RESEARCH PAPER

Prognostic Value of Resistive Index in Neonates with Hypoxic Ischemic Encephalopathy

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Objective: To evaluate the role of Resistive index measured by cranial doppler ultrasonography in predicting the risk of death/ abnormal neurodevelopmental outcomes in term neonates with hypoxic ischemic encephalopathy. ***Methods****:* We enrolled 50 term asphyxiated neonates with hypoxic ischemic encephalopathy and measured resistive index within 72 hours from the anterior cerebral artery. Participants underwent tone and developmental assessment at 6-12 months. ***Results:*** Among the 50 neonates, 25 (50%) had abnormal resistive index (<0.56 or >0.80). Presence of abnormal resistive index increased the risk of death/ abnormal neurological outcomes at 6-12 months [RR (95% CI): 7.5 (2.0,8.6), *P<0.01*]. ***Conclusion:*** An abnormal resistive index is associated with death/ neurodevelopmental impairment in neonatal hypoxic ischemic encephalopathy.

Keywords: *Cranial ultrasound, Mortality, Neurodevelopment, Outcome.*

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Among neonates with hypoxic ischemic encephalopathy (HIE), 15-20% die and nearly 25% develop permanent neurological deficits [1]. Apgar scores and cord blood acidosis have been used to predict long-term outcomes of neonates with HIE with limited usefulness [2-4]. More sensitive techniques like neuroimaging are limited by cost and expertise [5]. It is therefore, essential to have evidence-based prognostic tools to inform families regarding possible long-term sequelae.

Resistive index (RI), calculated from the cerebral arteries by cranial doppler ultrasonography, reflects cerebral hemodynamic changes in asphyxia, and has been evaluated as a bedside marker of risk of subsequent neurodevelopmental impairment in HIE [6]. Studies from high income countries have found decreased cerebral RI to differentiate asphyxiated neonates from healthy controls and to reasonably predict the risk of subsequent neurodevelopmental impairment [7-10]. There is paucity of data on the prognostic role of RI in low- and middle-income countries. This study was designed to evaluate the role of abnormal RI measured from anterior cerebral artery in predicting adverse neurodevelopmental outcomes among term neonates with HIE.

METHODS

This prospective cohort study was conducted between February 2013 and May 2015 at a tertiary-care hospital in India catering to outborn neonates. We enrolled neonates born at ≥37 weeks gestational age with (*a*) birth asphyxia, defined as: Having not cried or breathed at birth or Apgar score of ≤5 at 5 minutes of life or need for positive pressure ventilation for ≥1 minute [11]; and (*b*) evidence of moderate to severe HIE based on Sarnat and Sarnat's classification [12]. Neonates with major congenital anomalies and admitted beyond 72 hours of postnatal age were excluded. Enrolled neonates received standard respiratory, hemodynamic and supportive management. No neonate received therapeutic hypothermia as a treatment modality.

The primary outcome of the study was the risk of mortality and/or abnormal neurodevelopmental outcomes assessed between 6-12 months age. Death was defined as all-cause mortality occurring before 12 months of age or last follow up. Abnormal neurodevelopment was considered as either abnormal tone (assessed using Amiel-Tison's method), or 'suspect' report on Denver Developmental Screening Test II (DDST II) performed by a trained developmental pediatrician blinded to the initial values of RI. Secondary outcomes were to evaluate the association of abnormal RI with short term morbidities such as death before discharge, neonatal seizures, shock, respiratory failure and abnormal electroencephalogram (EEG).

RI was measured for all enrolled neonates within 72 hours of life using pulse wave Doppler ultrasound (General Electric, Connecticut, United States) with 3.5 MHz transducer, by the principal investigator, who was trained under a pediatric radiologist for 3 months. Signals were recorded from the anterior cerebral artery (ACA) in the sagittal plane, keeping the angle of insonation as close to 15^0 as possible. Images were cross-checked by the expert pediatric radiologist. Resistive index was calculated as RI=(S-D)/S, where S-Peak systolic velocity, D-End diastolic velocity.

A RI between 0.56 and 0.80 was considered normal [8,13] and neonates were classified as having either normal or abnormal RI.

Based on the assumption that 20% and 70% neonates were likely to die or develop abnormal neurodevelopmental outcomes in the normal and abnormal RI groups, respectively [9], with 80% power and 5% alpha error, 19 neonates were needed in each group. Assuming 20% attrition during follow-up, it was decided to enrol 25 neonates in each group. The primary outcome was evaluated using chi-square test. Continuous variables were compared using either Student's t test or Mann Whitney U test. Institutional ethics committee approved the study. Data was analyzed using SPSS version 15.0 and *P* value <0.05 was considered statistically significant.

