Transcranial Ultrasound in Evaluation of Hypoxic-Ischemic Encephalopathy and Bleed in Preterm Neonates

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INTRODUCTION

Hypoxic-ischemic injury in preterm neonates remains a catastrophic condition causing substantial mortality and morbidity.¹ It is an important cause of permanent central nervous system (CNS) damage or cerebral palsy and mental deficiency. Different modalities used to detect...
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hypoxic-ischemic encephalopathy (HIE) and intracranial hemorrhage are transcranial ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI).

Transcranial ultrasound has the advantage of easy availability, being radiation free, bedside, low cost, suitable for screening, and follow-up. MRI has advantage of superior soft tissue contrast differentiation and locates exact size, extent, site of brain injury and its disadvantages are high cost, requirement of transportation/mobilization of sick neonates and being time consuming. CT has the disadvantage of radiation exposure.

We aimed to detect typical ultrasound findings on transcranial ultrasound of HIE and intracranial hemorrhage and to evaluate the role of ultrasound in the diagnosis of HIE and intracranial hemorrhage in preterm neonates.

Aims and Objectives
The objectives are as follows:
1. To study ultrasound characteristics of HIE and intracranial hemorrhage, i.e. periventricular leukomalacia, periventricular cyst, germinal matrix hemorrhage (GMH), intraventricular hemorrhage (IVH), intra parenchymal hemorrhage (IPH), and ventricular dilatation
2. To evaluate the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of transcranial ultrasound for hypoxic-ischemic encephalopathy and intracranial hemorrhage in preterm neonate as isolated parameters in comparison to clinical diagnosis.

MATERIALS AND METHODS

It was a non-interventional prospective cross-sectional observational study conducted over a period of 1.5 years in the Department of Radiodiagnosis of Seth Gordhandas Sunderdas Medical College and King Edward Memorial (KEM) Hospital. A total of 66 cases were evaluated during the study.
Inclusion Criteria
The following criteria were included in the study:
1. Preterm neonates <37 weeks of gestation age admitted in our hospital NICU
2. Patients having registration at this institute
3. Clinically suspected HIE and intracranial bleed.

Exclusion Criteria
The following criteria were excluded from the study:
1. Parents or guardians being unwilling to give consent for the study
2. All suspected cases of congenital malformation, severe infection, and failed resuscitation.

Study Procedure
All patients were scanned on Philips HD 11XE machine using a 5–12 MHz linear transducer and high-frequency transducer. For all preterm neonates <37 weeks transcranial ultrasound scans were done on 7th, 14th, and 30th days of life through anterior (sagittal, parasagittal, and coronal view) posterior and mastoid fontanel. The examination procedure was explained to the parents/guardian. With the neonate lying in the supine position, ultrasound gel (warmed to room temperature) was spread over the anterior, posterior, and mastoid fontanels. The transducer, held in the examiner's hand was moved across the anterior, posterior and mastoid fontanels to study neonate brain in sagittal, parasagittal, axial, and coronal planes, until the requisite structures were studied.[5]

The following parameters were evaluated:
- For intracranial hemorrhage
  1. Germinal matrix hemorrhage
  2. IVH
  3. IPH
  4. Ventricular dilatation.
- For HIE
  1. Abnormal periventricular echogenicity
  2. Periventricular cyst small and large
  3. Cystic lesion in subcortical brain.
- Obstetric history
  1. Type of delivery (vaginal or lower segment cesarean section [LSCS])
  2. Presence of any obstetric complications (e.g., abruptio placentae, placenta previa, preeclampsia, intrauterine growth restriction [IUGR], and infection).

Figure 5: Pie diagram showing the distribution of the patients in clinically diagnosed intracranial hemorrhage

Figure 6: Pie diagram distribution of patients clinically having hypoxic-ischemic encephalopathy

Figure 7: Pie diagram showing the distribution of mode of delivery in the neonates

Figure 8: Bar diagram showing the mode of delivery in patients with intracranial hemorrhage
- Neonatal history
  1. 1 min Apgar score
  2. 5 min Apgar score
  3. Neonatal sepsis
  4. Age and sex
  5. Weight at birth.

**Statistical Analysis**
Using this basic cross-tabulation, software inferences and associations were performed. To test the association of different study variables, Chi-square test was used. When Chi-square was not applicable, Fisher exact test was used.

<table>
<thead>
<tr>
<th>Findings of intracranial hemorrhage</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
<td>18 (27.3)</td>
</tr>
<tr>
<td>No intracranial hemorrhage</td>
<td>48 (72.7)</td>
</tr>
<tr>
<td>Total</td>
<td>66 (100.0)</td>
</tr>
</tbody>
</table>

To test the significance of the difference between two proportions, Z-test (standard normal deviate) was used.

