TO DETERMINE THE DIAGNOSTIC ACCURACY OF TRANSCRANIAL ULTRASOUND IN THE DETECTION OF HYPOXIC ISCHEMIC INJURY IN NEONATES KEEPING MAGNETIC RESONANCE IMAGING AS A GOLD STANDARD

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ABSTRACT

Objective: To ascertain the accuracy of transcranial ultrasound diagnosis in the detection of hypoxic ischemic injury in neonates, keeping magnetic resonance imaging as the gold standard.

Material & Methods: A cross-sectional study was conducted on 147 Male and female patients with an age range of 1-28 days in the Department of Radiology, Hayatabad Medical Complex, Peshawar, from 28 February 2023 to 28 August 2023 (06 months). The patients were suspected of hypoxic-ischemic injury, i.e., suffered from perinatal asphyxia. The diagnostic accuracy of transcranial sonography in detecting neonatal hypoxic-ischemic injury was determined.

Results: The mean age of the patients was 14.44±7.77 days. The accuracy of transcranial ultrasound diagnosis in the detection of hypoxic ischemic injury by taking magnetic resonance imaging as the gold standard was 76.19%, with sensitivity 81.61%, specificity 68.33%, Positive Predictive Value 78.89%, and Negative Predictive Value 71.93%.

Conclusion: From our study, we conclude that transcranial ultrasound is an accurate modality in detecting neonatal hypoxic ischemic injury with a diagnostic accuracy of 76.19%, a sensitivity of 81.61%, and a specificity of 68.33%.

Keywords: Hypoxic Ischemic Injury, Magnetic Resonance Imaging, neonates, transcranial ultrasound.

INTRODUCTION

Newborn encephalopathy remains a major contributor to infant death and morbidity world-wide. It mainly occurs on a background of fetal asphyxia resulting in hypercapnia and hypoxemia. Hypoxic-ischemic injury (HII) is the subset of encephalopathy in neonates which results from a hypoxic or ischemic event.[1] Reduced cerebral blood flow caused by hypotension is hypothesized to trigger acidosis, the generation of inflammatory processes and excitatory neurotransmitters, and the generation of free radicals.[2] According to the criteria utilized to identify neonatal encephalopathy, the incidence of HII is estimated to range from 0.4 to 1.6 per 1000 live births. Many infants with HII don't make it past the newborn stage; the mortality rate ranges from 20% to 50%. Up to a quarter of the survivors develop long-term neurological issues such as mental retardation or lifelong seizures.[3]

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Imaging tools like transcranial ultrasound, Computed Tomography (CT) scan, and Magnetic Resonance Imaging (MRI) have all been tested to see how well they portray HII. Diffusion-Weighted Imaging (DWI) and Magnetic Resonance Spectroscopy (MRS) are two of the most recent radiological techniques added to the diagnostic toolkit. Magnetic resonance imaging (MRI) has the highest sensitivity and is generally accessible.[4] Improved specificity and new insights into HIE may be gained with the incorporation of cutting-edge modalities including MR spectroscopy and DWI.[5]

Normal imaging findings in preterm newborns, term infants, and older children are different from those in term neonates. Neonatologists need to know how babies normally grow and develop in order to spot abnormalities.[6] HII Injury to the periventricular white matter, presenting as PVL due to ischemic parenchyma, is the most common type of brain injury in premature infants when mild to severe hypotension is present. Germinal matrix hemorrhage and damage to the white matter around the ventricles may occur simultaneously. A study reported the rate of Hypoxic Ischemic injury (34.8%).[7] Another study reported the sensitivity of (80%), and specificity of (66.67%) of transcranial ultrasound in the detection of neonatal HII.[8]

One of the chief reasons of neurological disability and death due to neurological causes in children is HIE. Very limited data is available related to this condition and about the

diagnostic tools for effective screening. Therefore, this study is initiated to ascertain the accuracy of transcranial ultrasound diagnosis in the detection of hypoxic ischemic injury among neonates keeping magnetic resonance imaging as a gold standard.

