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Role of Transcranial Ultrasound for Hypoxic Ischemic Insult Keeping MRI as a Gold Standard

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ABSTRACT

Background: Hypoxic-ischemic insult is an important cerebral pathology in neonates, which is caused by reduced oxygen and blood flow during parturition. Early diagnosis of hypoxic-ischemic insult in neonates is important to prevent sequelae. Magnetic resonance imaging is considered an effective diagnostic tool; however, it is not easily accessible and is quite expensive. **Objective:** To determine the diagnostic accuracy of transcranial ultrasound in detecting hypoxic ischemic encephalopathy taking MRI as gold standard. **Study Design:** Cross sectional validation study. **Duration and Place of Study:** This study was conducted from 2 January 2025 to 2 May 2025 in Department of Radiology, Gujranwala Teaching Hospital Gujranwala. **Methodology:** A total of 156 newborns with birth asphyxia and gestational age more than 32 weeks were included. Transcranial ultrasound was performed using high frequency probe through anterior fontanelle. Magnetic resonance imaging was done on 1.5 tesla machine. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were calculated by 2×2 contingency table. **Results:** Mean gestational age was 36.87±1.99 weeks and mean birth weight was 2.66±0.51 kg. Sensitivity was 85.5%, specificity 70.3%, diagnostic accuracy 75.6%, positive predictive value 61% and negative predictive value 89.9%. **Conclusion:** Transcranial ultrasound is useful screening tool with good sensitivity and high negative predictive value for detecting hypoxic ischemic insult in neonates.

INTRODUCTION

The hypoxic-ischemic insult is a critical pathological state of the brain that results from inadequate supply of oxygen and blood to the brain for a specified period of time.[1] The hypoxic-ischemic insult is most commonly seen in neonates who have had a difficult birth, birth asphyxia, a long labor, a prolapse of the umbilical cord, placental abruption, or severe hypotension of the mother.[2] The lack of oxygen and blood supply to the brain results in a lack of cellular energy production, causing lactic acid to accumulate and resulting in cell death.[3] The brain areas most susceptible to hypoxic-ischemic insults include the basal ganglia, thalamus, cortex, and watershed areas depending on the severity of the insult.[4]

The diagnosis of hypoxic-ischemic insult is based on clinical history and examination, with laboratory and imaging results.[5] A history of perinatal asphyxia, low Apgar score, need for resuscitation, and evidence of metabolic acidosis in cord blood are suggestive.[6] Neurological examination helps in staging encephalopathy by demonstrating abnormal tone, abnormal reflexes and seizures.[7] Blood gas analysis confirms the presence of metabolic acidosis, with laboratory investigations helpful in demonstrating evidence of organ dysfunction, as evidenced by elevated liver enzymes or renal failure.[8] Neuroimaging is essential in confirming brain injury. Magnetic resonance imaging is said to be a sensitive tool in demonstrating injury patterns and severity of brain damage, with diffusion-weighted imaging being helpful in the early stages.[9]

Transcranial ultrasound is an important, safe and non-invasive tool in diagnosing hypoxic-ischemic injury especially in neonates, as an open anterior fontanelle acts as an acoustic window.[10] Ultrasonography may reveal increased echogenicity in the periventricular white matter, loss of normal gray-white matter differentiation, cerebral edema, slit-like ventricles, and, in severe cases, cystic changes.[11] Doppler can also be used to assess cerebral blood flow and calculate resistance index. Although less sensitive than MRI in demonstrating early subtle changes, transcranial ultrasound is very helpful in demonstrating moderate to severe changes, as well as associated complications like intraventricular hemorrhage.[12]

This study is justified in the region of Gujranwala due to the large number of neonates born in peripheral

centers, which lack access to advanced neuroimaging facilities such as MRI. Birth asphyxia and delayed referral are common issues in this region, thus increasing the risk of hypoxic ischemic damage. Transcranial ultrasound has the advantage of being easily accessible, cost-effective, and able to be done at the patient's bedside in any tertiary care hospital of Gujranwala. There is limited local data regarding the accuracy of this investigation in this population, hence the rationale for this study.

