mean [SD] or median [CI]) 10.1 (2.2) mm Hg; 10.3 (3.5) mm Hg; 11.0 (2.0) to 13.3 (2.9) mm Hg depending on postnatal/postconceptional age; 13.7 (3.28) and 13.8 (3.67) mm Hg in the right and left eye, respectively, of premature infants born by in vitro fertilization or natural conception; 15.7 (±2.3) and 16.3 (±3.7) mm Hg in two separate control groups; 15.5 (±3.5–18.2) mm Hg; and 18.6 (±2.3) mm Hg. The discrepancy of measurements between studies performed in the 1950s and those in the recent era is probably attributable to different categories of survivors of preterm infants (i.e., no ventilator-dependent survivors in 1950s), as well as the different instrument and techniques of measurement used between studies. In fact, in the latest studies by McKibbin et al. and Axer-Siegel et al., the mean IOPs ranging between 15.5 and 16.3 mm Hg are in good agreement with the results of the present study. Further, an analysis of data obtained from all recent studies suggests that the mean/median IOP varies between 10.1 and 18.6 mm Hg. Similarly, our cohort of preterm infants had a median IOP within this range (14.6–16.9 mm Hg) after adjustment of perinatal factors. In addition, our study provided the percentile distribution of IOP between 26.1 and 46.4 weeks of postconceptional age (Fig. 1). Although the previous recommendation proposed by Tucker et al. suggested that a measurement >18.0 mm Hg could probably be considered elevated, our results suggested that the top (90th percentiles) and bottom (10th percentiles) 10% of measurements were distributed between 20.5 and 22.8 and 8.8 and 11.0 mm Hg, respectively, depending on the postconceptional age. A review of the indirect ophthalmoscopy findings during ROP screening showed that none of the infants had optic disc abnormalities related to raised IOP such as significant cupping of the optic nerve head, and no study patient received treatment for ocular hypertension. As our results were derived from a relatively large sample size, with serial measurements, and more importantly, adjusted for critical perinatal factors, the percentile charts should more accurately reflect the normative variation of IOP within the specified postconceptional age in preterm infants.

In contrast to the findings of most previous studies, our data suggest a strong negative association between IOP and postconceptional age or anthropometric parameters, including body weight, body length, and head circumference. The postconceptional age was the most consistent and significant factor determined by the mixed-effects models. As there was a wide variation in IOP between individual patients (Figs. 1) and most studies involved only cross-sectional measurements, our longitudinal data were...
probably the key element in revealing a significant relationship between IOP and postconceptional age or maturity. The results further suggested that the IOP slowly decreased at an average rate of 0.11 mm Hg with every week increase in maturity after birth. In accordance with our findings, the only other study with serial IOP measurements also demonstrated a decrease in the mean IOP during the first month of postnatal life in preterm infants with gestational age ranged between 26 and 32 weeks. As it is a well-recognized phenomenon that the neonatal blood pressure increases with gestational age, it is not unexpected to find a significant negative correlation between IOP and mean blood pressure. However, the exact mechanism giving rise to a decline in IOP with increasing maturity is not fully understood and is beyond the scope of this study. Whether this phenomenon represents a programmed maturation process, related to an increase in the dimension of ocular structures, or under the influence of complex neuroendocrine control, requires further investigation. Perhaps, this negative correlation is related to central corneal thickness, which in turn influences IOP measurement.