MATERIAL AND METHODS

A cross-sectional investigation was carried out on 147 patients both Male & Female having age range (1-28) days with suspected hypoxic ischemic injury i.e., suffered with perinatal asphyxia in the Department of Radiology, Hayatabad Medical Complex, Peshawar from 28th Feb, 2023 to 28th August, 2023 (06 months). Written consent was taken from the parents/attendants of the neonates. Patients with respiratory distress, sepsis and congenital anomalies were not included in the study.

The sample size was calculated with the help of WHO sample size calculator through non-Probability consecutive sampling technique.

To carry out the research work, approval was taken from the ethical board of the hospital. Subjects who meet the study's recruitment criteria were enrolled in the study, the goal, benefits, and risks were clearly explained to the guardians/attendants, before collecting the informed written consent form from all the guardians/attendants. Gender, age, and address were recorded as demographic information. A comprehensive medical history was noted down, followed by a physical examination. Suspected patients of hypoxic ischemic injury i.e., suffered with perinatal asphyxia undergone transcranial ultrasound, and these patients were later examined through Magnetic Resonance Imaging. The findings of transcranial ultrasound and Magnetic Resonance Imaging were compared under the supervision of an experienced radiologist with minimum 3 years of post-fellowship experience. A pre-designed Performa were used to record the patients' information.

The data entry and analysis were performed by using the SPSS 21 software. Mean $\pm$ SDs were described for numerical data age. Frequency and percentages were described for categorical data like gender, Transcranial Ultrasound findings, Magnetic Resonance Imaging findings, and residence area. 2x2 Contingency table was utilized to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of Transcranial Ultrasound in the diagnosis of hypoxic ischemic injury by taking Magnetic Resonance Imaging as the gold standard. Diagnostic accuracy was stratified by age, gender and residence area. Post-stratification Chi-Square test was used by keeping the value of $p \leq 0.05$ as significant. All the results were presented as tables, charts.

RESULTS

This study was conducted on 147 suspected patients of hypoxic ischemic injury i.e., suffered with perinatal asphyxia. The mean age of the patients was 14.44±7.77 days . Regarding the age distribution there were 71 (48.3%) patients in the age group of 1 to 14 days while there were 76 (51.7%) patients in the age group of > 14 days (Table-1). Regarding gender distribution there were 84 (57.1%) males while 63 (42.9%) female patients in our study (Table-2). The Hypoxic Ischemic Injury on Transcranial USG was positive in 90 (61.2%) patients and negative in 57 (38.8%) patients (Table-3). The Hypoxic Ischemic Injury on MRI was positive in 87 (59.2%) patients and negative in 60 (40.8%) patients (Table-4). According to the resident status 89 (60.5%) patients were from rural areas and 58 (39.5%) patients were from urban areas (Table-5). The accuracy of transcranial ultrasound diagnosis in the detection of hypoxic ischemic injury by taking Magnetic Resonance Imaging as the gold standard was 76.19%, with sensitivity 81.61%, specificity 68.33%, Positive Predictive Value 78.89% and Negative Predictive Value 71.93% (Table-6). Stratification of Diagnostic accuracy of Transcranial Ultrasound in the diagnosis of Hypoxic Ischemic Injury by taking Magnetic Resonance Imaging as the gold standard with age, gender, and residence status can be seen from Tables 7-9.

Table 1: Age distribution

Age distribution	Frequency	Percentage
1 to 14 days	71	48.3 %
> 14 days	76	51.7 %
Total	147	100.0

Table 2: Gender distribution

Gender	Frequency	Percentage
Male	84	57.1 %
Female	63	42.9 %
Total	147	100.0

Table 3: Hypoxic Ischemic Injury on Transcranial USG

Hypoxic Ischemic Injury on Transcranial USG	Frequency	Percentage
Positive	90	61.2 %
Negative	57	38.8 %
Total	147	100.0

Table 4: Hypoxic Ischemic Injury on MRI

Hypoxic Ischemic Injury on MRI	Frequency	Percent
Positive	87	59.2 %
Negative	60	40.8 %
Total	147	100.0

Table 5: Residence status

Residence status	Frequency	Percent
Rural	89	60.5
Urban	58	39.5
Total	147	100.0

Table 6: Diagnostic accuracy of Transcranial Ultrasound in the diagnosis of Hypoxic Ischemic Injury by taking Magnetic Resonance Imaging as the gold standard

