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Transcranial Doppler in hypoxic-ischemic encephalopathy babies as a prognostic marker in the short-term outcome

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ABSTRACT

Background: Birth asphyxia is a lack of blood flow or gas exchange to or from the fetus in the period immediately before, during, or after the birth process. Birth asphyxia can result in profound systemic and neurologic sequelae due to decreased blood flow and/or oxygen to the developing fetus or infant. Birth asphyxia is one of the most common causes of neonatal mortality and morbidity globally. **Aims and Objectives:** The aims of this study were to assess the importance of cranial Doppler as investigation tool for the early prognostic marker of babies with hypoxic-ischemic encephalopathy (HIE) in short term. **Materials and Methods**: This prospective study was carried out in a tertiary care teaching hospital. The present study includes 50 newborns, out of which 30 newborns admitted with birth asphyxia were considered as a case, while 20 healthy term newborns were taken as control. Transcranial Doppler of middle cerebral artery (MCA) was done on day 1 of life. They were followed up at discharge for neuromotor outcome by Hammersmith Neonatal neurological examination (HNNE). The outcome was correlated with, Doppler findings of MCA. $P<0.05$ was taken significant. **Results:** Abnormality detected by transcranial Doppler within 24 h of life in neonates with birth asphyxia was significantly associated with poor neuromotor outcome when compared to healthy term neonates. HNNE score in HIE babies was lesser than healthy term neonates on discharge. **Conclusion**: Cranial Doppler within 24 h of birth in term HIE babies has very high sensitivity in predicting short-term outcome in babies with HIE, such as Low HNNE score.

Key words: Doppler; Hammersmith neonatal neurological examination; Hypoxic-ischemic encephalopathy

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INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is still associated with abnormal neurological outcome, even after the introduction of therapeutic hypothermia. About 20–40% of the newborn with HIE die in the neonatal period. EEG is used for the prediction of neurodevelopmental outcome in the HIE. Cerebral Hypoxia occurring in the newborn is a major cause of acute mortality.[1] Birth asphyxia is one of the leading causes of neonatal mortality and childhood morbidity worldwide. According to the national neonatal perinatal database of India, it accounts for 28.8% of deaths in neonates. Perinatal asphyxia may lead to HIE, which contributes to chronic sequelae such as global developmental delay, deafness, loss of vision, and even death. Trans-fontanelle sonography with spectral analysis of the cerebral blood flow allows calculation of the resistive index (RI), pulsatility index (PI), end-diastolic velocity (EDV), and peak systolic velocity (PSV) is a safe, bed-side, and cost-efficient method to measure cerebral hemodynamics. Transcranial Doppler and its parameters of middle cerebral artery (MCA) in Predicting Neuromotor Outcomes in Newborns with HIE are of great value.[2] During the post-asphyxiated period, there is cerebral vasodilatation resulting in a fall of vascular resistance. This hyperemic phase is responsible for secondary brain

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injury. Doppler indices calculated from MCA reflect hemodynamic changes in HIE and serves as an early predictor for the neuromotor outcome.[3,4] Studies have found decreased cerebral vessels RI to reasonably predict the risk of subsequent neurodevelopmental impairment.[5-8] Since birth asphyxia is one of the leading causes of neonatal mortality in our country and as trans-fontanelle colour Doppler is a non-invasive relatively inexpensive and easily repeatable bedside imaging modality, it was decided to take up the study of cranial Doppler finding in HIE in term infants and its clinical correlations.

Aims and objectives

The aims of this study were to assess the importance of cranial color Doppler as investigation tool for the early prognostic marker of babies with HIE in short term.

Need of the study

Structured neurological examination of a newborn like Hammersmith neonatal neurological examination (HNNE) has been developed in the past few decades for assessing neonatal neurological status and to prognosticate the outcome of babies suffering from neonatal encephalopathy.

The above-mentioned modalities have been studied separately in past for prognostication of HIE in babies. The combined use of cranial colour Doppler and structured neurological examination may have a better predictive value for the short-term outcome of HIE babies. Hence, this study was done to evaluate the value of combined use of these modalities in predicting the outcome of babies with HIE.

MATERIALS AND METHODS

Study design

This study was prospective case–control study.