METHODOLOGY

This cross sectional validation study was carried out in the Department of Radiology, Gujranwala Teaching Hospital, Gujranwala, from 2 January 2025 to 2 May 2025. Ethical permission was taken from the institutional ethical review committee before start of study and the research was conducted according to hospital protocols. Sample size was calculated by using WHO sensitivity and specificity calculator with expected Sensitivity 80%,[13] Specificity 66.6%,[13] Prevalence 44.8%,[14] Confidence interval 95% and Precision 10% for both sensitivity and specificity. The final calculated sample size was 156 newborns. Newborns with gestational age >32 weeks on LMP of both genders and having birth asphyxia were included in study. Birth asphyxia was considered when newborn was not breathing for >90 seconds after birth chest was not rising symmetrically with respiratory frequency >30/minute on examination and umbilical artery blood pH was <7.1 on laboratory testing. Newborns having history of CNS infections, sepsis, respiratory distress, or major congenital malformations were excluded from study.

Detailed history was taken from parents regarding perinatal events and clinical examination was performed. All included newborns underwent transcranial ultrasound in radiology department. Examination was performed on GE machine without sedation. High-frequency phased array transducer of 5–8 MHz with small footprint probe was used. Multiple acoustic windows including anterior and posterior fontanels, temporal, mastoid and occipital regions were utilized to visualize central and peripheral brain structures. Transducer frequency was adjusted between 8.2–11 MHz for assessment of cortical and subcortical regions. Deep gray matter structures including basal ganglia, thalami and brainstem were assessed independently. Probe angulation was changed to assess subcortical white matter and gray-white matter differentiation in both cerebral hemispheres. After ultrasound, Magnetic resonance imaging was performed on 1.5 tesla superconducting system (Phillips MRI machine) using head coil. Neonates were monitored throughout procedure by experienced neonatal pediatrician. Sedation with oral 10% chloral hydrate in dose 50–75 mg/kg was given only to irritable neonates under supervision, while stable neonates were scanned without sedation. MR imaging protocol included 4-mm sagittal T2 spin-echo images, 4-mm axial T1 and T2 spin-echo images, and 4-mm coronal T2 spin-echo images covering entire brain. Diffusion weighted imaging was obtained. In 1H-MR spectroscopy, proton spectra were acquired from 2 voxels, one placed in deep gray matter nuclei including thalamus and lentiform nucleus, and other in frontal or occipital watershed zone or at site of abnormality detected on conventional MRI and DW-MRI.

Diagnosis of hypoxic-ischemic encephalopathy was made by demonstrating any three or more of the following criteria by transcranial ultrasonography: increased echogenicity of the basal ganglia and thalami bilaterally; peripheral hyperechogenicity in subcortical white matter and cortex in watershed areas; slit-like compression of the lateral ventricles due to cerebral edema; decreased resistive index; and cerebellar hyperechogenicity compared to the diffuse supratentorial edema, which is known as the white cerebellum sign. For magnetic resonance imaging, HIE diagnosis was considered if any two or more of the following criteria were demonstrated by MRI: restricted diffusion by diffusion-weighted imaging (DWI) in the basal ganglia, thalami, cortex, cerebellum, and brainstem in the acute phase; T2 hyperintensity with swelling of deep gray matter in the subacute phase; delayed cortical hyperintensity on T1-weighted images indicating necrosis; and increased lactate peaks and decreased NAA peaks by magnetic resonance spectroscopy in the acute phase.

All data were entered and analyzed using SPSS version 23. Mean ± standard deviation was calculated for quantitative variables including gestational age at birth and weight. Frequency and percentage were calculated for categorical variables including gender, transcranial ultrasound and MRI test results. Sensitivity, specificity, Positive predictive value, Negative predictive value and diagnostic accuracy of transcranial ultrasound against MRI were computed by using 2×2 contingency table. Effect modifiers such as gestational age at birth, gender and weight were controlled through stratification. Post stratification Chi-square test was applied and $p \leq 0.05$ was considered statistically significant.

RESULTS

The mean gestational age at birth of study participants were 36.87±1.99 weeks and mean birth weight was 2.66±0.51 kg. Among all participants, majority were male gender with 87 (55.8%) cases while female were 69 (44.2%) cases (Table-I).

Table I

Patient Demographics

Demographics	Mean ± SD
Gestational Age at Birth (weeks)	36.87±1.99
Birth Weight (kg)	2.66±0.51
Gender	
Male n (%)	87 (55.8%)
Female n (%)	69 (44.2%)

When overall results of both diagnostic modalities was compared, ultrasound showed positive findings in 77 (49.4%) cases and negative in 79 (50.6%) cases. MRI which was used as gold standard showed positive findings in 55 (35.3%) cases and negative findings in 101 (64.7%) cases out of total 156 cases (Table-II).