		Hypoxic Ischemic Injury on MRI		Total
		Positive	Negative	
Hypoxic Ischemic Injury on Transcranial USG	Positive	**(TP)** 71	**(FP)** 19	90
		81.6%	31.7%	61.2%
	Negative	**(FN)** 16	**(TN)** 41	57
		18.4%	68.3%	38.8%
Total		87	60	147
		100.0%	100.0%	100.0%

Sensitivity = 81.61% Specificity = 68.33% Positive Predictive Value= 78.89%. Negative Predictive Value=71.93%. Diagnostic accuracy = 76.19%

Table 7: Stratification of Diagnostic accuracy of Transcranial Ultrasound in the diagnosis of Hypoxic Ischemic Injury by taking Magnetic Resonance Imaging as the gold standard with age

Age Distribution			Hypoxic Ischemic Injury on MRI		Total	P- value
			Positive	Negative		
1 to 14 days	Hypoxic Ischemic Injury on Transcranial USG	Positive	36	7	43	<0.001
			80.0%	26.9%	60.6%	
		Negative	9	19	28	
			20.0%	73.1%	39.4%	
	Total		45	26	71	
			100.0%	100.0%	100.0%	
> 14 days	Hypoxic Ischemic Injury on Transcranial USG	Positive	35	12	47	<0.001
			83.3%	35.3%	61.8%	
		Negative	7	22	29	
			16.7%	64.7%	38.2%	
	Total		42	34	76	
			100.0%	100.0%	100.0%	

Age distribution (Days)	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
1 to 14	80%	73.08%	83.72%	67.86%	77.46%
> 14	96.88%	64.71%	74.47%	75.86%	75%

Table 8: Stratification of Diagnostic accuracy of Transcranial Ultrasound in the diagnosis of Hypoxic Ischemic Injury by taking Magnetic Resonance Imaging as the gold standard with gender

Gender			Hypoxic Ischemic Injury on MRI		Total	P-value
			Positive	Negative		
Males	Hypoxic Ischemic Injury on Transcranial USG	Positive	38	11	49	<0.001
			79.2%	30.6%	58.3%	
		Negative	10	25	35	
			20.8%	69.4%	41.7%	
	Total		48	36	84	
			100.0%	100.0%	100.0%	
Females	Hypoxic Ischemic Injury on Transcranial USG	Positive	33	8	41	<0.001
			84.6%	33.3%	65.1%	
		Negative	6	16	22	
			15.4%	66.7%	34.9%	
	Total		39	24	63	
			100.0%	100.0%	100.0%	

Gender	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Male	79.17%	69.44%	77.55%	71.43%	75%
Female	84.62%	66.67%	80.49%	72.73%	77.78%

Table 9: Stratification of Diagnostic accuracy of Transcranial Ultrasound in the diagnosis of Hypoxic Ischemic Injury by taking Magnetic Resonance Imaging as the gold standard with residence status

Residence			Hypoxic Ischemic Injury on MRI		Total	P-value
			Positive	Negative		
Rural	Hypoxic Ischemic Injury on Transcranial USG	Positive	45	9	54	<0.001
			80.4%	27.3%	60.7%	
		Negative	11	24	35	
			19.6%	72.7%	39.3%	
	Total		56	33	89	
			100.0%	100.0%	100.0%	
Urban	Hypoxic Ischemic Injury on Transcranial USG	Positive	26	10	36	<0.001
			83.9%	37.0%	62.1%	
		Negative	5	17	22	
			16.1%	63.0%	37.9%	
	Total		31	27	58	
			100.0%	100.0%	100.0%	

Residence status	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Rural	79.17%	69.44%	77.55%	71.43%	75%
Urban	84.62%	66.67%	80.49%	72.73%	77.78%

DISCUSSION

Hypoxic Ischemic Injury (H.I.I) leading to encephalopathy usually results due to ischemic event in neonates as a result of perinatal asphyxia leading to hypercapnia and hypoxia. As a result of reduced blood flow to the brain, there is release of excitatory neurotransmitters inflammatory mediators and free radicles besides acidosis.

