Feasibility of Transcranial Ultrasound as a Screening Tool for Hypoxic Ischemic Injury in Preterm Infants

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Abstract:

Background:Preterm neonates less than 37 weeks of gestational age are more liable to both hemorrhagic and ischemic injuries due to vascular, cellular and anatomical features of developing brain and physiological instability due to limited cerebral circulatory autoregulation, Cranial ultrasoundis a safe imaging modality with no need to radiationexposure or sedation.

Aim and objectives:To verify the role of transcranial ultrasound as a screening tool for hypoxic ischemic injury for preterm infant(below 37 weeks of gestation).

Subjects and methods:This cross sectional descriptive screening study was carried out at Radio-diagnosis department upon 165 preterm neonates admitted to the neonatal intensive care unit (NICU). It was conducted from April 2020 to Mars 2021 and designed to include all neonates born before 37 GW after obtaining institutional review board approval from our university and informed consent from the parents.

Results:Among all studied preterm 30.9% had abnormal cranial US findings, the commonest abnormalities found were hemorrhage (47%), followed by hypoxic ischemic injury (41.1%) then hydrocephalus among (25.4%).

Conclusion:We recommend screening for all preterm babies for hypoxic ischemic injuries. If routine screening is not feasible in all newborns born under 37 weeks of gestational age, a targeted screening for infants with at least one risk factor may be useful.

Keywords:transcranial ultrasound, preterm, hemorrhagic and ischemic injuries

Introduction:

Prematurity is a term for the broad category of neonates born at less than 37 weeks' gestation. Children who are born prematurely have high rates of intra-ventricular hemorrhage, respiratory illness, patent ductus arteriosus, sepsis and visual abnormalities like retinopathy of prematurity compared with children born at term. It is the single most important cause of death in the critical first month of life. Those who survived are at high risk of severe neurological impairment, about (2%) of all live births are premature with less than 32 weeks of gestational age and (1.5%) of them are of very low birth weight (VLBW) [1].

Fetal brain is at risk for both hemorrhagic and ischemic injuries during late second and third trimesters. Preterm infants, especially those younger than 32 weeks gestation are prone to both germinal matrix /intraventricular hemorrhage and ischemic white matter injuries [2].

Since the late 1970s, cranial Ultrasonography (USG) has become the most widely used neuroimaging procedure in premature infants as it provides information about perinatal brain injury

for the prediction of long-term outcomes. Cranial sonography is less expensive, free from radiation, does not require sedation, and its portability allows for bedside evaluation of gravely ill patients. US helps in assessing the neurological status of the child as clinical examination and symptoms are often nonspecific [3].

It is known that near-term infants can develop brain lesions typical of preterm (periventricular leukomalacia [PVL] and intraventricular hemorrhage [IVH]) and term neonates (stroke, asphyxial damage, and sinovenous thrombosis), but in the literature, there are few studies regarding the usefulness of cranial ultrasonography for infants born before 37 weeks of gestational age [5].

The aim of this study was to verify the role of transcranial ultrasound as a screening toolfor hypoxic ischemic injury for preterm infants.

Patients and methods

Study design: thiscross sectional descriptive screening study was carried out at Radio-diagnosis department;it was conducted from April 2020 to Mars 2021.

Administrative considerations:A written informed consent was obtained from all participants' parents and the research ethical committee of Faculty of Medicine (Institutional Research Board IRB) approved the study. The work was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patients:

Sample size: the study included 165 preterm neonates.

Inclusion criteria: All the preterm babies born before 37 weeks of gestation and admitted to NICU, both sexwere included.

Exclusion criteria: Parental refusal and poor image quality, Otherwise no exclusion criteria.

Among all studied preterm, 60% were males and 17.6% were of GA less than 30ws. While age of examination ranged from day 1 up to 30 days with mean of 6.04 days,9.1% were of low birth weight <1.5 kg and 16.4% were of gestational weight ranged from 1.5 kg to 2 kg.

Operational design:

Steps of performance

I.   **Full clinical history taking.**Patients were classified according to their GA at delivery in to three groups:

- Extreme preterm (<28 weeks) (n=5).
- Very preterm (28- <33 weeks) (n=36).
- Moderate to late preterm (33-37 weeks) (n=124).

II.   **Radiological examination** including Transcranial Ultrasound for all preterm infants using (SONOSITE M-Turbo-– KPI health care) ultrasound machine with transcranial transducer of 5-8 MHz . Each patient was examined for congenital brain malformation and acquired brain lesions.

