Original article

Cranial sonography as diagnostic tool for neonatal hypoxic ischemic encephalopathy in premature neonates

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ABSTRACT

Background: Perinatal asphyxia plays a major role in neonatal morbidity and death throughout the world. An estimated 130 million infants are born each year, of which 4 million die within first 28 days of life. Pakistan has the third highest neonatal death rate in the world with incidence of prenatal asphyxia reaching up to 9%. Magnetic resonance imaging (MRI) of the brain is the standard imaging modality in such cases, but a good correlation between cranial sonography and MRI of brain has been reported. The aim of this study was to determine diagnostic accuracy of cranial sonography in detection of neonatal hypoxic ischemic encephalopathy (HIE) in clinically suspected premature neonates.

Patients and methods: This cross-sectional survey was conducted in Sir Ganga Ram Hospital, Department of Radiology and Medical Imaging between March-August, 2017. Total 303 premature neonates were included in the study hospitalized in Neonatology unit of the hospital with clinical suspicion of hypoxic ischemic encephalopathy. Transcranial sonography (CUS) was performed in first month of life and findings were recorded. Then 1.5 Tesla MRI machine was used for imaging brain using T1-weighted, T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. The sonographic results were then compared with MRI findings.

Results: The mean age of mothers was 29.3years. The mean gestational age at birth was 33.9weeks. In this study, there were 157 (51.8%) males and 146 (48.2%) female neonates. The sensitivity, specificity, PPV, NPV and diagnostic accuracy of cranial sonography were 97.8%, 96.0%, 97.2%, 96.8% and 97.0%, respectively taking MRI as gold standard.

Conclusion: Cranial sonography has high accuracy in detection of hypoxic ischemic encephalopathy in neonates and can be used as initial imaging modality.

Keywords:
Diagnostic accuracy, Cranial sonography, Hypoxic ischemic encephalopathy, Premature neonates, MRI

INTRODUCTION

Perinatal asphyxia plays a major role in neonatal mortality and morbidity throughout the world. Of the estimated 130 million infants born each year worldwide 4 million die within first 28 days of life.[1] Pakistan ranks third highest in neonatal death rate in the world.[2] Fifty-five per 1000 live births according to Pakistan Demographic and Health Survey (PDHS) 2012-2013. Incidence of prenatal asphyxia in Pakistan is 3.3% which increases to 9% when considering neonates of less than 36 weeks of gestational age alone and accounts for 20-31% of perinatal deaths.[3]It remains one of the leading causes of hospital admissions in neonatology.[4]

Hypoxic ischemic encephalopathy (HIE) is defined as "an acute non-static encephalopathy caused by intrapartum or late antepartum brain hypoxia and ischemia".[5] This clinical condition develops during the first few days of life and is a leading predictor of neurodevelopmental disability.[6] Asphyxia compromises the exchange of gases between the fetus and placenta, with resultant fetal hypercarbia, hypoxia, and metabolic acidosis.[7] It has been reported that multiple-organ failure occurs in 50-60% of neonates with severe perinatal asphyxia.[8]The severity of the disease depends upon extent of brain maturation, location and duration of injury.[9] It has serious neurological sequelae such as cerebral palsy, mental retardation and epilepsy.[10,11]

The standard modality of imaging the brain in asphyxiated neonates is MRI as it provides anatomical and functional information which aids in determining severity and prognosis of the disease.[12] It demonstrates different patterns of injury, including watershed injury and involvement of basal ganglia and thalami. Good correlation between cranial sonography (CUS) and MRI of the brain has been established for assessing hypoxic-ischemic injury.[7,13] It implies that cranial sonography may be an equally efficient modality for this purpose. Adequate technique, taking benefit from

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multiple sonographic windows and using variable frequency probes allows a detailed and comprehensive examination of brain parenchyma.[14] This portable bedside tool is especially excellent in neonates that are critically ill and cannot be shifted to the MRI suite. Some lesions are even better depicted with sonography than MRI.[15] The rationale of this study was to assess the diagnostic accuracy of cranial sonography taking MRI findings as gold standard in clinically suspected premature neonates in local population.

