Optic Nerve Sheath Diameter for Preterm Infants: A Pilot Study

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Abstract

Objective: In preterm infants, early diagnosis and management of a raised intracranial pressure (ICP) may be important to improve neurodevelopmental outcomes. While invasive ICP monitoring is not recommended, ultrasonography of the optic nerve sheath diameter (ONSD) could provide a noninvasive alternative to evaluate ICP. The objective of this pilot study was to document ranges of ONSD in preterm infants.

Methods: This prospective cohort pilot evaluated preterm infants who were admitted to the neonatal intensive care unit without suspected raised ICP. Three images per eye were obtained from a 20–5 MHz linear array ultrasound transducer placed on the patient’s superior eyelid. The ONSD was measured 3 mm behind the globe. A second ultrasonographer duplicated half of the scans. Multiple linear regression analysis was conducted for both right and left ONSD with corrected gestational age, weight, and head circumference as predictors. Lin’s concordance assessed interrater reliability.

Results: In 12 preterm infants 114 scans were performed on both eyes. The median age was 33 weeks (corrected gestational age) with a range of 29–36 weeks. Corrected gestational age was the strongest predictor for ONSD, and preliminary measurements at each gestational age were established. Interrater reliability demonstrated substantial agreement (Qc = 0.97). Conclusion: In preterm infants, ONSD strongly correlates with corrected gestational age. These data should be validated with other imaging modalities before abnormal ranges can be considered.

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Keywords
Intracranial pressure increase · Neonate · Ultrasonography

Introduction

Evaluation of intracranial pressure (ICP) in neurocritical care is often necessary to provide prompt and essential treatment [1]. In patients at risk for raised ICP, invasive monitoring can be utilized but harmful side effects have been reported [1–3]. For this reason, measurement of the optic nerve sheath diameter (ONSD) through ultrasonography has been established as a safe, noninvasive alternative [1, 3–8]. Briefly, pressure variations within the chiasmal cistern are transmitted to the subarachnoid space surrounding the optic nerve, directly influencing the ONSD [9]. When the ICP is increased, the ONSD also increases [1, 4]. Ultrasonography of the ONSD has been documented in several different pediatric populations at...
risk for raised ICP including: diabetic ketoacidosis [5, 10],
craniosynostosis [6], hydrocephalus [7, 11], ventriculoperi-
toneal shunts [3, 8], metabolic disorders (hepatic fail-
ure) [12, 13], suspected intracranial lesions (traumatic 
brain injury and nontraumatic brain injury) [9, 10, 13, 14],
hypoxic injury [13], intracranial hemorrhage [11, 13], infection [11, 14], meningoceles [11], and spina bi-
fida.

In preterm infants (live births before 37 weeks of ges-
tation), invasive ICP monitoring is not recommended [9, 15] and normative ONSD data has yet to be established. These infants, however, may be at high risk for raised ICP because their common neurological presentations in-
clude intraventricular hemorrhages, birth trauma/sub-
arachnoid hemorrhage, neoplasms, and infection [16]. Early diagnosis and management of raised ICP may be 
important for improving neurodevelopmental outcomes by attenuating the risk of seizures, cranial nerve palsies, 
and cerebral ischemia [15, 16]. Given that preterm infants 
account for approximately 7.8 and 11.4% of all births in 
Canada [17] and the USA [18], small improvements in 
management could be very effective.

Establishment and validation of ONSD norms through 
ultrasonography is a necessary step before recognition of 
pathology can be appreciated. Therefore, the aim of this 
pilot study was to document ranges of ONSD for preterm 
infants and inaugurate the utility of ultrasonography as a 
clinically relevant monitoring tool for raised ICP.

Research Design and Methodology

Approval to conduct this study was given by the Uni-
vity of Saskatchewan Biomedical Ethics Research 
Board. Twelve children admitted to the Neonatal Inten-
sive Care Unit (NICU) at the Royal University Hospital 
(RUH) in Saskatoon, SK, Canada, took part in this study. 
All of the participants were between the ages of 28 and 37 
weeks (postconceptual age). No patients with suspected 
or confirmed raised ICP or intraocular pressure were in-
cluded in this study.

Optic Nerve Sheath Diameter

Once consent had been obtained from a parent or le-
gally acceptable representative, premature infants were 
scanned over consecutive weeks. A Zonare (Mindray 
Medical International Limited, Mountain View, CA, 
USA) 20–5 MHz linear array transducer set at factory 
ONSD settings was utilized. After the sterile gel at room 
temperature had been applied, the probe was gently 
placed on the superior eyelid of the patient’s closed eye.