Table II

Overall results of MRI and Ultrasound in diagnosis of hypoxic ischemic insult

Hypoxic Ischemic Insult	Ultrasound	MRI
Positive	77 (49.4%)	55 (35.3%)

Negative	79 (50.6%)	101 (64.7%)
Total	156 (100%)	156 (100%)

The comparison between ultrasound and MRI findings was showed that out of 77 ultrasound positive cases, 47 were true positive (TP) and 30 were false positive (FP) when compared with MRI. Among 79 ultrasound negative cases, 8 were false negative (FN) and 71 were true negative (TN) cases. From total 55 MRI positive cases, ultrasound correctly identified 47 cases while from 101 MRI negative cases, ultrasound correctly identified 71 cases (Table-III).

Table III

Comparison of Ultrasound versus MRI in diagnosis of hypoxic ischemic insult

Ultrasound	MRI		Total
	Positive	Negative	
Positive	47 (TP)	30 (FP)	77
Negative	8 (FN)	71 (TN)	79
Total	55	101	156

Key: TP = True positive, FP = False positive, FN = False negative, TN = True negative

The overall diagnostic performance of ultrasound against MRI as gold standard was demonstrated sensitivity of 85.5%, specificity of 70.3%, diagnostic accuracy of 75.6%, positive predictive value of 61% and negative predictive value of 89.9% (Table-IV).

Table IV

Sensitivity, Specificity, Diagnostic Accuracy, PPV and NPV of Ultrasound in diagnosis of hypoxic ischemic insult

Diagnostic Parameter	Result
Sensitivity	85.5%
Specificity	70.3%
Diagnostic Accuracy	75.6%
PPV	61%
NPV	89.9%

Stratified analysis according to gestational age at birth showed that for neonates with ≤37 weeks, sensitivity was 82.10%, specificity was 78.40%, diagnostic accuracy was 80.00%, PPV was 74.20% and NPV was 85.30%. For neonates with >37 weeks gestational age, sensitivity was 88.90%, specificity was 65.60%, diagnostic accuracy was 72.50%, PPV was 52.20% and NPV was 93.30%. When stratified by gender, male neonates showed sensitivity of 83.90%, specificity of 73.20%, diagnostic accuracy of 77.00%, PPV of 63.40% and NPV of 89.10% while female neonates demonstrated sensitivity of 87.50%, specificity of 66.70%, diagnostic accuracy of 73.90%, PPV of 58.30% and NPV of 90.90%. Regarding birth weight stratification, neonates with ≤2.5 kg showed sensitivity of 88.50%, specificity of 73.00%, diagnostic accuracy of 79.40%, PPV of 69.70% and NPV of 90.00% whereas neonates with >2.5 kg birth weight demonstrated sensitivity of 82.80%, specificity of 68.80%, diagnostic accuracy of 73.10%, PPV of 54.50% and NPV of 89.80% (Table-V).

Table V

Stratified analysis of Sensitivity, Specificity, Diagnostic Accuracy, PPV and NPV of Ultrasound in diagnosis of hypoxic ischemic insult with gestational age at birth, gender and birth weight

Variables	Groups	Diagnostic Parameter	Result
Gestational Age at Birth (weeks)	≤37	Sen	82.10%
		Spec	78.40%
		DA	80.00%
		PPV	74.20%
		NPV	85.30%
	>37	Sen	88.90%
		Spec	65.60%
		DA	72.50%
		PPV	52.20%
		NPV	93.30%
Gender	Male	Sen	83.90%
		Spec	73.20%
		DA	77.00%
		PPV	63.40%
		NPV	89.10%
	Female	Sen	87.50%
		Spec	66.70%
		DA	73.90%
		PPV	58.30%
		NPV	90.90%
Birth Weight (kg)	≤2.5	Sen	88.50%
		Spec	73.00%
		DA	79.40%
		PPV	69.70%
		NPV	90.00%
	>2.5	Sen	82.80%
		Spec	68.80%
		DA	73.10%
		PPV	54.50%
		NPV	89.80%

DISCUSSION

The ultrasound showed positive results in 77 cases (49.4%), whereas the MRI showed positive results in 55 cases (35.3%), indicating a better detection rate of the ultrasound. This could be attributed to the modality's ability to detect minor changes in the parenchyma and its increased sensitivity to the formation of edema. The sensitivity of the ultrasound was found to be 85.5%, a figure within the acceptable range and indicating the modality's ability to detect the majority of hypoxic-ischemic cases. This increased sensitivity of the ultrasound could be attributed to the modality's ability to detect acute changes such as cerebral edema and hemorrhages in the neonatal period. The specificity of the ultrasound was found to be 70.3%, a moderate figure and indicating a certain degree of false positives, amounting to 30 cases or 19.2%. This could be attributed to the overestimation of minor changes and artifacts in the brain tissue of the preterm neonates. The accuracy of the ultrasound was found to be 75.6%, indicating a reasonable degree of accuracy and acceptable performance of the modality as a screening tool. The positive predictive value was found to be 61%, indicating that only 61% of the positive cases detected by the ultrasound were actually positive when subjected to the MRI.

