Original Article

Role of Transcranial Ultrasound and Doppler Studies to Evaluate Intracranial Pathologies in Preterm and High-risk Term Neonates

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Abstract

Background: Transcranial grayscale neurosonography (NSG) and Doppler studies have major role in diagnosing neonate intracranial pathologies. The aim of the study is to evaluate the role of NSG and Doppler studies in correlation with clinical hypotonia and seizures in preterm neonates and high-risk term neonates. The prevalence of intracranial pathology is the second aim of this study. **Methods:** The present cross-sectional study was done in a tertiary care teaching hospital for 2 years. The study population of 120 cases comprised two groups: one group of 60 preterm neonates and the other of 60 high-risk term neonates with a history of well-defined episode of fetal distress. The NSG and Doppler findings (resistance index ≤0.62 is the optimum cutoff point for diagnosing perinatal asphyxia) are recorded. The sensitivity and specificity values for the NSG study alone, the Doppler study alone, and the combined NSG and Doppler studies are calculated. **Results:** The majority (46%) of preterm neonates had presented with germinal matrix hemorrhage, whereas a majority (46%) of high-risk term neonates had presented with periventricular and subcortical cysts. Comparison of the sensitivity of NSG versus Doppler versus combined NSG and Doppler in evaluating hypotonia and seizures in preterm ($P = 0.0442$) and high-risk term neonates ($P = 0.0399$) was significant. **Conclusion:** NSG combined with the Doppler study has significantly higher sensitivity than NSG alone in both groups. The specificity of the Doppler study is also high in both groups. Thus, it is strongly recommended to include Doppler during every NSG study to increase the detection rate.

Keywords: Doppler, intracranial pathologies, neonate, transcranial ultrasound

Introduction

Transcranial grayscale neurosonography (NSG) and Doppler studies have a significant role in detecting and estimating the prevalence of various intracranial pathologies in preterm and high-risk term neonates. Preterm birth, defined as delivery before 37 weeks of gestation, occurs yearly in over 15 million infants worldwide.[1] Brain damage is still a common and clinically significant issue in preterm infants.[2] The preterm infant's brain may suffer from hemorrhagic, ischemic, or maturation arrest lesions, among other conditions.[3] Periventricular leukomalacia (PVL) is the predominant form of brain injury and the leading cause of cerebral palsy and cognitive deficits in premature infants.[4] Premature babies are more likely to develop PVL than term babies, and the frequency rises as gestational age decreases.[5] The prevalence of PVL ranged from 19.8% to 34.1%, whereas the cystic PVL variety ranged from 2.5% to 23% [Figure 1].[6] PVL with multicystic encephalomalacia mainly affects preterm neonates with multiple subcortical and periventricular cysts.[7] It involves bilateral thalami, which is difficult to recognize on NSG.[8]

Periventricular-intraventricular hemorrhage (IVH), the second-most frequent cause of death in preterm children, is one of the major causes of cerebral injury in preterm infants.[2] The severity of IVH is rated from 1 to 4: grade 1 IVH is defined as germinal matrix hemorrhage (GMH) only; Grade 2 IVH is defined as GMH without ventricular dilatation; Grade 3 IVH is defined as GMH with dilation of the ventricles [Figure 2];

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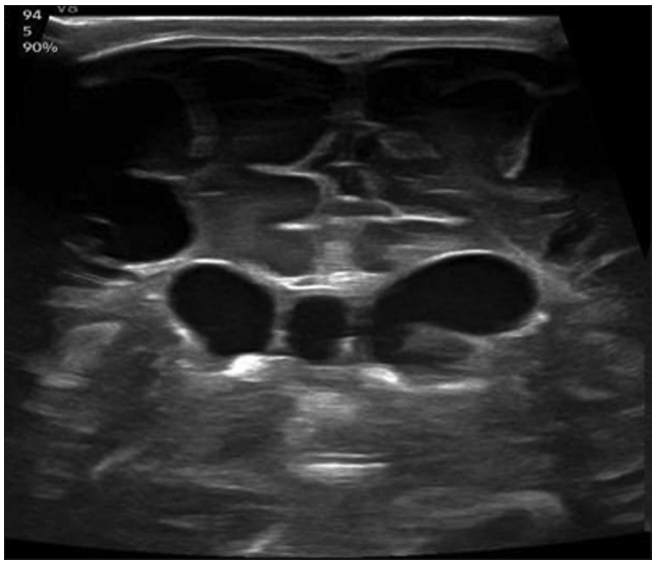