Sample size

After taking clearance from the Institutional Ethic Committee (mc/2020/4149) and informed consent from parents, total of 50 term neonates out of which 30 neonates admitted with birth asphyxia were taken as case, while 20 term healthy neonates were taken in control group. An outline of study design is shown in Figure 1.

Inclusion criteria

The following criteria were included in the study:

- Gestational age (GA) of 37–42 weeks
- Postnatal age <6 h
- Any One of the following:
  - Fetal distress at delivery
  - Need for resuscitation at birth
  - Apgar score <6 at 5 min, metabolic acidosis PH <7.1 or base deficit >10)[6]
  - Symptoms of HIE within 48 h of life.

Exclusion criteria

The following criteria were excluded from the study:

- Congenital heart disease and other major congenital anomalies
- Inborn errors of metabolism; Chromosomal disorder
- Genetic syndromes.

Color Doppler ultrasound (USG) was performed at the bedside within the first 24 h after birth. Measurements were done with a 2–5 MHz convex or phased array transducer of the computed sonography system. The transducer was placed on the temporal fontanelle to detect hemodynamic parameters of the right middle cerebral arteries, including peak systolic flow velocity (cm s^{1}), end-diastolic flow velocity (cm s^{1}), PI, and RI.

RI = (PSV–EDV)/PSV = (peak systolic velocity – end-diastolic velocity)/peak systolic velocity

PI = (PSV–EDV)/TAV = (peak systolic velocity – end-diastolic velocity)/time-averaged velocity.

All the babies were examined on admission and detail history was documented in a preform pro forma. Special importance was given to GA, nature of delivery, duration of 2nd stage of labor, and evidence of intrauterine asphyxia. All the babies were clinically graded according to the severity of HIE asper "Sarnat and Sarnat" staging.

Statistical analysis

1. "Gaussian Test for normal distribution/Test for single mean" was used as the statistical tool as a test for significance of observed single mean of continuous data or numerical variables and were presented by mean±standard deviation
2. "Paired |t|-test" was used for comparing means of the same group under two separate scenarios
3. The qualitative or categorical variables were presented in the form of frequency and percentage. For all those data, statistical analysis was done using "Chi-square test"
4. The qualitative variables were presented in the form of frequency and percentage. For all those data, statistical analysis was done using "|Z| proportion Test"
5. "Analysis of variance" or "ANOVA" was used for comparing more than two continuous data at a time.

Statisticaly methods would be used to find the significance of homogeneity of study characteristics among the patients. Finally, the calculated values were compared with