The current study showing reasonable concordance with several previous studies but also demonstrating some variations. Khan *et al.* [15] reported comparable findings with sensitivity of 81.61%, specificity of 68.33%, diagnostic accuracy of 76.19%, PPV of 78.89% and NPV of 71.93% in 147 neonates which is almost similar to present study results, this similarity can be attributed to comparable study design, similar population characteristics and use of MRI as gold standard in both studies. Aun *et al.* [13] found slightly lower performance with overall sensitivity of 80% and specificity of 66.6% in 36 neonates which is close to present findings and suggesting

that ultrasound maintaining consistent moderate to good diagnostic capability across different settings. The present study sensitivity of 85.5% was lower than Sheikh *et al.* [17] who reported perfect sensitivity of 100% but higher specificity of 90.62% in detection of intracranial hemorrhage in 103 preterm neonates, this discrepancy is likely because Sheikh *et al.* [17] was focused specifically on hemorrhage detection which is easier to visualize on ultrasound compared to ischemic changes that was assessed in present study.

The specificity of 70.3% in present study was considerably lower than Sheikh *et al.* [17] (90.62%) and Maji *et al.* [18] (75.0%) which indicating higher false positive rate of 30 (19.2%) cases in current study, this reduced specificity may be explained by interpretation of subtle parenchymal echogenicity changes as positive findings which might not represent true ischemic injury on MRI, additionally operator dependency and lack of standardized criteria for defining positive ultrasound findings could contribute to overdiagnosis. Sinha *et al.* [19] reported much lower sensitivity for ultrasound (55.0%) compared to present study (85.5%) in evaluation of various etiologies of neonatal seizures including HIE where MRI showed 93.3% sensitivity, this substantial difference is possibly due to Sinha *et al.* [19] including diverse pathologies like metabolic encephalopathies and infections where ultrasound performance is inherently limited while present study was focused on hypoxic ischemic changes which are relatively better detected by ultrasound. The diagnostic accuracy of 75.6% in present study was lower than Khan *et al.* [15] who found 77.46% accuracy in age group 1-14 days but comparable to 75% accuracy in age group >14 days, suggesting that timing of examination may influence diagnostic performance with earlier scans possibly capturing acute changes more reliably.

The PPV of 61% in current study was substantially lower than Sohail *et al.* [20] who reported 100% PPV when correlating with both DWI and MRS, and also lower than Maji *et al.* [18] who found 91.67% PPV, this marked difference in PPV is likely related to different reference standards used where Sohail *et al.* [20] used advanced MRI sequences like DWI and MRS which showing better correlation with ultrasound positive findings while present study used conventional MRI that may detect more subtle abnormalities not visible on ultrasound. The NPV of 89.9% in present study was considerably higher than Aun *et al.* [13] (40%) and Sohail *et al.* [20] (28.7% when correlated with MRS), this high NPV is clinically important as it indicating that ultrasound is reliable for excluding significant hypoxic ischemic injury when findings are negative, the lower NPV in other studies might be due to higher disease prevalence or inclusion of subtle cases that ultrasound was unable to detect. Thakkar *et al.* [21] reported sensitivity of 83.33% and specificity of 92.59% for HIE diagnosis in preterm neonates which showing higher specificity than present study (70.3%), this could be explained by Thakkar *et al.* [21] focusing exclusively on preterm population where specific ultrasound features like periventricular echogenicity and cysts are more characteristic and easier to interpret compared to mixed gestational age population in present study.

There are certain limitations to this study, which need to be acknowledged. One of the limitations of this study is that it is a single-center study which means the results of this study might not be easily generalizable to other populations. Another limitation of this study is that the sample of 156 neonates might not be enough to show the differences between various groups. A third limitation of this study is that it did not measure the inter-observer variability of radiologists who performed ultrasound, which is a user-dependent test with a wide range of variability between observers.

CONCLUSION

The current study concludes that transcranial ultrasound is an important diagnostic modality in the detection of hypoxic-ischemic insult in neonates, which is highly sensitive and specific compared to MRI, which is considered the gold standard. This modality is highly specific in excluding significant brain injury and can be considered a first step in screening for brain injury in resource-limited countries where access to MRI is limited.

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