Technique of examination

a.   **Transcranial grey scale Ultrasound**:The anterior fontanel was used as the principal acoustic window, and the scanning procedure included:

- Six standard coronal views:frontal lobes, frontal horns of the lateral ventricles, foramen of Monro and the third ventricle, body of the lateral ventricles, trigone of the lateral ventricle, and occipital lobes.

- Five standard sagittal planes: midsagittal plane, left and right parasagittal planes through the lateral ventricles, right and left parasagittal planes through the insula.
- Posterior fontanelle, the temporal and mastoid windows were additional helpful windows for far sites as posterior fossa, brainstem, basal cisterns and fourth ventricle.

b. **Transcranial Doppler Examination** :
- Transcranial color-coded Doppler to assess vascular lesions in all patients by scanning through the anterior fontanel to image, flow in the circle of Willis in both coronal and sagittal scans.
- The MCA was assessed in its echogenic fissure in the axial plane through temporal approach.
- Cerebral blood flow pattern and indices of MCA&ACA was automatically calculated(Resistance index; RI).

III.   Image Interpretation:two radiologists with 5 and 7 years' experience in transcranial ultrasonography performed the examinations.

IV.   Statistical Analysis: Data were analyzed using IBM SPSS 23.0 for windows (SPSS Inc., Chicago, IL, USA) and NCSS 11 for windows (NCSS LCC., Kaysville, UT, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Suitable statistical tests of significance were used after checked for normality. The results were considered statistically significant when the significant probability was less than 0.05 (P <0.05). P-value < 0.001 was considered highly statistically significant (HS), and P-value ≥ 0.05 was considered statistically insignificant (NS).

Results:

In our study,the commonest clinical finding found among studied preterm on examination was RD II (32.7%), then jaundice (22.4%) and followed by RD III and hypotonia among 18.8% and 4.8% of studied group respectively, with note that the only cause of admission of 23 neonates was being preterm baby.

According to the radiological findings patients were subdivided into either normal(69.1%, n:114)or abnormal (30.9%, n: 51).

Among 114 preterm patients with abnormal cranial US findings, the commonest abnormalities found were hemorrhage (47%), followed by hypoxic ischemic injury (41.1%) then hydrocephalus (25.4%)**(Table 1).**

Among all examined preterm neonates, there was 142 cases with normal arterial resistive index represent (86.1%), 19 cases with low resistive index represent (11.5%) and 4 cases with high resistive index represent (2.4 %) of studied group**(Table 2).**

On follow up examination we noticed 69.1% of the studied preterm was normal, while 4.8% of them died, 21.1% showed stationary course and 4.8% presented with progressive course.

A statistical significant difference was noted among preterm with abnormal cranial US finding and those with normal finding regarding gestational age, weight and age of examination**(Table 3).**

Alsoa statistical significant increased incidence of RD II, RD III, poor suckling, hypotonia and coma was found among preterm with abnormal cranial US finding (p: 0.001).

Table (1): Distribution of 165 preterm neonates according to cranial US abnormalities

	Preterm neonates N=165	
	N	**(%)**
Normal	114	(69.1%)
Abnormal	51	(30.9 %)
Hemorrhage	24	(47%)
Hypoxic ischemic injury	21	(41.1%)
Hydrocephalus	13	(25.4%)
Brain atrophy	6	(11.7%)
Brain edema	3	(5.8%)
Choroid plexus cyst	1	(1.9%)

Table (2): Anterior crlerberal artery resistive index among studied cases

`	Studied cases N=165	
	N	**(%)**
Normal	142	(86.1 %)
Low	19	(11.5 %)
High	4	(2.4 %)