With the patient in supine position, axial images through 
the eye including a longitudinal section of the optic nerve 
were generated. The ONSD was measured 3 mm poste-
rior from the scleral surface of the globe with electronic 
calipers. Three scans per eye were conducted at every ses-
sion; 1 session was conducted each week for every patient 
between 29 and 36 weeks of corrected gestational age. A 
second ultrasonographer duplicated half of the scans. Im-
ages were obtained after routine handling of the patient and did not require more than 2 min in total. Changes in 
vital signs using continuous cardiorespiratory monitoring 
during ultrasonography were recorded.

Statistics

Data was stratified by corrected gestational age, weight, 
and head circumference. Descriptive statistics for ONSD 
included means and SD. Multiple linear regression analy-

sis was conducted for both right and left ONSD with cor-
rected gestational age, weight, and head circumference as 
predictors; the $F$ statistic and $R^2$ were also calculated. If 
appropriate, a line of best fit was established for the best 
single predictor determined by regression analysis. Inter-
rater reliability was assessed by Lin’s concordance, with 
the following strengths of agreement ($Q_c$) determined a 
priori: almost perfect, $>0.99$; substantial, $0.90$ to $0.99$; 
moderate, $0.90$–$0.95$; and poor, $<0.9$.

Results

A total of 114 scans were performed on both eyes of 7 
male and 5 female preterm infants. The median corrected 
gestational age was 33 weeks, with a range of 29–36 weeks. 
Their mean birth weight was 1,624 (±520) g.

The multiple linear regression analysis for both right 
and left ONSD is summarized in Tables 1 and 2. The $F$ 
statistic was 22.8 and 20.1 for the right and left ONSD 
model; the significance of $F$ change was 0 for both eyes. 
$R^2$ was 0.709 and 0.683 for the right and left ONSD mod-
els, respectively.

The data on gestational age, the strongest predictor for 
ONSD, is summarized in Table 3. A line of best fit is dis-
played in Figures 1 and 2, with an $R^2 > 0.95$ for both eyes.

A total of 60 scans were conducted to assess interrater 
reliability. A $Q_c$ of 0.97 was calculated (95% CI 0.95–0.99).

Only 1 scan (0.9%) caused a brief decrease in oxygen 
saturation and heart rate in a patient. The scan was im-
mediately stopped and both vital signs returned rapidly 
to baseline.

Ardell/Daspal/Holt/Hansen
In this pilot study we safely collected pilot ONSD data in preterm infants. A linear association in premature infants aged between 29 and 36 weeks was demonstrated, with increasing ONSD correlating strongly with advancing corrected gestational age.

The accurate reflection of ONSD measurements and corrected gestational age may be rooted in nervous system embryology. In this study we have demonstrated a linear nature of ONSD growth in the premature population. However, central nervous system growth itself is likely not linear [19], as its development is dependent on the activation of proteins that appear at specific gesta-

Discussion

Table 1. Multiple linear regression model for the right ONSD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized coefficient (β)</th>
<th>95% CI</th>
<th>Collinearity tolerance</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected gestational age</td>
<td>0.675</td>
<td>0.007 to 0.020</td>
<td>0.392</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight</td>
<td>0.083</td>
<td>0.000 to 0.000</td>
<td>0.856</td>
<td>0.46</td>
</tr>
<tr>
<td>Head circumference</td>
<td>0.164</td>
<td>-0.003 to 0.008</td>
<td>0.379</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Table 2. Multiple linear regression model for the left ONSD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized coefficient (β)</th>
<th>95% CI</th>
<th>Collinearity tolerance</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected gestational age</td>
<td>0.560</td>
<td>0.005 to 0.020</td>
<td>0.392</td>
<td>0.003</td>
</tr>
<tr>
<td>Weight</td>
<td>0.037</td>
<td>0.000 to 0.000</td>
<td>0.856</td>
<td>0.75</td>
</tr>
<tr>
<td>Head circumference</td>
<td>0.296</td>
<td>-0.001 to 0.011</td>
<td>0.379</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Table 3. Corrected gestational age and ONSD