T-test was used to compare the means. Diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were calculated to compare the findings of different diagnostic tools. The odds ratio was calculated to find the risk factors with 95% confidence interval. \( P < 0.05 \) was considered to be statistically significant.

**Statistical Software**
Statistical analysis was performed with help of Epi Info (TM) 7.2.2.2 Epi Info is a trademark of the Centers for Disease Control and Prevention.

**RESULTS**

**Diagnostic Findings based on Findings of Ultrasonography (USG)**
Intracranial hemorrhage was found in 18 (27.3%) of the patients. Thus, the prevalence of intracranial hemorrhage was 27.3%.

No intracranial hemorrhage was found in 48 (72.7%) of the patients (\( Z = 9.14; P < 0.001 \)). About 18 (27.3%) of
the patients that had hemorrhage. Thus, the prevalence of intracranial hemorrhage was 27.3% out which Grade-I hemorrhage was highest in proportion (13.6%).

No abnormal periventricular echogenicity was found in 78.8% of the patients \((Z = 9.47; P < 0.001)\). About 14 (23.3%) patients had abnormal periventricular echogenicity. Ten patients had periventricular cyst and 2 patients had coalescence of cysts.

The presence of abnormal periventricular echogenicity with periventricular cyst was in the highest proportion (23.3%) followed by periventricular cyst (16.6%). Only 2 (3.03%) of the patients had coalescence of the cyst.

### Diagnostic Findings based on Clinical Findings

As per the clinical diagnosis, intracranial hemorrhage was found in 18 (27.3%) of the patients.

As per clinical diagnosis, 18.9% of the patients had abnormal periventricular echogenicity. However, most of the patients had no abnormality (81.1%) \((P < 0.001)\).

Proportion of vaginal delivery (68.2%) was significantly higher than that of LSCS (31.8%) \((Z = 5.14; P < 0.0001)\). Chi-square test showed that there was no significant association between the mode of delivery and intracranial hemorrhage.

### Table 2: Distribution of grade in patients of intracranial hemorrhage

<table>
<thead>
<tr>
<th>Intracranial hemorrhage</th>
<th>(n)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>6</td>
<td>(9.1)</td>
</tr>
<tr>
<td>Grade 1+Grade 2</td>
<td>2</td>
<td>(3.1)</td>
</tr>
<tr>
<td>Grade 1+Grade 3</td>
<td>1</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4</td>
<td>(6.1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3</td>
<td>(4.5)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2</td>
<td>(3.1)</td>
</tr>
<tr>
<td>Nil</td>
<td>48</td>
<td>(72.7)</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>(100.0)</td>
</tr>
</tbody>
</table>

### Figure 13: Bar diagram showing the distribution of gestational age, and Apgar score at 1 and 5 min in neonates with respect to abnormal periventricular echogenicity.

### Figure 14: Bar diagram showing the distribution of birth weight in patients with respect to abnormal periventricular echogenicity.

### Figure 15: Bar diagram showing percentage of patients with true positive, true negative, false positive, and false negative test in diagnosing hypoxic-ischemic encephalopathy.

### Figure 16: Bar diagram showing the percentage of neonates with true positive, true negative, false positive and false negative test in diagnosing intracranial hemorrhage.
hemorrhage in the patients of this study ($P = 0.45$). However, the proportion of LSCS was higher among the patients with intracranial hemorrhage (38.9%) as compared to the patients without intracranial hemorrhage (29.2%), but it was not significant ($Z = 1.44; P = 0.26$).

The risk of LSCS was 1.54 times more among the patients with intracranial hemorrhage as compared to the patients without intracranial hemorrhage but the risk was not significant (OR-1.54 [0.49, 4.80]; $P = 0.45$).

### Table 10: Distribution of Apgar score at 5 min in the neonates

<table>
<thead>
<tr>
<th>Apgar score at 5 min</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6</td>
<td>66</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Mean±SD: 8.61±0.89
Median: 9
Range: 6–10

SD: Standard deviation

### Table 11: Distribution of neonatal sepsis in the neonates

<table>
<thead>
<tr>
<th>Neonatal sepsis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>5 (7.6)</td>
</tr>
<tr>
<td>Absent</td>
<td>61 (92.4)</td>
</tr>
<tr>
<td>Total</td>
<td>66 (100.0)</td>
</tr>
</tbody>
</table>

**Obstetric Complication**

Prevalence of preeclampsia (19.7%) was the significantly highest of all ($Z = 2.13; P = 0.042$).

The mean (mean ± standard deviation) Apgar score at 5 min in the neonates was $8.61 \pm 0.89$ with range 6–10 and the median was 9.

All the neonates had Apgar score at 5 min ≥6 (100.0%) which was significantly higher ($Z = 14.12; P < 0.0001$).