Table (3): Association of cranial US finding and basic data among studied cases

|	Normal N=114	Abnormal N=51	Test	P value
Gestational age (weeks):				
Mean ± SD	34.5 ± 2.15	32.4 ± 3.1	**t-test**	**<0.001**
Range	26 – 36	27 - 36	**4.93**	**HS**
Gestational age: N (%)				
Extreme preterm (n=5)	2 (1.7%)	3 (5.8%)	X^2	**<0.001**
Very preterm (n=36)	15 (13.1%)	21 (41.1%)	**27.1**	**HS**
Moderate to late (n=124)	97 (85%)	27 (52.9%)		
Age at examination time (months):				
Mean ± SD	4.74 ± 4.3	9.32 ± 7.9	**MW**	**<0.001**
Median (Range)	3 (1 – 23)	7 (1 – 30)	**4.1**	**HS**
Gestational weight:				
<1.5 kg (n=15)	2 (1.8%)	13 (25.5%)		**<0.001**
1.5-2 kg (n=27)	10 (8.9%)	17 (33.3%)	**45.1**	**HS**
>2 kg (n=123)	102 (89.5%)	21 (41.2%)		
Sex:				
Male (n=99)	69 (57.9%)	33 (64.7%)	X^2	0.41
Female (n=66)	48 (42.1%)	18 (35.3%)	0.68	NS
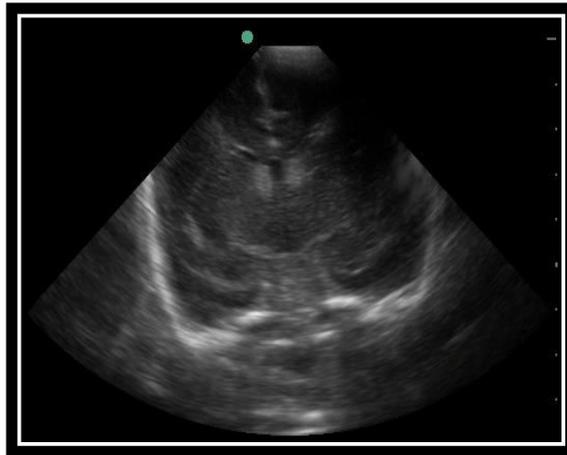
Figure 1: coronal plane of both lateral ventricles (Anterior fontanelle window) showing bilateral caudothalamic grove subependymal echogenic material not extended to the ventricular space (yellow arrow).
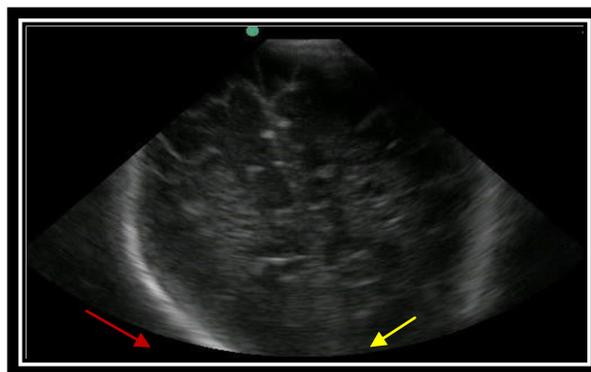

Figure 2: coronal plane (Anterior fontanelle window) showing bilateral periventricular echodense lesions (red arrow) represent infarction with multiple small echolucencies represent cystic changes (yellow arrow) and enlarged subarachnoidal space denoting reduced brain volume (blue arrow).
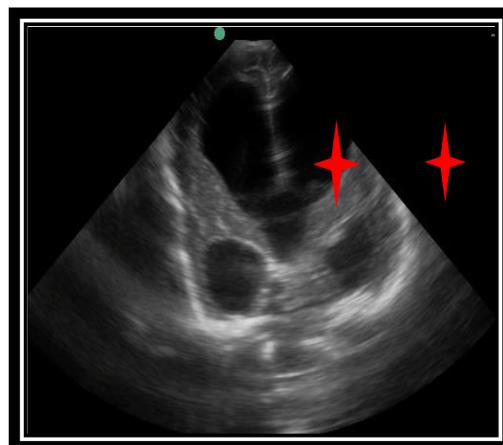

Figure 3: coronal plane (Anterior fontanelle window) showing marked dilation of cerebral ventricular system (AHW= 13mm) with clear CSF (red star) with parallel orientation of both lateral ventricles.

Discussion:

It is documented that under 37 weeks of gestational age, newborns have a higher probability of adverse outcome, poor cognitive development, and cerebral palsy compared with term infants. The American Academy of Neurology and the Practice Committee of Child Neurology recommends routine cranial ultrasonography screening on all newborns born before 30 weeks of gestational age [5].

In our study, 60%of cases (n:99) were males, and 40%(n:66) were females, the age of examination ranged from day 1 up to 30 days with mean of (6.04 days ± 5.96). This comes in agreement with a study carried by **Mohamed, 2020** [39] and the significant of this finding is still questionable.

In agreement with**Prithviraj et al.**[40]and **Nazparveen et al.**[41]who reported in their studies that 31% and28.75 % of studied cases had abnormal cranial ultrasound findings respectively, 30.9% of our patients had abnormal cranial ultrasound findings.