<table>
<thead>
<tr>
<th>Age, weeks</th>
<th>Patientsa, n</th>
<th>Scans, n</th>
<th>Right ONSD, cm</th>
<th>Left ONSD, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>2</td>
<td>8</td>
<td>0.21±0.01</td>
<td>0.21±0.02</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>10</td>
<td>0.22±0.01</td>
<td>0.23±0.02</td>
</tr>
<tr>
<td>31</td>
<td>3</td>
<td>9</td>
<td>0.24±0.01</td>
<td>0.24±0.01</td>
</tr>
<tr>
<td>32</td>
<td>4</td>
<td>13</td>
<td>0.27±0.03</td>
<td>0.27±0.04</td>
</tr>
<tr>
<td>33</td>
<td>4</td>
<td>15</td>
<td>0.27±0.02</td>
<td>0.27±0.03</td>
</tr>
<tr>
<td>34</td>
<td>6</td>
<td>21</td>
<td>0.29±0.02</td>
<td>0.30±0.03</td>
</tr>
<tr>
<td>35</td>
<td>7</td>
<td>25</td>
<td>0.32±0.04</td>
<td>0.32±0.03</td>
</tr>
<tr>
<td>36</td>
<td>4</td>
<td>12</td>
<td>0.31±0.03</td>
<td>0.32±0.02</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD unless otherwise stated.

a Twelve patients had serial weekly scans.
tional ages [20]. For example, myelin basic protein – which is integral to nervous system myelination – only appears within oligodendrocytes at 32 weeks of gestational age and influences the growth rate of the ONSD [20]. Whether our techniques or the small sample size lacked the sensitivity to detect non-linear growth should be addressed in subsequent studies.

In contrast, our 2 other predictors – head circumference and weight – did not strongly correlate with ONSD. Although skull growth in an infant is partially dependent on the hemispheric growth of the brain [21], the cerebral growth acceleration seen in later gestation is impeded in the preterm population [22]. Additionally, premature infant weight gain can lag in infants born at term and be inconsistent with head circumference growth [23, 24].

ONSD measurements were validated through a high interrater reliability. An individual’s observations of measurements can be a source of error and influence the calculated means [25]. However, our very strong interrater reliability should have attenuated personal influences that could influence final calculations. To achieve this, our principal ultrasonographer was trained over a 2-week period that included both theory and bedside teaching. This is consistent with a previous report that demonstrated the ease of learning the ONSD technique in novice ultrasonographers [26]. Workshops just 4 hours in length were adequate to teach learners to measure with the accuracy and reliability comparable to published “experts” [26].

ONSD in preterm infants was well tolerated. One scan did elicit a brief and slight decline in heart rate and oxygen saturations, which was likely due to activation of the oculocardiac reflex. The afferent limb, which consists of the ophthalmic branch of the trigeminal nerve, can be stimulated by mild pressure from the ultrasound transducer as it is placed on the superior eyelid. This should serve as a reminder that the infant should be on continuous cardiorespiratory monitoring during the scan, and that pressure to the globe should be mitigated as much as possible through the proper transducer technique.

To increase the validity of our findings, confirming the pilot ONSD through magnetic resonance imaging (MRI) will be our next step. This has corroborated the accuracy of ultrasonography measurements in other studies with older patients [27, 28]. The obvious advantage that ultrasonography has over MRI is its allowance for rapid clinical decision making in urgent situations and serial evaluations for unknown pathophysiologic trajectories without transferring an unstable patient to a distant magnet.

Our study has several limitations. First, while ONSD has yet to be validated by further imaging modalities such as MRI, previous studies have reported good agreement. Second, although our sample size was quite small, our data groupings were consistent with studies that created normative data for children [3]. However, at this point our data should not be considered as normative, as further research is absolutely necessary. Finally, despite standard screening of intracranial abnormalities, it was difficult to definitively rule out raised ICP. Due to higher risks of intracranial abnormalities in premature infants, a pathological measurement may have been included in our analysis [16].

Conclusion

Our primary objective was to establish pilot ONSD data in premature infants between 29 and 36 weeks. We demonstrated that ONSD is strongly correlated with gestational age and established preliminary normative measurements. Future studies are indicated to validate the current findings before this rapid, safe, and reliable imaging modality may be used in the clinical setting.

Statement of Ethics

The parents or guardians of the subjects provided written informed consent. The study protocol has been approved by the University of Saskatchewan Biomedical Ethics Research Board.

Disclosure Statement

The authors do not have conflicts of interests to declare.

Funding Sources

This project was funded through the Dean’s Summer Research Project by the College of Medicine at the University of Saskatchewan.

Author Contributions

G.H. and T.H. coconceptualized and designed this study and applied for funding. S.A. and S.D. collected data. G.H. analyzed the data. S.A. wrote the first draft of this paper. All authors revised this paper and approved the final version as submitted.
References