Figure 1: Preterm neonate with cystic periventricular leukomalacia features

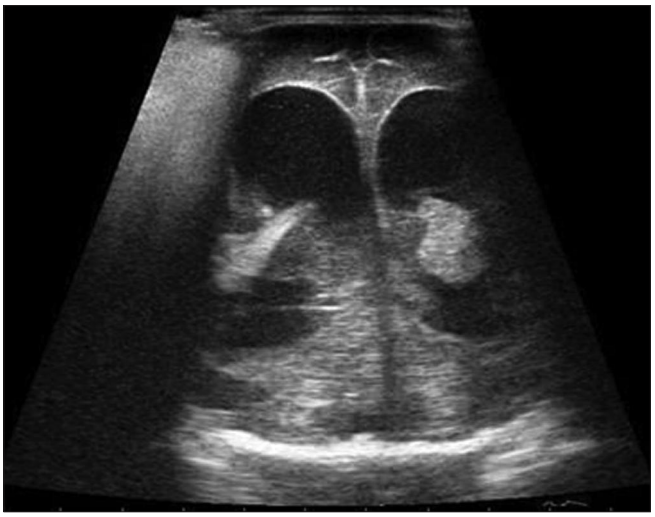

Figure 2: Preterm neonate with Grade 3 germinal matrix hemorrhage showing dilated bilateral lateral ventricles

and Grade 4 constitutes Grade 3 IVH features along with intraparenchymal hemorrhage. Severe IVH refers to Grade 3 and 4.[5] According to Papile's categorization, Grade 1 and 2 IVH has reported incidence rates of 12%.[9] Grade 3 IVH and Grade 4 IVH have reported incidence rates of 5.8% and 6.1%, respectively.[10] Other intracranial disorders, such as cerebral edema and hydrocephalus, also have significant morbidity; early detection of these conditions improves prognosis. Brain edema is a pathological change characteristically observed after asphyxia, and the primary ultrasound manifestation of brain edema is diffuse parenchymal echo enhancement. More intense patterns of parenchymal echo indicate more severe neuronal damage. With brain edema, the intracranial structures appear fuzzy, with shallow sulci and narrowed or undetected ventricles.[11] Multiple variables, including vascular, hemodynamic, and inflammatory, contribute to these illnesses, which may lead to neuropsychomotor sequelae, cerebral palsy, and behavioral and cognitive deficits.

High-risk term neonates are those born after 37 weeks with a greater chance of morbidity and mortality, especially within the 1st 28 days of life.[6] These are term neonates with high-risk factors such as asphyxia needing mechanical ventilation, low APGAR score (<7) at 1 min, low birth weight (<2.5 kg), and associated perinatal risk factors, such as gestational diabetes mellitus (GDM) and pregnancy-induced hypertension (PIH). These neonates often suffer neurological symptoms, most commonly hypotonia and motor seizures. The primary injury pattern found in high-risk full-term newborns involves predominantly the deep gray matter, in which areas of hyperechogenicity develop 24–72 h from birth.

IVH occurs less frequently in term neonates, mainly from the choroid plexus and thalamus instead of the germinal matrix. It is associated with perinatal risk factors such as PIH and asphyxia.[12] Early identification and implementation of supportive therapies at the right time improve prognosis. In the newborn intensive care unit, transcranial ultrasound imaging is frequently utilized to detect brain abnormalities. It permits a quick assessment of newborns in intensive care units without anesthesia and with almost zero risk. Because of its portability, affordability, speed, and lack of ionizing radiation, it is an ideal imaging technique for newborns. The preferred method for a better strategy during the intensive care of the premature infant is transcranial Doppler ultrasonography.[13] While Doppler provides information on cerebral hemodynamics by analyzing the main branches of the Willis circle, ultrasonography enables imaging diagnosis.