About 5 (7.6%) of the neonates had sepsis.
About 54.5% of the neonates were male, which was higher than that of females (45.5%), but it was not significantly higher ($Z = 1.27; P = 0.13$) [Figures 1-27 and Tables 1-17].

**DISCUSSION**

In our study, there were a total of 36 male (54.5%) and 30 female (45.5%) neonates. Total number males were greater than that of females. However, it was not significantly higher statistically ($P = 0.13$).

In our study, the mean birth weight of neonates was 1244.62 g with a standard deviation of 333.2 g. About 69.7% of the neonates were in the category of very low birth weight (VLBW), which was significantly higher than that of LBW ($P < 0.0001$).

The mean gestational age of the neonates in our study was 30.6 weeks with a standard deviation of 2.35 weeks, with range 27–35 weeks and median was 30 weeks.

In our study, proportional of vaginal delivery (68.2%) was significantly higher than that of LSCS (31.8%) ($P < 0.0001$).

The mean Apgar score at 1 min was 7.92 with standard deviation of 1.64, with range of 4–10. The median Apgar score at 1 min was 9. Most the neonate had Apgar score at 1 min >6 (86.4) which was significantly higher than score <6.

The mean Apgar score at 5 min was 8.61 with standard deviation of 0.89, with range of 6–10. The median Apgar score at 5 min was 9.

About 13 patients (19.7%) had preeclampsia as an obstetric complication, followed by IUGR (6 patients, 9.1%), abruption (5 patients, 7.6%), placenta previa (3 patients, 4.6%), and other complications.

<table>
<thead>
<tr>
<th>Table 12: Distribution of gender in the neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

![Image of sagittal section of brain showing Grade I germinal matrix hemorrhage](image17.png)

**Figure 17:** Sagittal section of brain showing Grade 1 germinal matrix hemorrhage

![Image of coronal view of brain showing Grade II germinal matrix hemorrhage](image19.png)

**Figure 19:** Coronal view of brain showing Grade II germinal matrix hemorrhage

![Image of coronal view of brain showing Grade II germinal matrix hemorrhage on both side](image18.png)

**Figure 18:** Coronal view of brain showing Grade I germinal matrix hemorrhage on both side

![Image of coronal view of brain showing resolving Grade III germinal matrix hemorrhage](image20.png)

**Figure 20:** Coronal view of brain showing resolving Grade III germinal matrix hemorrhage
Prevalence of preeclampsia (19.7%) was the significantly highest of all.

Intracranial Hemorrhage
Out of 66 patients, total 18 patients had ultrasound findings of intracranial bleed. Out of which Grade I was in highest proportion (13.6%). Two patients had Grade IV bleed which had lowest proportion (3%). Total 9 patients had Grade I intracranial hemorrhage, 6 patients had Grade II intracranial hemorrhage, 4 patients had Grade III intracranial hemorrhage, 2 patients had Grade IV intracranial hemorrhage, 2 patients had Grade I and II intracranial hemorrhage, and 1 patient had Grade I and III intracranial hemorrhage.

On comparing the ultrasound findings with clinical diagnosis for diagnosing intracranial bleed in preterm neonates, the sensitivity was 88.89% and specificity was 95.83%. The diagnostic accuracy of the test was 93.94%.

According to Babcock and Han, sensitivity and specificity of USG for intracranial hemorrhage were 95% and 100%, respectively.

The mean gestational age in patients with intracranial bleed was 29.83 ± 2.20 weeks. Early gestational age was significantly associated with intracranial bleed in neonates.

Twelfth male and 6 female preterm neonates had finding of intracranial bleed. Proportion of male in respect to female was high; however, there was no significant correlation.
Seven patients had LSCS mode of delivery and 11 patients had vaginal mode of delivery. There was no significant association between mode of delivery and intracranial bleed in preterm neonates.

The mean Apgar score of preterm neonates with intracranial bleed at 1 min and 5 min was 7.05 ± 1.62 and 8.22 ± 0.74, respectively, which was statistically significant.

The mean birth weight of preterm neonates with intracranial bleed was 1138.11 ± 369 g. There were 3 preterm neonates with LBW and 15 neonates had VLBW. There was significant association of preterm neonate of LBW and VLBW with intracranial bleed.

In this study out of 18 patients of intracranial bleed, 4 patients were associated with preeclampsia and another 4 patients were associated with intrauterine growth retardation. The association of intracranial bleed in preterm neonate with preeclampsia and IUGR was significant.