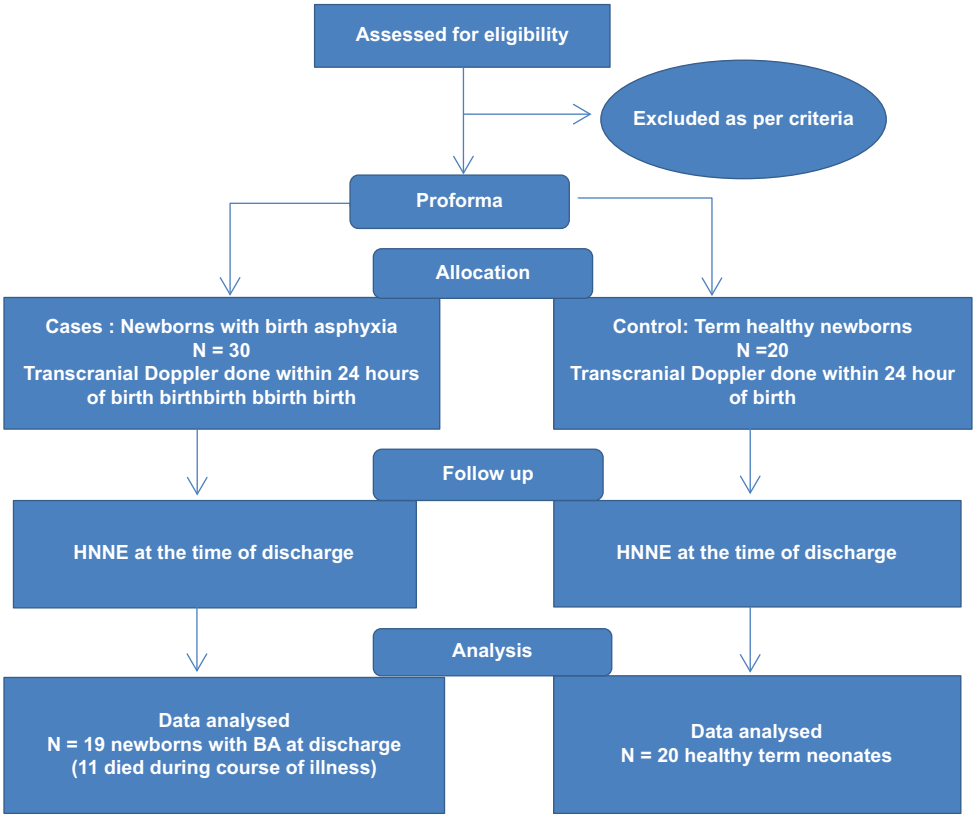

Figure 1: Flow chart showing outline and various stages under which study has gone through

the tabulated values at a particular degree of freedom and the level of significance was determined. P<0.05 was considered as statistically significant.

RESULTS

In the present study, 26 (86.7%) out of 30 cases were male and 4 (13.3%) out of 30 cases were female, as shown in Table 1.

Each domain of HNNE was compared individually between cases and the control group. Newborn with birth asphyxia has a lesser score when compared with a control group, as depicted in Table 2. Total of 39 neonates (case=19 and control=20) were assessed for neuromotor outcomes by HNNE. Each domain of HNNE was compared individually between cases and the control group. Newborns with birth asphyxia have been found to have lesser score when compared with the control group, as depicted in Table 2.

Tone items score in the case was 5.58±2.6 when compared to control 8.73±1.5, Tone pattern score for the case was 3.79±0.97 and 4.5±0.66 for control, reflex score for case is 3.97±1.65 and found to be 5.65±0.46 in control group, movements score for case was 1.26±0.8 and for control, it was 2.7±0.84, abnormal signs and patterns score in for case were 1.71±0.73 and for control group, it was 2.7±0.55, orientation behavior score for case group was 4.6±1.48, and for control it was 6.05±0.87 which are shown in Table 2.

A composite score was calculated after summing each domain and if the cumulative score was >30.5 which was considered an optimal HNNE and if score <30.5, its said

Table 1: General characteristics of cases and control

Characteristics	Case		Control	
	n=30	%	n=20	%
Sex				
Male	26	86.7	7	35
Female	4	13.3	13	65
Religion				
Hindu	28	93.3	20	100
Muslim	2	6.7	0	0
Family type				
Nuclear	3	0	1	5
Joint	27	90	19	95
Socioeconomic status				
Uppermiddle	12	40	5	25
Lowermiddle	13	43.3	10	50
Upperlower	3	10	5	25
Lower	2	6.7	0	0

Out of 50 patients included in study 33 (66%) were male and 17 (34%) were female. Out of 50 patients, 48 (96%) were Hindu and 2 (4%) was Muslim. Seventeen patients belong to upper middle status, 23 were from lower middle, eight from upper lower, and two from lower social economic status

Table 2: Neuromotor examination finding at time of discharge

HNNE PARAMETERS	Tone item	Tone pattern	Reflex	Abnormal pattern	Movement	Behavior
Case	5.58±2.61	3.78±0.17	3.91±1.65	1.71±0.73	1.26±0.80	4.61±1.48
Control	8.72±1.53	4.5±0.66	5.65±0.46	2.75±0.77	2.70±0.846	6.05±0.88
P-value	0.00	0.01	0.001	0.00	0.00	0.00

Tone items score in the case was 5.58±2.6 when compared to control 8.73±1.5, tone pattern score for the case was 3.79±0.97 and 4.5±0.66 for control, reflex score for case is 3.97±1.65 and found to be 5.65±0.46 in control group, movements score for case was 1.26±0.8 and for control, it was 2.7±0.84, abnormal signs and patterns score in for case was 1.71±0.73 and for control group, it was 2.7±0.55, orientation behavior score for case group was 4.6±1.48 and for control, it was 6.05±0.87. All are statistically significant with P<0.005

to be sub-optimal, as shown in Figure 2. In our study, we found that newborns with birth asphyxia (case) have more suboptimal HNNE than newborns in the control group, as shown in Figures 2 and 3.

