Original Article

DOI: 10.7860/IJNMR/2018/34326.2224

Paediatrics Section

Prediction of Neurological Outcome in High Risk Neonates: Prospective Study

PIKALA TARAKESWARA RAO, MANEM SAISUNIL KISHORE, GUNDAPANENI MANASA, CHOKKAKULA SANYASI NAIDU

ABSTRACT

Introduction: High risk babies are vulnerable to neurological brain injury. Early identification of injury will help in initiating strategies to reduce the neurological damage and hence prevent long term sequeale. It's also help in counselling the parents regarding the prognosis. Neurosonography and Doppler are point of care tests commonly used to identify neurological damage.

Aim: To identify spectrum of neurological abnormalities in high risk neonates. Second objective is to know the predictive ablility of initial findings of neurosonogram and Doppler findings on neurological outcome.

Materials and Methods: This is a prospective study conducted in neonatal care unit of tertiary hospital. Total of 138 neonates admitted to hospital are enrolled in the study. All neonates underwent transcranial USG using standard probe and Resistive Index (RI) measured in right anterior and right Middle Cerebral Artery (MCA) with color Doppler equipment within 72 hours of life. Babies upon discharge followed up in neonatal clinic and neurological assessment done at six months of age. Analysis was done using statistical software packages SPSS and Microsoft Excel.

Results: Diffuse cerebral ooedema was detected by neurosonogram in 20 (19.2%) of high risk neonates. RI index less than 0.6 was observed in 32 (30.8%) Anterior Cerebral Artery (ACA) and 47 (45.3%) MCA. Statistically significant neonates with initial abnormal USG findings had abnormal outcome at six months of age compared to neonates with normal USG findings (p=0.014). Low RI in the middle and ACA was associated with abnormal outcome at six months in significant number of neonates (p<0.001). RI of right MCA is more specific in predicting neurological outcome at six months of age. The positive likelihood ratio is more for low RI of MCA (18) as compared to neurosonogram.

Conclusion: Abnormal neurological outcome was significantly more in neonates with abnormal findings on USG and Doppler. Doppler RI abnormalities done within 72 hours had more specificity and better likelihood ratio for predicting abnormal neurological outcome than neurosonogram.

Keywords: Cerebral ooedema, Neurological injury, Neurosonogram

INTRODUCTION

Advances in the neonatal care resulted in increased survival of high risk neonates. High risk neonates particularly asphyxiated and preterm frequently require respiratory and circulatory support and are subjected to various painful interventional procedures which result in interruption of cerebral flow and oxygenation. Hypoxic ischaemic damage due to lack of cerebral blood flow and oxygenation of developing brain is common in high risk neonates. Neonates who survive neurological insult frequently have neurological deficits later on in life. There is a pressing need to identify neurological injury at earliest to initiate interventional and rehabilitative strategies to reduce long term morbidity. Review of literature suggests MRI is the imaging of choice in indentifying neurological injury in neonates [1]. Ultrasound and Doppler are widely used cranial imaging modality in the neonatal ICU as they are portable and the images can be acquired at bedside, and the cumbersome transport of the neonates to the Computerised Tomography (CT) or the Magnetic Resonance Imaging (MRI) suite is avoided. Prognostic abilities of neurosonography and Doppler sonography in high risk neonates is under researched [2,3] With the advances in imaging techniques like neurosonogram and Doppler, there is a chance that neurological abnormalities can be picked up early and "early intervention" can be initiated in high risk neonates.

The Indian literature is sparse regarding cranial ultrasonography and transcranial Doppler in high risk neonates. Hence, this study was conducted to look at the spectrum of abnormalities in high risk neonates and to assess whether NSG and Doppler changes can predict the neurological outcome.

MATERIALS AND METHODS

This prospective study was conducted in Neonatal unit of Maharajah Institute of Medical Sciences, Nellimarla Andhra Pradesh, India from Oct 2014 to October 2016. Total 138 high risk neonates admitted to neonatal unit were enrolled in the study after obtaining informed consent from the parents.

Neonates with history of asphyxia, seizures, severe hyperbilirubenaemia requiring phototherapy, sepsis, and premature neonates ≥34 weeks gestation were included in the study. Neonates with congenital malformations, cardiac diseases and preterm ≤34 weeks and neonates admitted after 72 hours of life were excluded from the study. Relevant data recorded in the standard proforma. Detailed clinical examination of all the enrolled neonates was done. Investigations and treatment of all the neonates was done as per NICU unit protocols. All the babies were followed from time of enrollement upto six months of age.