Thus, there was a significant association of intracranial bleed in preterm neonates with early gestational age, low Apgar score at 1 min and 5 min, LBW, preeclampsia and IUGR as maternal complication.\[8\]

HIE
Out of 66 patients, total 14 (prevalence-12.1%) patients had ultrasound findings of HIE. Out of which abnormal periventricular echogenicity was present in all 14 patients, 10 patients had abnormal periventricular echogenicity with small periventricular cysts, 2 patients had all three changes of HIE, i.e. abnormal periventricular echogenicity, small periventricular cyst with coalescence to form large cyst.\[9\]

On comparing the ultrasound findings with the clinical diagnosis for identifying HIE in preterm neonates, the sensitivity was 83.33% and specificity was 92.59%. The
diagnostic accuracy of the test was 90.91%. In the study conducted by Shen et al., the sensitivity and specificity for detecting HIE by USG were 90% and 75%, respectively.\[10\]

A systemic review by van Laerhoven et al., T1/T2 changes in neonatal brain MRI had a sensitivity of 98% and specificity of 76%. However, diffusion-weighted MRI changes had a sensitivity of 58% and specificity of 89%, respectively. Thus, MRI has a sensitivity of up to 98% and specificity up to 89%.[11]

The mean gestational age in patients with HIE was 30.7 ± 2.22 weeks. In preterm neonates with HIE, early gestational age at delivery was statistically significant.

Nine patients had LSCS as the mode of delivery and 5 patients had a vaginal mode of delivery. The proportion of LSCS was significantly higher among patients with abnormal periventricular echogenicity (64.3%) as compared to that of the patients without abnormal periventricular echogenicity. This finding was consistent with the study by Itoo et al. that LSCS being the mode of delivery was a risk factor of HIE.[12]

Nine male and 5 female preterm neonates had finding of HIE. The proportion of males with respect to female was high; however, there was no statistically significant correlation.

The mean Apgar score of preterm neonates with HIE at 1 min and 5 min was 6 ± 1.57 and 7.57 ± 0.72, respectively,
which was statistically significant. Our findings were consistent with the results of the study done by Ehrenstein which shows that a low Apgar score at 5 min <7 was associated with HIE.\[13\]

The mean birth weight of preterm neonates with HIE was 1069.13 \pm 368.61 g. There was 1 preterm neonate with LBW and 13 neonates with VLBW. There was a significant association of preterm neonates of LBW and VLBW with HIE. These findings were consistent with the study done by Pálsdóttir et al. which had shown that LBW is a significant risk factor for HIE.\[14\]

Thus, there was a significant association of HIE in preterm neonates with early gestational age at delivery, low Apgar score at 1 min and 5 min, and LBW.

In this study, out of 14 patients of HIE, 8 patients had associated maternal pre eclampsia. There was a strong association of HIE in preterm neonates with pre eclampsia in the mother. This finding was consistent with the study done by Badawi et al.\[15,16\] that HIE is associated with pre eclampsia.

In two patients, the intracranial bleed was associated with neonatal sepsis, which was not found to be statistically significant.

### SUMMARY AND CONCLUSION

Hypoxic-ischemic injury in preterm neonates is a serious condition with significant morbidity and mortality. It is the important cause of permanent CNS damage resulting in cerebral palsy and mental deficiency. HIE and intracranial bleed are two ends of the spectrum of hypoxic-ischemic events.

The purpose of the study was to identify the ultrasound findings in HIE and intracranial bleed, which would help in grading them accordingly. Although the sensitivity and specificity of transcranial USG are less than that of MRI, (which is the gold standard in detecting HIE and intracranial bleed in preterm neonates) considering its sensitivity and specificity it can still be considered as the first-line imaging modality of choice for screening preterm neonates for HIE and intracranial bleed.

Even though MRI is the gold standard, it has multiple disadvantages such as need for mobilization and cumbersome transportation of sick neonates which are on life supports (CPAP/ventilator), requirement of sedation/general anesthesia, limited availability, and high cost.

In intracranial bleed, the sensitivity and specificity of transcranial ultrasound were found to be 88.89% and 95.83%, respectively, with a diagnostic accuracy of 93.94%. In HIE, the sensitivity and specificity of transcranial ultrasound were found to be 83.33% and 92.59%, respectively, with a diagnostic accuracy of 90.91%.

The proportion of cases that had vaginal delivery was significantly higher than that of those born through LSCS in preterm neonates. Neonatal risk factors that were found to be significantly associated with intracranial bleed and hypoxic encephalopathy were LBW, prematurity, and Apgar score <6 at 1 min and 5 min of birth.

Preeclampsia and IUGR were important maternal risk factors for intracranial bleed in preterm neonates. Preeclampsia and LSCS as a mode of delivery were important maternal risk factors for HIE in preterm neonates. Comparison with long-term neurological outcomes was not possible due to the short duration of our study. Transcranial USG is operator dependent.

Transcranial ultrasound should be used as a routine screening imaging modality for all preterm neonates born before 37 weeks.

Follow-up scan should be done on days 7, 14, and 30 to detect persistent abnormal periventricular echogenicity, and cystic changes in HIE and in intracranial bleed to
detect the resolution or progression of hemorrhage and ventricular enlargement.

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**REFERENCES**