According to the criteria used to define neonatal ischemic injury, about 1-4 infants /1000 live births are estimated to be affected. It has been observed that 20-50 % of these neonates do not survive. 25% of those who survives definitely exhibit permanent neurological deficit as mental retardation, cerebral palsy or seizures.[9]

Different radio-diagnostic techniques have been used regarding their sensitivity and specificity to detect ischemic encephalopathy in neonates including transcranial ultrasonography (TCUS), Computerized Tomography (CT) and MRI along with newer diagnostic techniques such as Magnetic Resonance Spectroscopy (MRS) and Diffusion-Weighted Imaging (DWI) which may provide further information about HIE, for possible therapeutic management.[10] However, imaging findings in full-term infants vary from those in pre-term neonates and older pediatric population. Recognizing pathological processes requires a thorough grasp of the typical anatomy and developmental stages of neonatal brain.[11]

The periventricular white matter is the most frequent site of injury in the premature brain. Due to severe hypotension, the area having high metabolic activity like thalami, brain stem and cerebellum of the immature brain are more susceptible to ischemic injury and this is manifested as altered signal on T2 weighted MRI images and diffusion restriction on Diffusion Images (DWI). There is also injury to the white matter of the periventricular region and hemorrhage in the germinal matrix in these cases.[12]

Hypoxic ischemic encephalopathy (HIE) which is major outcome of HII and is responsible for neurologic morbidity and mortality in neonates, was included in our study. The Diagnostic accuracy of Transcranial Ultrasound in the diagnosis of Hypoxic Ischemic Injury was 76.19%, with sensitivity of 81.56%, specificity 68.33% which are similar to the results of a study carried out by Aun et all in Egypt who have reported the sensitivity to be 80% and specificity 66.67%.[8]

Genedi et al have also reported that diagnostic accuracy of Cranial US compared to MRI was 78.9%, while the overall sensitivity and specificity were 81.8% and 60% respectively which is nearly the same as in our study.[13] In

another similar study carried out in Baltimore by Ghe et al, the sensitivity of cranial sonography was found to be as high as 100%, specificity 96%, PPV 77% and predictive probability to be 96% considering MRI as gold standard which was higher than our results likely due to large sample size .[3] Epelman et al also reported 100% sensitivity, 33.3% specificity and accuracy of 95.7% for CUS.[14]

Diffusion weighted imaging is helpful to diagnose in early days after ischemic insult and usually shows diffusion restriction within few hours. DWI changes then become false negative about one week after the ischemic injury which is called pseudo normalization.[3]

In contrast to conventional MRI, brain injury related to hypoxia and ischemia is observed more distinctly with Diffusion-Imaging (DWI). DWI is valuable for early detection of abnormal changes, making it is a useful technique to assess the pattern and degree of insult to the brain.[15]

Another study carried out by Yasin et al in neonates who born at gestational age of 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 considering MRI as gold standard.[16]

Proton MR Spectroscopy is more specific and may depicts additional information, when conducted within the initial 24 hours and proves particularly valuable as conventional methods often underestimate the degree of injury or are false positive.[17]

Transcranial ultrasound and MRI both are useful techniques for detection of HII however, Transcranial Ultrasonography is an economical, bedside, readily available, operator dependent and fast technique for imaging NE. This bed side, non-invasive tool is readily available in all secondary and tertiary setups. MRI is an essential tool to diagnose the degree, timing and severity of neonatal brain injury and it plays a major role in the prognosis of neurological sequalae.

Despite the promising findings of this study, several limitations must be acknowledged. First, the sample size was relatively small, which may limit the generalizability of the results to a larger neonatal population. Second, transcranial ultrasound (TCUS) has inherent operator dependency, and variations in technique and expertise may influence the accuracy of detection. Third, while magnetic resonance imaging (MRI) was used as the gold standard, the timing of imaging may have influenced the detection of hypoxic-ischemic injury (HII), as some lesions evolve over time. Additionally, ultrasound has limited sensitivity in detecting subtle cortical and deep gray matter injuries compared to MRI.

Future research should focus on conducting larger, multicenter studies to validate the findings and improve the reliability of TCUS in detecting neonatal HII.

CONCLUSION

The transcranial ultrasound is an accurate modality for detection of hypoxic ischemic injury in neonates with high accuracy and can be performed several times without sedation and any hazards, recommends it as first line imaging modality in diagnosis of HIE .

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