All the patients included in this study underwent transcranial USG using standard probe coupled with color Doppler equipment within 72 hours of life. Philips Envisor CHD and Philips HD7 and Sonosite ultrasound machines coupled with color Doppler equipment used for study. The scans were performed in the coronal (anterior, middle and posterior), sagittal (median and paramedian) and axial plane. RI was measured for all enrolled neonates within 72 hours of life using pulse wave Doppler ultrasound. Signals were recorded from the ACA and MCA in the sagittal plane, RI was calculated as RI=(S-D)/S, where: S-Peak systolic velocity, D-End diastolic velocity. Neonates with RI between 0.6 to 0.8 is considered normal and those having values less than 0.6 considered low [4].

Babies were followed up in high risk neonatal clinic for six months of corrected age. Neonates were subjected to detailed neurological examination by Amiel-Tison's method. Abnormal neurodevelopment was considered as abnormal tone assessed using Amiel-Tison's method.

STATISTICAL ANALYSIS

Descriptive statistics was used to describe baseline variables. Categorical outcome variables were analysed by Chi square test with continuity correction or Fisher's exact test wherever one or more expected cell size was less than 5. Numerical variables were first tested for normality. Variables whose skewness statistic was more than 1.96 times the standard error of skewness was considered to have skewed distributions whereas, the rest were considered to have normal distributions. Normally, distributed variables were compared by Student's-'t'-test after evaluating equality of variance by Levene's test. Variables with skewed distribution were compared by Mann-Whitney U test. The p-value of less than 0.05 was taken as significant. Analysis was done using statistical software packages SPSS 15.0 for windows and Microsoft Excel.

RESULTS

Out of 138 neonates enrolled in the study 25 neonates who failed to fulfill the inclusion criteria were excluded. Four neonates expired during treatment and five were lost to follow-up. Total 104 (n) neonates included in the final analysis.

Baseline characteristics of the study group: Out of 104 neonates 74 (71.2%) are preterm ≥34 weeks of gestation and 30 (28.8%) are term neonates. Total 22 (21%) had asphyxia with APGAR score less than ≤7 at 5 min, 13 (12.5%) had hyperbilirubinaemia with bilirubin levels ≥15 mg/dL at 72 hours, 4 (3.8%) had ≥2 clinical seizures and 3 (2.9%) had clinical sepsis [Table/Fig-1].

Characteristics	Number/percentage
Preterm (%)	74 (71.2%)
Term (%)	30 (28.8%)
Asphyxia (%)	22 (21%)
Hyperbilirubinaemia(%)	13 (12.5%)
Seizures (%)	4 (3.8%)
Sepsis (%)	3 (2.9%)

[Table/Fig-1]: Baseline characteristics of study subjects.

Initial neurosonogram done in the present study showed normal findings in 68 (65.4%) and abnormal in 36 (34.6%) neonates. The commonest abnormality detected in the neonates was diffuse cerebral ooedema in 20 (19.2%) followed by Grade1 IVH in 6 (5.8%), Grade 2 IVH in 4 (3.8%), Grade 3 IVH in 1 (1%), PVL in 4 (3.8%) and hyper intensity of the basal ganglia in 2 (1.9%) neonates [Table/Fig-2].

Doppler done on neonates measured Peak Systolic Velocity (PSV), End Diastolic Velocity (EDV) and RI is calculated from peak systolic and peak diastolic pressure in the cerebral arteries in the right anterior and middle cerebral arteries mean, median and standard deviation of RI measurements [Table/Fig-3].

Neurosonogram	Number
Diffuse Cerebral Oedema	20 (19.2%)
Grade I IVH	6 (5.8%)
Grade 2 IVH	4 (3.8%)
Grade 3 IVH	1 (1%)
PVL	4 (3.8%)
Basal Ganglia Hyperdensity	2 (1.9%)
Normal	68 (65.4%)

[Table/Fig-2]: Spectrum findings on neurosonogram.