Transcranial Doppler of right MCA showed abnormal RI 0.55±0.102 in the case group, while in the control group, we found RI to be 0.71±0.1 which is consider as normal and PI 0.92±0.24 in case group was abnormal, whereas PI 1.27±0.24 in control group was normal that both were statistically significant with neuromotor outcome of the neonates with P<0.05, as shown in Table 3. Whereas PSV 44.48±11.28 in case and 52.97±13.68 in control group and EDV was 16.66±5.03 in the case, whereas in the control group, it was 16.05±5.06 which was not significantly associated with the neuromotor outcome, as shown in Table 3. Normal Doppler indices in healthy term neonate was shown in Figure 4 while Figure 5 dipicting the abnormal Doppler finding in asphyxiated newborn.

DISCUSSION

HIE is one of the main causes of death by acute and chronic neonatal neurological damage.[8] In this study, we evaluated the role of transcranial Doppler of MCA during the first 24 h of birth in neonates with birth asphyxia and correlated to neuromotor outcome at the time of discharge.

In the present study, 26 (86.7%) out of 30 cases were male and 4 (13.3%) out of 30 cases were female, as shown in Table 1. A similar study was done by Guan et al., in 2017 in which 82 were male and 76 were female.[8]

Although, in past, many studies were done on USG and birth asphyxia main purpose of doing Doppler is to see the extent of damage in the cerebral circulation.

Transcranial Doppler finding showed significant association with neuromotor outcome. In our study, we found that neonates with abnormal Doppler scan within 24 h of birth has shown poor neuromotor examination findings assessed by HNNE at discharge which is statistically significant with a P<0.05, as shown in Table 3.

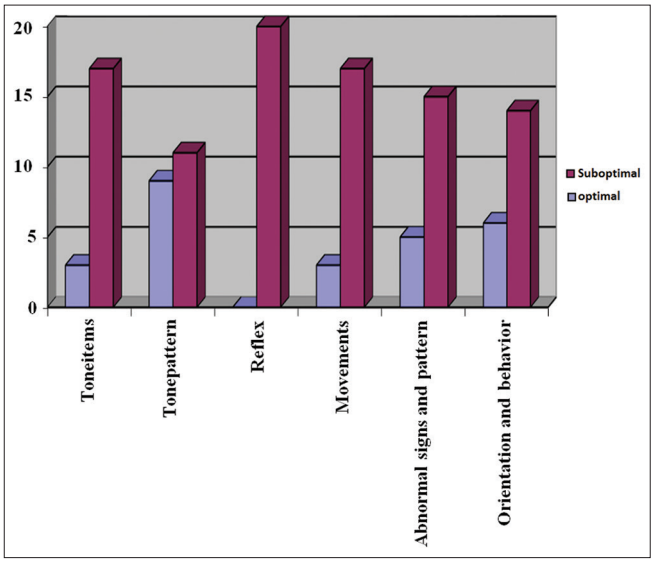

Figure 2: Various domains(optimal) of HNNE in control groups

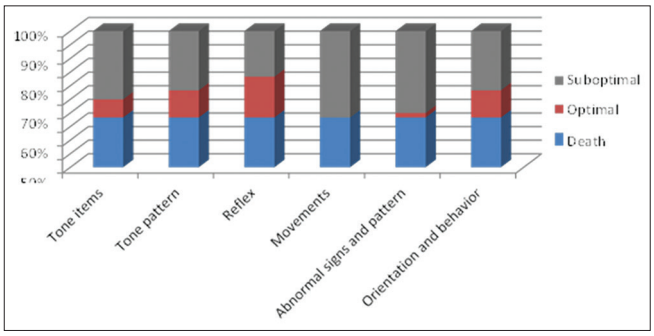

Figure 3: Various domains of HNNE in babies with HIE

Transcranial Doppler of the right MCA showed RI in case 0.55±0.102, while in control group, it was 0.71±0.1 and PI in case was 0.92±0.24 compared to 1.27±0.24 in control group, as shown in Table 3.