PATIENTS AND METHODS

This cross-sectional study was conducted in Sir Ganga Ram Hospital, Department of Radiology and Medical Imaging between March-August 2017. Total 303 premature neonates with gestational age below 37 completed weeks and birth weight between 0.75-2.4 kgs were included in the study. Neonates with clinical suspicion of hypoxic ischemic encephalopathy referred by Neonatalogy Unit of Sir Ganga Ram Hospital from indoor and neonatal intensive care unit, fulfilling the above mentioned criteria were enrolled in the study. Clinical suspicion of HIE was based on Apgar score of 0 to 3 for more than 5 minutes and neurological manifestations (e.g., seizures, coma, or hypotonia) as per definition of birth asphyxia according to American College of Obstetricians & Gynecologists and the American Academy of Pediatrics.[16] Premature babies with clinical and radiologically diagnosed congenital anomalies or premature still births were excluded from the study. Informed consent was obtained. Transcranial sonogram was carried out on Toshiba (Nemio®) ultrasound machine using 10-14 MHz frequency linear array transducer within first month of life. Anterior and posterior fontanelles were used as primary acoustic windows to brain by the corresponding author. Study was reviewed by the Professor of Radiology Department in the same sitting for confirmation. The features of brain swelling evident as asymmetry between cerebral hemispheres and loss of major landmarks such as sulci and major fissures or echogenic subcortical white matter which may represent hemorrhage were taken to confirm hypoxic ischemic encephalopathy. These patients were then sent for MR imaging on 1.5 Tesla MRI unit (vantage Atlas Z, Toshiba®, Medequips, Japan) using T1-weighted, T2-weighted and FLAIR sequences in axial, coronal and sagittal planes. Features including increased signal intensity on T1WI in basal ganglia and thalami along with absence of normal hyperintensity in posterior limb of internal capsule on T1WI were used to confirm HIE on MRI. All reports were verified by the senior author consultant to minimize any bias. The results of cranial sonogram and MRI were compared taking MRI as gold standard.

Data was analyzed using SPSS version 20. Presence or absence of hypoxic ischemic encephalopathy on ultrasound and MRI were used as variables. Quantitative data was represented as mean with standard deviation. Qualitative data was expressed as percentage. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (DA) were calculated by constructing a 2x2 table of the collected data. A p-value of <0.05 was regarded as statistically significant.

RESULTS

The mean age of mothers was 29.34±6.49years. The mean gestational age at birth was 33.92±1.43weeks. There were 157 (51.8%) males and 146 (48.2%) female neonates. Out of the total, 180 (59.4%) neonates were found positive for HIE while 123 (40.6%) were negative on CUS. On MRI, 179 (59.1%) were positive for HIE while 124 (40.9%) were negative. The sensitivity, specificity, PPV, NPV and diagnostic accuracy of CUS were 97.8%, 96.0%, 97.2%, 96.8% and 97.0%, respectively taking MRI as gold standard. Table 1 summarizes the diagnostic accuracy of CUS when compared with MRI.

Data was stratified for age of mothers. In neonates born to 18-29 years old mothers, sensitivity, specificity, PPV, NPV and diagnostic accuracy of CUS were 97.7%, 93.4%, 95.4%, 96.6% and 95.9%, respectively taking MRI as gold standard. In neonates born to 30-40 years old mothers, sensitivity, specificity, PPV, NPV and diagnostic accuracy of CUS were 97.9%, 98.4%, 98.9%, 96.9% and 98.1%, respectively taking MRI as gold standard (Table 1).

Data was also stratified for gestational age at birth. In neonates born at 32-34 weeks, sensitivity, specificity, PPV, NPV and diagnostic accuracy of CUS were 98.2%, 97.6%, 98.2%, 97.6% and 97.9%, respectively taking MRI as gold standard. In neonates born at gestational age 35-36 weeks, sensitivity, specificity, PPV, NPV and diagnostic accuracy of CUS were 97.1%, 92.9%, 95.8%, 95.1% and 95.5%, respectively taking MRI as gold standard (Table 1).

DISCUSSION

Neonatal hypoxic ischemic encephalopathy is a devastating condition that may result in severe neurologic deficits in children or even death.