A significant negative association was also demonstrated between IOP and Apgar score at 1 minute. The clinical significance of this finding has not been fully elucidated but suggests that the condition of infants at birth can potentially influence the IOP. The poorer the condition at birth (i.e., the lower the Apgar score at 1 minute), the higher will be the IOP. Whether this observation is related to a mild degree of cerebral insult or edema, causing a transient increase in intracranial pressure that transmits to the eyes, is not certain. Further studies with sophisticated radiologic imaging for detection of cerebral edema or direct intracranial pressure measurement in animal models are warranted to confirm this finding and to delineate the underlying mechanism. We did not expect, however, to find a significant negative association between IOP and the use of inhaled corticosteroids. Our previous study suggested that inhaled fluticasone could be absorbed systematically via the pulmonary circulation, causing moderately severe hypothyroidism-pituitary-adrenocortical axis suppression in preterm infants. As systemic corticosteroids and steroids applied locally to the eye have been shown to induce ocular hypertension in children and adults, a paradoxical decrease in IOP associated with the use of inhaled preparations in preterm infants is unusual. There are a few plausible explanations. First, the dosage of fluticasone used in the previous study was very high (1000 μg/d), being five times the dosage used in the present study. Hence, its systemic effect may have been minimized in the present study. Second, although regular users of high doses of inhaled corticosteroids prescribed for a prolonged period (>3 months) are at an increased risk of ocular hypertension, short-term usage with normal therapeutic dosage has not been associated with a significant increase in IOP. Third, the mixed-effects models analysis indicated that the use of HIF OV could significantly increase IOP (Fig. 1). After treatment with inhaled fluticasone, all infants on HFOV were subsequently weaned off mechanical ventilation, and this factor could have contributed at least partially to the decrease of IOP in treated infants. However, it is difficult to be certain exactly which component of HFOV (e.g., the positive pressure or constant vibration) causes the increase in IOP.

There are limitations to this study. Ideally, serial IOP measurements should be measured in normal uncomplicated preterm infants. However, all preterm infants are by definition not normal. Even relatively uncomplicated infants, including those who do not require mechanical ventilation, are not on medications such as inhaled or systemic corticosteroids, and are free of serious complications of prematurity, are difficult to find and likely to be of older gestational age at birth. Hence, without an ideal group of normal patients, the only alternative method to establish a normative range of IOP is to construct an appropriate statistical model and adjust for significant perinatal factors that may affect the ocular pressure. In this respect, we have successfully developed a quantitative statistical model and constructed a percentile chart (Fig. 1) that can be used for future reference purposes. In addition, we have identified specific perinatal factors so that the measured IOP can be appropriately corrected. Second, with recent advances in neonatology, serious complications of prematurity are relatively uncommon, including severe stages of ROP, intracranial hemorrhage, and hydrocephalus. Thus, the impact of these rare adverse IOP events may not be adequately reflected in this study. Third, artificial elevation of IOP may occur in infants who are awake and react with vigorous resistance to ophthalmic examination, or associates with the use of eyelid speculum during the procedure. A previous study suggests that the use of an eyelid speculum in anesthetized children may increase the IOP by an average of 4 mm Hg (mean IOP was 20.16 and 16.44 mm Hg, with and without the eyelid speculum, respectively). The low scleral rigidity in preterm infants may further exaggerate this effect. Nonetheless, it is not ethical or practical to administer general anesthesia just for measuring IOP, and the commonly used anesthetic gas can inadvertently suppress the ocular pressure, giving rise to falsely low readings. Further, it is not possible to perform an adequate ophthalmic examination without assistance of an eyelid speculum, as this age group of patients is not able to cooperate. Therefore, we consider that the best approach in establishing a normative range is to simulate the real-life situation and to measure the IOP in resting preterm infants using the most accessible tools and the routine procedures for eye examinations. We meticulously minimized the discomfort of infants and undesirable effects of the eyelid speculum by (1) applying a local anesthetic eyedrop before the ophthalmic examination, (2) gently opening the eyelid with the smallest infant speculum available, and (3) patiently waiting for the infant to become accustomed to the procedure. Thus, the IOP obtained in this study represents the standard method of eye assessment normally used in clinical practice for this age group.

In summary, our findings suggest that the median (10th-90th percentile) IOP varies between 16.9 (12.3–21.5) and 14.6 (10.1–19.2) mm Hg at 26.1 and 46.4 weeks postconceptional age, respectively. Important physiologic and environmental factors, including postconceptional age, mean blood pressure, use of inhaled corticosteroids, and Apgar score at 1 minute have been demonstrated to be negatively correlated, whereas HFOV is positively associated with the IOP. Pediatric ophthalmologists and neonatal clinicians will be able to compare the IOP measurement against the percentile chart (Fig. 1) and make appropriate adjustments for critical perinatal factors so that the ocular pressure of the preterm infant can be properly evaluated. More important, the percentile chart should be useful in assisting surveillance and revealing complications of prematurity or therapeutic agents that may cause a sustained and abnormal increase in IOP.

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