In addition, since a Doppler scan is carried out using an anterior and temporal transfontanelle approach, it enhances blood vessel visualization, allows for the quantification of variations in cerebral blood flow over time, and measures the resistance index (RI) using a spectral representation of the wave. Doppler has been widely used to assess changes in cerebral hemodynamics in premature newborns and high-risk term neonates. Investigations in the literature have proven that these changes are related to the pathophysiological mechanism of hemorrhages and hypoxic–ischemic events.[13] Nonetheless, some questions remain about Doppler's sensitivity to detect cerebral diseases in preterm and high-risk newborns.[14]

Materials and Methods

The study is a cross-sectional study in a tertiary care teaching hospital. A total of 120 neonates were selected for the study, 60 preterm and 60 high-risk term neonates, according to inclusion and exclusion criteria after obtaining informed consent from parents. The study was conducted in accordance with the Declaration of Helsinki. The institutional review board approved the study protocol (IEC/IMS.SH/SOA/2022/326, Dated: 14th March 2022). Doppler was used in every case of neurosonogram in this study using the "GE Voluson 6E" machine. The study was conducted for 2 years, from 2020 to 2022. Neonates between 28 and 37 weeks (preterm)

and neonates >37 weeks (term) with high-risk factors such as low APGAR score (<7) at 1 min, mechanically ventilated, with comorbidities such as GDM, PIH, sepsis, meconium-stained amniotic fluid, and anemia, with a history of a well-defined episode of fetal distress, were included in the study. All suspected cases of failed resuscitation, congenital malformations, and intracranial mass, neonates with heart disease, which alter cerebral flow velocities, were excluded from the study.

Statistical analysis

Data were collected and analyzed statistically using descriptive statistics mean and standard deviation. A two-tailed *t*-test is done to find the relative difference between the sensitivity of combined (NSG and Doppler) and the sensitivity of gray scale NSG alone. Sensitivity is the percentage of true positives of clinically symptomatic neonates presenting with hypotonia and motor seizures and showing findings on NSG or Doppler. Hypotonia is decreased resting tone of muscle and reduced resistance to passive movements. As in infants, normal tone requires the integrity of the central and peripheral nervous systems; hypotonia is a sign of central and/or peripheral neurological system dysfunction.[15] In infants, if the muscle tone is loose and floppy without activity, the Apgar score is 0. If the infant demonstrates some tone and flexion, the score becomes 1. When the infant is in active motion with a flexed muscle tone that resists extension, the score for muscle tone is 2. Specificity is the percentage of true negatives of clinically asymptomatic neonates that do not display any results on NSG or Doppler. Considering $P < 0.05$, all the statistical analyses are taken as significant.

Results

The present study comprised two groups, 60 preterm and 60 high-risk terms, which were evaluated by diagnostic modalities such as grayscale NSG and Doppler. In preterm neonates, 34 (57%) are clinically symptomatic (hypotonia and seizures), and 26 preterm are asymptomatic (43%) [Table 1]. NSG findings are found in 32 preterm cases (53%). The most common abnormality found in the NSG study is GMH in 14 patients (43%), followed by 8 (25%) cases of periventricular echogenicity [Table 2]. Grade 1 GMH limited to caudothalamic groove is the most common grade in six patients (19%). The sensitivity and specificity of NSG are estimated to be 70% and 69%. The Doppler parameter used is the resistive index of the anterior cerebral artery (ACA). RI ≤ 0.62 in the Doppler study is the optimum cutoff point for diagnosing perinatal asphyxia with an accuracy of 95% (for the ACA).[16] Doppler findings were abnormal in 19 preterm neonates (32%). The sensitivity and specificity of Doppler in preterm are 50% and 82%, respectively. The sensitivity and specificity of combined NSG and Doppler studies in preterm are 88% and 65%, respectively. Comparison of the sensitivity of NSG versus Doppler versus combined NSG and Doppler in evaluating hypotonia and seizures in preterm ($P = 0.0442$) was significant [Table 3].