Table 1. Accuracy of cranial ultrasonography (CUS) taking magnetic resonance imaging (MRI) as gold standard

	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
Overall	175	5	4	119	97.8	96.0	97.2	96.8	97.0
Maternal age (years)									
18-29	83	4	2	57	97.7	93.4	95.4	96.6	95.9
30-40	92	1	2	62	97.9	98.4	98.9	96.9	98.1
Gestational age (months) at birth									
32-34	107	2	2	80	98.2	97.6	98.2	97.6	97.9
35-36	68	3	2	39	97.1	92.9	95.8	95.1	95.5

PPV: positive predictive value; NPV: negative predictive value

Neuroimaging with cranial sonography, CT and MRI are valuable tools in the workup of patients with HIE. Portable cranial sonography using grey-scale and color Doppler techniques can provide comprehensive and reliable information in neonates with asphyxia.[12] Although MRI is considered the imaging modality of choice for assessment of injury severity and prognostication in HIE, cranial ultrasonography is being recommended as the initial imaging modality for this purpose. Cranial sonography has certain limitations, however using supplemental acoustic windows and taking advantage of 3D and 4D imaging greatly improves its diagnostic accuracy.[17] Easy availability, low cost, portability without having to take the neonate out of the incubator and NICU, ability to perform real-time ultrasound without sedation and performing interval studies several times without any harm makes it highly preferable over other expensive arduous investigations as MRI. This study aimed to determine diagnostic accuracy of cranial sonography in detecting neonatal hypoxic ischemic encephalopathy keeping MRI as 'gold standard'. On CUS, 180 (59.4%) were positive for HIE while 123 (40.6%) were negative. On MRI, 179 (59.1%) were positive for HIE while 124 (40.9%) were negative. The sensitivity, specificity, PPV, NPV and diagnostic accuracy of CUS were 97.8%, 96.0%, 97.2%, 96.8% and 97.0%, respectively. One previous study demonstrated the sensitivity of cranial sonography to be as high as 100%, specificity 96%, PPV 77% and predictive probability to be 96% keeping MRI as gold standard. These results are comparable to findings in this study.[13] The results are also well within the figures quoted in a previously published large scale study which demonstrated sensitivity of cranial sonography to be 91% and specificity of 81%.[15] Shen and coworkers reported that the sensitivity and specificity for ultrasound were 80% and 90%, respectively taking MRI as gold standard.[18] Genedi and colleagues reported that diagnostic accuracy of CUS compared to MRI was 78.9%, while the overall sensitivity and specificity were 81.8% and 60% respectively which are variable than our results possibly due to smaller sample size.[19] Epelman and group demonstrated 100% sensitivity for CUS and specificity 33.3% and accuracy 95.7%.[20]

The mean gestational age at birth was 33.92±1.43weeks. Data was stratified for gestational age at birth. In neonates born at 32-34 weeks, sensitivity, specificity, PPV, NPV and diagnostic accuracy of CUS were 98.2%, 97.6%, 98.2%, 97.6% and 97.9%, respectively taking MRI as gold standard. In neonates born at gestational age 35-36 weeks, sensitivity, specificity, PPV, NPV and diagnostic accuracy of CUS were 97.1%, 92.9%, 95.8%, 95.1% and 95.5%, respectively taking MRI as gold standard. These findings were in accordance with study by De Vries and coauthors.[11] The mean age of mothers was 29.34±6.49 years. Data was stratified for age of mothers. In neonates of 18-29 years old mothers, sensitivity, specificity, PPV, NPV and diagnostic accuracy of CUS were 97.7%, 93.4%, 95.4%, 96.6% and 95.9%, respectively taking MRI as gold standard. In neonates of 30-40years old mothers, sensitivity, specificity, PPV, NPV and diagnostic accuracy of CUS were 97.9%, 98.4%, 98.9%, 96.9% and 98.1%, respectively taking MRI as gold standard. Maternal age at delivery has not been reported to be significant. However, some researchers reported that maternal age above 35 years is a risk factor (OR 4.35) for neonatal encephalopathy.[21]

CONCLUSION

The accuracy of CUS is high in detection of HIE in neonates which advocates its use as first line imaging modality in detection of HIE in preterm neonates. This non-invasive bedside tool is easily available in virtually all secondary and tertiary centres. The ability to perform real-time ultrasound without sedation and performing interval studies several times without any hazards makes it highly preferable over other expensive arduous investigations as MRI.

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