RESULTS

Among 82 term neonates admitted with HIE during the study period, 50 were included (***Fig.* 1**). Neonates with normal RI (*n*=25) were comparable to those with abnormal RI (*n*=25) (***Table* I**). Presence of an abnormal RI was associated with a significantly higher risk of death/ abnormal neurodevelopmental outcome at 6-12 months (75% (15/20) *vs*. 10% (2/20); RR (95% CI) = 7.5 (2.0, 8.6), *P*<0.01). An abnormal RI was also associated with 2.5 times higher risk of death or abnormal neurological examination before discharge (60% *vs*. 24%; RR (95% CI) = 2.5 (1.2,5.4), *P*=0.01), neonatal seizures as well as abnormal neurosonogram and EEG (***Table* II**).

The sensitivity, specificity, positive predictive value, negative predictive value and positive likelihood ratio of abnormal RI to detect the composite outcome of death or abnormal neurological outcome was 88%, 78%, 75%, 90% and 4.06, respectively.

DISCUSSION

In the present study, we observed that having an abnormal RI within 72 hours increased the risk of death or abnormal neurodevelopment at 6-12 months among term neonates with HIE. Short term morbidities such as abnormal neurological examination at discharge, seizures, abnormal neurosonogram and EEG were also

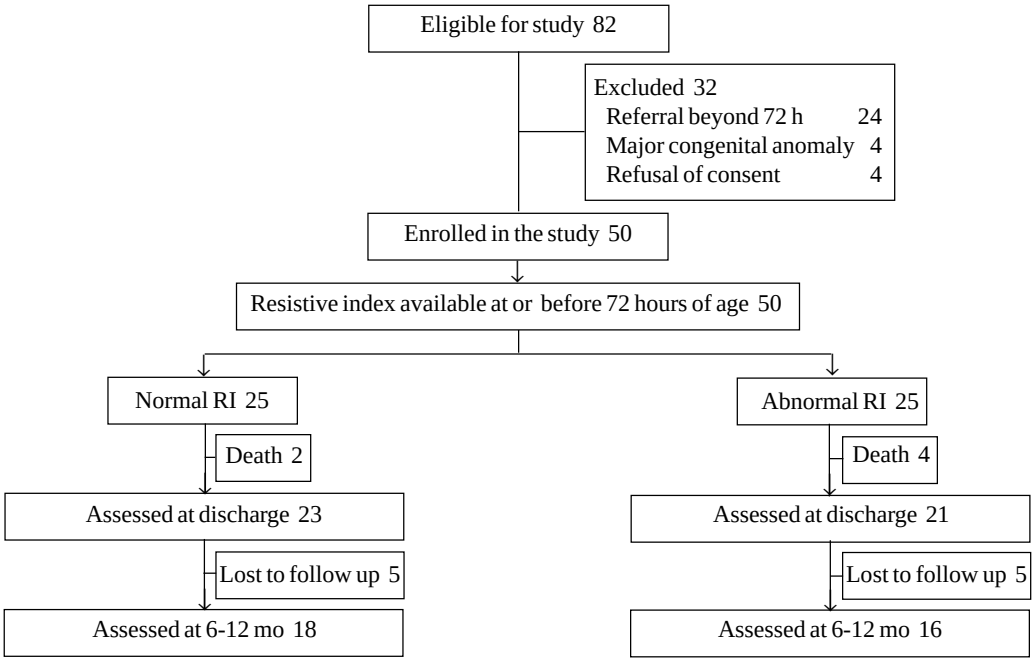

FIG. 1 *Study flow.*

TABLE I BASELINE CHARACTERISTICS OF ENROLLED POPULATION

Baseline variable	*Neonates with normal RI (n=25)*	*Neonates with abnormal RI (n=25)*
Gestational age, (weeks), Mean (SD)	38.8 (0.9)	38.8 (0.9)
Birth-weight, (g), Mean (SD)	3288 (337)	3258 (352)
Male gender, No. (%)	17 (68)	18 (72)
Delivered by normal vaginal delivery, No. (%)	18 (72)	16 (64)
Small for gestational age*, No. (%)	3 (12)	4 (16)
Postnatal age at first evaluation, (h)#; median (IQR)	47 (22-68)	53 (18-67)
Need for resuscitation, No. (%)		
Initial steps	12 (48)	3 (12)
Bag and mask ventilation	9 (36)	9 (36)
Bag and tube ventilation	2 (8)	10 (40)
Chest compressions/ Adrenaline	2 (8)	3 (12)
Stage of HIE (Sarnat and Sarnat system), No. (%)		
Moderate	18 (72)	16 (64)
Severe	7 (28)	9 (36)