Among high-risk term neonates, 24 (40%) neonates require mechanical ventilation, 37 (61%) neonates have low APGAR scores (<7 at 1 min), and 33 (55%) neonates have associated perinatal risk factors. Our study's most common perinatal risk factor is PIH, associated with 14 cases (43%), followed by GDM in 12 patients (36%). Herein, 31 (52%) clinically symptomatic (hypotonia and seizures) term neonates were found, whereas 29 (48%) were clinically asymptomatic. NSG findings were seen in 30 cases (50%), periventricular cysts in 7 cases (23%), subcortical cysts in 7 cases (23%), and cerebral edema in 9 cases (30%). The sensitivity and specificity of NSG are 71% and 72%, respectively, in term neonates. Doppler findings are positive in 17 neonates (28%). The sensitivity and specificity of Doppler are calculated to be 48% and 83%, respectively, in term neonates. The combined sensitivity and specificity of NSG and Doppler are estimated to be 90% and 66%, respectively. Comparison of the sensitivity of NSG versus Doppler versus combined NSG and Doppler in evaluating hypotonia and seizures in high-risk term neonates ($P = 0.0399$) was significant [Table 3].

Discussion

GMH was the most common finding in preterms, followed by PVL, as reported.[17,18] Out of different grades of GMH, Grade 1 GMH was the most common. The NSG finding of preterm intracranial pathology was periventricular echogenicity, followed by intracranial hemorrhage.[19] The present study evaluated 34 preterms with hypotonia or seizures, whereas 26 neonates were asymptomatic. Out of the total of 32 preterm neonates, 14 cases (43%) had shown different grades of GMH: grade 1 GMH in six patients (19%), Grade 2 GMH in four patients (13%), and Grade -3 GMH in four patients (13%). Periventricular echogenicity was found in eight patients (24%).

High-risk full-term neonates had cysts in both periventricular and subcortical white matter regions, as reported.[20] Another

Table 1: Distribution of study group cases showing modality-wise positive findings

Diagnostic modality	Study groups			
	Preterm neonates ($n=n1+n2=60$)		High-risk term neonates ($n=n1+n2=60$)	
	Symptomatic ($n1=34$)	Asymptomatic ($n2=26$)	Symptomatic ($n1=31$)	Asymptomatic ($n2=29$)
NSG	24 (71)	8 (31)	22 (71)	8 (28)
Doppler	17 (50)	2 (8)	15 (48)	2 (7)
Combined	30 (88)	9 (35)	28 (90)	10 (34)

Numerical in parentheses are percent values. NSG: Neurosonography

Table 2: Prevalence of grayscale neurosonography findings in preterm and high-risk term neonates

Neonates	NSG findings	*n* (%)
Preterm	PVE	8 (25)
	PVC	3 (9)
	GMH (Grade 1)	6 (19)
	GMH + IVH (Grade 2)	4 (13)
	GMH + IVH + Hydrocephalus (Grade 3)	4 (13)
	Hydrocephalus	3 (9)
	Cerebral edema	4 (13)
High-risk term	PVE	3 (10)
	PVC	7 (23)
	SCC	7 (23)
	IVH	1 (4)
	Hydrocephalus	3 (10)
	Cerebral edema	9 (30)

PVE: Periventricular echogenicity, PVC: Periventricular cysts, GMH: Germinal matrix hemorrhage, IVH: Intraventricular hemorrhage, SCC: Subcortical cysts, NSG: Neurosonography

Table 3: Modality-wise sensitivity and specificity values for both study group cases

	Preterm	High-risk term
NSG		
Sensitivity	70	71
Specificity	69	72
Doppler		
Sensitivity	50	48
Specificity	92	93
Combined		
Sensitivity	88	90
Specificity	65	66
P-value	0.0442	0.0399

Numerical are percent values, Comparison between sensitivities of NSG and combined (NSG and Doppler) is done for calculating *P*-value. NSG: Neurosonography

study revealed that the common abnormality in high-risk term neonates was cysts and IVH.[19] Similar work by Kalyani showed cysts and IVH as significant findings in high-risk term neonates.[21] Our present study evaluated 60 high-risk term neonates associated with common risk factors such as PIH (43%). Hypotonia or seizures were presented by 31 neonates (52%), whereas 29 neonates (48%) were asymptomatic. NSG findings were seen in 30 (50%) term neonates, and the common abnormalities were subcortical cysts and periventricular cysts, each accounting for seven patients (23%). These findings are consistent with the previous literature, which proves that the cystic form of PVL is the most common form of leukomalacia found in term neonates.