A study done by Himpens et al., observed that USG findings of brain injury increases the chances of cerebral palsy by seven-fold in their study.[9] A similar study was conducted by Blankenberge et al., found that one-third of full-term newborns with neuromotor and mental abnormalities during 2nd year of life had abnormal USG scans related to HIE at birth.[3] In another study done by

Table 3: Transcranial doppler finding within 24 h of birth showing abnormal PI and RI with *P*<0.05

Doppler Finding	PSV	EDV	PI	RI
Case	44.81±11.28	16.66±5.03	0.927±0.24	0.55±0.102
Control	52.96±13.68	16.05±5.06	1.27±0.24	0.71±0.100
P-value	0.21	0.68	0.00	0.00

PSV: Peak systolic velocity, EDV: End-diastolic velocity, RI: Resistive index, PI: Pulsatility index

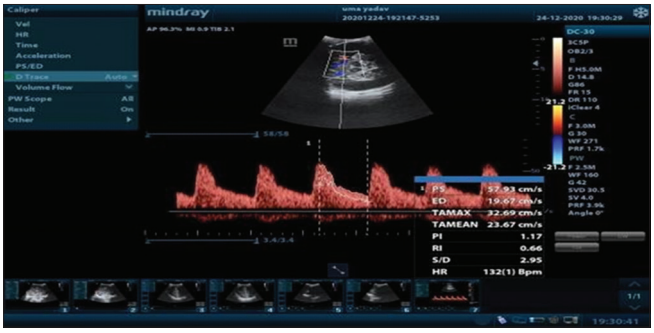

Figure 4: Cerebral blood flow spectrum in normal neonates. It shows PSV 57.8 cm, EDV 19.7, PI 1.17, RI 0.66

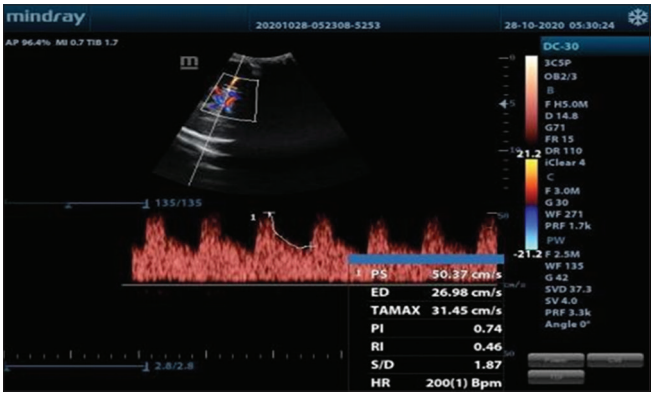

Figure 5: Cerebral blood flow spectrum in hypoxic neonates. Its shows PSV: −50.1 cm, EDV: −26.98 cm, PI: −0.74, and RI: −0.46

Narayan et al., they observed that abnormal cranial USG scans were associated in a larger number of cases with abnormal neuromotor outcomes.[10] They also observed the ability of anterior cerebral artery (ACA)-RI and MCA-RI to predict neuromotor outcome in neonates with perinatal asphyxia. Both ACA-RI and MCA-RI show high AUCs in differentiating children with poor neuromotor outcome from those with good outcome.

In addition, a cutoff of 0.63 for ACA-RI and 0.64 for MCA-RI appeared to be optimal in predicting neuromotor abnormality on follow-up.[10]

A study done by of Romeo et al., elaborated the predicted value of the examination to the outcome at 2 years, as it was done on preterm neonates at 3, 6, 9, and 12 months of corrected age.[11] Compared to previous investigators in this study, we performed HNNE examination on the term newborns with HIE at discharge and found that cranial Doppler within 24 h of birth can predict the neuromotor outcome at discharge.

With the prospect of new neuroprotective herapies on the horizon,[12,13] an indicator with a high positive predictive value would be a great help in choosing those patients likely to benefit from therapy while decreasing the risks to those patients likely to recover without sequelae. Hence, based on our study, we can early initiate neuroprotective therapy in cases of birth asphyxia.

Limitations of the study

Small number of subjects.

CONCLUSION

The result of the present study suggested that abnormality detected by transcranial Doppler, lower RI, and PI of MCA within 24 h of life in cases of birth asphyxia was significantly associated with poor neuromotor outcome. These findings may be important for devising the follow-up and rehabilitation plan for such neonates during the postnatal period and later.

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Authors Contribution:
JA- Concept and design of the study, prepared first draft of manuscript; **SJ-** Interpreted the results; reviewed the literature and manuscript preparation; **SP-** Concept, coordination, statistical analysis and interpretation, preparation of manuscript and revision of the manuscript; **SVS-** Interpretation and revision of manuscript.

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