Artery	Mean	Median
Right Anterior Cerebral Artery	0.62±0.08	0.6 (0.6, 0.7)
Right Middle Cerebral Artery	0.59±0.097	0.6 (0.6, 0.6)

[Table/Fig-3]: Resistive index in anterior cerebral artery and middle cerebral artery by Doppler sonography.

The mean RI of right ACA and right MCA was 0.62±0.08 and 0.59±0.097 respectively. In all 32 (30.8%) had low RI values in ACA and 47 (45.3%) in MCA. An RI value of less than 0.6 taken as low value with normal reference value being 0.6 to 0.8.

At six months follow-up 36 neonates who had abnormalities on neurosonogram 15 (41.6%) neonates had abnormal outcome and only 19% neonates with normal initial sonogram had abnormal neurological outcome. The difference was statically significant (0.014).

Neurological outcome assessed at six months based on RI of right ACA and RI of right MCA. Out of 18 neonates with low RI of right ACA 16 (88%) had abnormal outcome. Total of 24 neonates with intial low RI Right MCA, 12 (50%) had abnormal outcome [Table/Fig-4].

On comparison of neurosonogram and Doppler abnormalities for predicting the neurological outcome at six months [Table/Fig-5]. The specificity is more for RI of MCA (91%) as compared to neurosonogram (72%). The positive likelihood ratio is more for RI of MCA (18) as compared to neurosonogram (2).

RI of Right Anterior Cerebral Artery	Neurological Outcome at 6 months		p-value
	Normal	Abnormal tone	
Low	2	16	<0.001
Normal	74	12	
RI of Right Middle Cerebral Artery	**Neurological Outcome at 6 months**		**p-value**
	Normal	**Abnormal tone**	
Low	12	12	<0.001
Normal	74	16	

[Table/Fig-4]: Neurological outcome by Amiel-Tison's method at 6 months based on resistive index (RI).

	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Initial NSG	53	72	41	80	2	0.6
Doppler RI of ACA	57	91	88	86	18	0.4
Doppler RI of MCA	42	86	50	82	3.1	0.7

[Table/Fig-5]: Performance of neurosonogram and Doppler for assessment of neurological examination at 6 months.

DISCUSSION

Perinatal asphyxia and preterm birth are the most common causes of neonatal mortality and morbidity. There is often a delay in development of clinical signs in neonates following neurological insult [5] Brain damage resulting from hypoxic ischaemic insults take time to evolve. Moreover, clinical signs of hypoxic cerebral injuries in preterm neonates are nonspecific [6]. Hence, there has been quest to identify the brain lesions that can predict the long term neurological outcome. With the advances in imaging techniques like neurosonogram and Doppler, there is a chance that these abnormalities can be picked up early and "early intervention" can be initiated in high risk neonates. Majority of neonates (66%) showed normal findings and abnormality detected in 34%. Most common abnormality noted in this study is diffuse cerebral oedema (20%). In contrast a study by Perlman SA et al., screening ultrasound identified abnormalities in 57% of neonates [6]. Higher percentage of abnormality on ultrasound may be due the fact that there study was conducted in preterm, VLBW neonates. The commonest abnormality noted was intraventricular haemorrhage [7]. Brain abnormalies picked up by Cranial Ultrasonogram (CUS) depend on gestational age, hypoxic insult and timing of CUS. Multiple studies suggested that >90% of all IVH cases occur in VLBWPT infants were detected during initial 72 hours [1]. Review of literature suggests that although CUS in infants with BW of <1500 grams or GA of <33 weeks shows some abnormalities in 12% to 51% of infants in the first two weeks of life. Abnormalities such as Grade 3 and Grade 4 IVH or bilateral cystic PVL occur in >20% of infants [7]. In our study the incidence of IVH was 11% and PVL was observed in 5.6% of neonates. Neonates <34 weeks were excluded in this study may be reason for low incidence of IVH and PVL. Neonates who had abnormalities in USG within the first five days of life have significantly high motor and mental abnormities. Study by Kudreviciene A et al., showed that USG can be used for prognosticating motor and severe mental impairment [8]. In a study by Boo N et al., severe neuromotor impairment at the age of one year observed in 56.8% of the subjects in whom diffuse cerebral oedema was detected on initial USG [9]. In the present study among 34% of neonates who showed abnormal initial sonogram 41% had abnormal neurological outcome at six months of age resistance in cerebral vascular bed varies with changes in cerebral perfusion pressure to maintain constant blood flow. Cerebral autoregulation is impaired with abnormal fluctuations of blood pressure resulting ischaemic damage [10]. Doppler sonography is used to evaluate RI in the intracranial arteries in asphyxiated high risk neonates. RI is found to be low on day 1 in asphyxiated neonates and degree of lowering correlate with clinical severity [10]. RI is also used for predicting clinical outcome in infants with HIE. Low RI (<0.56) on the first day after birth was associated with poor outcomes by 23.4-fold. The specificity and sensitivity of low RI in predicting long-term outcomes was 95% and 53% respectively. Positive predictive value and negative predictive value of RI in predicting outcome is 90% and 72% [11]. Liu J et al., in their study on 40 term neonates with HIE found RI < 0.50 or RI >0.90 in severely asphyxiated neonates within 24 hours after birth and RI >1.0 associated with later brain death [12]. RI can be measured in any intracranial artery and low values 0.5-0.6 are associated with poor outcome [13]. In the present study low RI values (<0.6) found in 18(17.3%) and 24 (23.1%) in right ACA and middle cerebral arteries respectively. In this present study neonate with