A previous study had estimated the sensitivity of NSG as 75% and the Doppler study as 35%.[22] Similarly, a survey estimated the sensitivity and specificity of NSG to be 53% and 72%, respectively.[23] They also estimated the sensitivity and specificity of Doppler (ACA) as 57% and 91%, respectively. A study determined that a Doppler could show abnormality in subtle cases, in which grayscale ultrasound was routine, indicating the necessity of Doppler in clinically suspected patients, in which NSG was normal.[20] A study demonstrated that, out of all neonates with low resistive index, only 50% showed abnormal NSG.[24] In preterm sensitivity and specificity of combined NSG and Doppler are calculated to be 88% and 65%, respectively, compared to the sensitivity and specificity of the grayscale alone (70% and 69%) and Doppler alone (50% and 92%), and six preterms have hypotonia and seizures but normal NSG. The Doppler parameter (RI of ACA) was abnormal in these neonates. Herein, Doppler detected an abnormality in neonates with hypotonia and seizures even with a normal neurosonogram, consistent with the previous studies.[20,24]

The combined sensitivity of NSG and Doppler is 88%, significantly higher than NSG alone (70%). On the other hand, the specificity of Doppler alone is very high (92%) used to exclude disease. In high-risk term neonates, the sensitivity and specificity of combined NSG and Doppler are calculated to be 90% and 66%, respectively, compared to the sensitivity and specificity of grayscale alone (71% and 72%) and Doppler alone (48% and 93%). Six symptomatic term neonates with normal grayscale NSG findings have shown Doppler abnormalities. Thus, like in preterm neonates, Doppler also detected an abnormality in symptomatic high-risk term neonates with normal NSG. The combined sensitivity of NSG and Doppler is estimated to be 90%, significantly higher than NSG alone, and the combined specificity is around 66%. This increase in sensitivity comes at the cost of a decrease in specificity, as sensitivity and specificity are inversely proportional. Doppler remains the most specific (93%), as we have seen in preterm neonates.

Limitation

The limited study period could not include long-term follow-up for developing neurological outcomes. As the study population sample size is small, further research may be awaited.

Conclusion

Neonatal care rapidly evolved in our country from community to tertiary care units. NSG is the screening method of choice in neonatal intensive care units as it is cheap, portable, repeatable, and without any risk for radiation. The intracranial pathologies noted in this study in preterm and high-risk term neonates differ. Herein, preterm GMH is more common, followed by PVL. GMH Grade 1 is the most common grade of GMH, whereas noncystic periventricular flaring/periventricular echogenicity (PVL Grade 1) is the most common form of PVL. In high-risk term neonates, the most common pathology was a cystic form of PVL (periventricular subcortical cysts), followed by cerebral edema. For a screening modality to be effective, it must detect pathologies at high sensitivity, even if it comes at the cost of specificity. Thus, the Doppler modality can be combined with the grayscale NSG modality to increase detection rates in both preterm and high-risk term

neonates, as many clinically suspected cases present with normal grayscale ultrasound findings but abnormal Doppler parameters. The most common parameter is the ACA's resistive index of a callosal branch, with a normal range of 0.6–0.8. Any value <0.6 or more than 0.8 is considered abnormal. Thus, it is recommended that all clinically suspected cases are routinely evaluated with both the gray scale and Doppler, even if the gray scale is normal, because, in combination, it has a greater sensitivity of around 90%. Doppler has a high specificity, about 90%, much more significant than the gray scale (approximately 70%), which is used to exclude pathologies.

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Conflicts of interest

There are no conflicts of interest.

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