Regarding gestational age of preterm neonates there were3% of cases (n: 5) of extreme preterm neonate, 21.8%(n: 36) of very preterm neonate and 75.2% of cases (n: 124) of moderate to late preterm neonate.

In correlation with abnormal ultrasound findings, we found high significant association between gestational age and abnormal cranial US as follow, there were 60 % of extreme preterm (3/5 cases), 58.3 % of very preterm (21/36 cases) and 21.7%of moderate to late preterm (27/124) had abnormal cranial ultrasound findings.

Regarding the weight of studied cases,9.1 %of cases (n:15) were of low birth weight <1.5 kg including 13 cases (86.6 %) with abnormal cranial ultrasound, 16.4% cases (n:27) were of gestational weight ranged from 1.5 kg up to 2 kg including 17 cases (55.5 %) with abnormal cranial ultrasound and 74.5% (n:123) were of weight more than 2 Kg including 21 cases (16.2 %) with abnormal cranial ultrasound. A high significant association was found between neonatal weight and abnormal cranial US findings (p: <0.001).

Our results agree**Badrawi et al.** [42]who reported in his study upon 175 preterm neonates that the incidence of intraventricular hemorrhage increases with decreasing gestational age, where the incidence was 37.5% in PT < 30 weeks and 23% in PT between 30 - <34 weeks and 6% in PT 34 - <37 weeks. Moreover, another study by **Kinikaret al.** [43]upon 100 preterm neonates showed that 65.96% of neonates with gestational age <32 weeks had abnormal neurosonogram and 63.8% neonates with birth weight <1.5kg had abnormal CUS. and that approve significant association between gestational age and neonatal weight and abnormal cranial US.

The commonest cranial ultrasound abnormality noted in our study was hemorrhage (fig.1) in 24 cases (47%), followed by hypoxic ischemic injury (fig.2)in 21 cases (41.1%), then hydrocephalus (fig.3) among 13 cases (25.4%) . Previous studies by **Plaisieret al.**[44] and **Shankaran et al.** [45]also reported similar findings with 32.6% and 41.08% incidence of intraventricular hemorrhage respectively**.**

In our study we noted the most common clinical data of our cases was respiratory distress grade II with 54 cases (32.7%), and then jaundice with 37 cases (22.4%), followed by respiratory distress grade III with 31 cases (18.8 %) and other clinical data like poor suckling, hypotonia, disturbed conscious level, metabolic disorder and coma came after.

In our study we found significant association between abnormal cranial ultrasound and clinical data like hypotonia, respiratory distress (specially grade II and III), jaundice and coma, that's in correlation with another study by **Fumagalli et al.**[48]which showed significant association between abnormal cranial ultrasound findings and respiratory distress.

Among 51 cases with abnormal ultrasound, 23 cases (38.3%) had abnormal Doppler finding in the form of low RI of ACA in 19 cases (82.6%) and highRI of ACA in 4 cases (17.3%).

Among 19 cases with low ACA RI, 6 cases (31.5%) had haemorrhage and 2 cases (10.5%) with brain edema and among 4 cases with high ACA RI, 2 cases (50%) hadhemorrhage, 1 (25%) case showedbrain atrophy and 1 case showed brain edema.

In our study 117 cases were normal and 48 cases showing abnormal cranial US. Three cases (1.8%) were normal at first examination and abnormal finding appeared at follow up after 3 days and 2 cases (1.7%) are passed away. On follow up examination of abnormal cases, 35 cases (72.9%) showing stationary course regarding previously noted finding, 5 cases (10.4%) showing progressive course and 6 cases (12.5%) are passed away before follow up examination.

This study faced some limitations: absence of standard reference (MRI), relative small sample size in extreme and very preterm neonates and the short duration of follow up.

Conclusion:

In conclusion, cranial US is accurate, safe and rapid and could be considered an imaging modality of choice for detecting brain injuries in preterm neonate especially hypoxic ischemic injuries. This technique is both sensitive and specific for detecting periventricular leucomalacia.

Recommendations:

We recommend screening of all preterm babies for hypoxic ischemic injuries. If routine screening is not feasible in all newborns born under 37 weeks of gestational age because of the need for dedicated personnel and high cost, atargeted screening of infants with at least one risk factor may be useful in early diagnosis thus reducing adverse outcomes.

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