**growth <10th centile for gestational age as per Fenton's charts [15].*

TABLE II ASSOCIATION OF RESISTIVE INDEX WITH MORBIDITY

Outcome variable	*Normal RI (n=25)*	*Abnormal RI (n=25)*	*Relative risk (95% CI)*	*P value*
*Death/ abnormal neurological outcome at 6-12 mo, (*n*=20)	2 (10)	15 (75)	7.5 (2.0-8.6)	<0.01
#Abnormal neurological examination at discharge	4 (16)	13 (52)	3.3 (1.2-8.6)	<0.01
Death during hospital stay	2 (8)	4 (16)	2.0 (0.4-9.9)	0.38
Death /abnormal neurological examination at discharge	6 (24)	15 (60)	2.5 (1.2-5.4)	0.01
Neonatal seizures	17 (68)	25 (100)	1.5 (1.1-1.9)	<0.01
Number of Anticonvulsants required to control seizures				
1	15	12		0.13
>1	5	12		
Anticonvulsants for neonatal seizures at discharge	1(4)	13 (52)	13.0 (1.8-92.0)	<0.01
Respiratory failure requiring mechanical ventilation	10 (40)	17 (68)	1.7 (1.0-3.0)	0.05
Median (IQR) Duration of ventilation, d	3 (3-6)	6 (5-8)	–	0.27
Need for inotropes	12 (48)	16 (64)	1.3 (0.8-2.2)	0.25
Inotrope score median (IQR)	10 (0-30)	10 (0-40)	–	1.00
Culture positive bacterial sepsis	5 (20)	12 (48)	2.4 (1.0-5.8)	0.04
$Abnormal neurosonogram	4 (16)	16 (64)	4.0 (1.6-10.3)	<0.01
‡Abnormal EEG	2 (8)	12 (48)	6.0 (1.5-24.1)	<0.01

**5 neonates lost to follow up in each group; #Abnormal neurological examination before discharge as assessed by Amiel Tison's method; $Abnormal neurosonogram was defined as basal ganglia hyperechogenecity, increased periventricular echogenecity and prominent thalamostriate vessels, ‡Abnormal electroencephalogram (EEG) was defined as discontinuous background, burst suppression pattern or seizures.*

higher among neonates with abnormal RI, although the study was not powered to determine these outcomes.

Loss of cerebral autoregulation in HIE can predispose to reduced/absent diastolic blood flow in cerebral arteries leading to increased RI (>0.80) or elevated diastolic flow due to arterial vasodilation resulting in reduced RI [10,14]. Decreased RI has been well documented in asphyxia and found to increase the risk of death or cerebral palsy by 23.4 times [7,8]. The negative predictive value (NPV) of RI was 90%, implying that finding a normal RI (0.56-0.80) within the first 72 hours in a neonate with HIE conferred 90% probability that the neonate will be subsequently normal.

WHAT THIS STUDY ADDS?

- Presence of an abnormally low (<0.56) or high (>0.80) RI within 72 hours significantly increases the risk of developing death or abnormal neurodevelopment at 6-12 months among term neonates with hypoxic ischemic encephalopathy

This was higher than the NPV of decreased RI in the study by Jongeling, *et al*. [8].

RI within 24 hours of age, could not be obtained. We acknowledge that formal developmental assessment such as Bayley Scales of Infant Development II (BSID-II) was desirable for identifying abnormal neurodevelopment.

Considering the modest prognostic potential of RI in neonates with HIE, it is desirable that neonatologists get familiar with the optimal usage of this imaging modality, especially in settings lacking sophisticated neuroimaging techniques. We need more studies evaluating the impact of neuroprotective strategies, especially therapeutic hypothermia on RI and its diagnostic accuracy.

Contributors: SK: designed the study protocol, recruited the participants, performed doppler ultrasonography, and drafted the initial manuscript; AC: supervised data collection, analyzed the data and revised the manuscript; RA: helped in designing the study, data collection, and critically reviewed the final manuscript; KG: study supervision and manuscript review. All authors approved the final manuscript
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