low RI of ACA, the incidence of abnormal outcome at six months was 83%. Similarly, among neonates with low RI of MCA 50% had abnormal outcome at six months. Neonates having low RI in the anterior cerebral had greater predicting ability of poor neurological outcome in high risk neonates. Low RI in the ACA obtained within 24 hours combined with history of asphyxia is associated with an adverse outcome and may be considered as earliest markers for poor neurodevelopmental outcome [14]. On comparison of sensitivity and specificity and likelihood ratios of neurosonogram and Doppler abnormalities for predicting the neurological outcome at six months Doppler is more specific as compared to neurosonogram (75%). The positive likelihood ratio is more for Doppler (6.6) as compared to neurosonogram (2.3) in predicting the neurological outcome at six months.

LIMITATION

Major limitation of this study is that follow-up period is short and the neonates need to be followed up for atleast 18 months for neurodevelopmental assessment.

CONCLUSION

In neonates with neurosonogram abnormalities and cerebral Doppler RI abnormalities, the incidence of abnormal neurological outcome was significantly more as compared to those with normal findings. Secondly, neurosonogram abnormalities and cerebral Doppler RI abnormalities had more specificity for predicting abnormal neurological outcome than sensitivity. Moreover, RI of Doppler done within three days of life has more specificity and better likelihood ratio than neurosonogram and it is a better predictor of neurological outcome at 6 months of follow-up.

REFERENCES

[1] Kudrevièienë A, Basevièius A, Lukoðevièius S, Laurynaitienë J, Marmienë V, Nedzelskienë I, et al. The value of ultrasonography and Doppler sonography in prognosticating long-term outcomes among full-term newborns with perinatal asphyxia. Medicina (Kaunas). 2014;50:100-10.

[2] Cowan F. Outcome after intrapartum asphyxia in term infants. Semin Neonatol. 2000;5:127-40.

[3] Leijser LM, de Vries LS, Cowan FM. Using cerebral ultrasound effectively in the newborn infant. Early Hum Dev. 2006;82:827-35.

[4] Zamora C, Tekes A, Alqahtani E, Kalayci OT, Northington F, Huisman TA. Variability of resistive indices in the anterior cerebral artery during fontanel compression in preterm and term neonates measured by transcranial duplex sonography. J Perinatol. 2014;34:306-10.

[5] Van Bel F, Shadid M, Moison RM, Dorrepaal CA, Fontijn J, Monteiro L, et al. Effect of allopurinol on postasphyxial free radical formation, cerebral hemodynamics, and electrical brain activity. Pediatrics. 1998;101(2):185-93.

[6] Paul DA, Pearlman SA, Finkelstein MS, Stefano JL. Cranial sonography in very-low-birth-weight infants: do all infants need to be screened? Clin Pediatr (Phila). 1999;38(9):503-09.

[7] Bracci R, Perrone SN, Buonocore G. The timing of neonatal brain damage. Biol Neonate. 2006;90(3):145-55.

[8] Boo N, Chandran V, Zulfiqar MA, Zamratol SM, Nyein MK, Haliza MS, et al. Early cranial ultrasound changes as predictors of outcome during first year of life in term infants with perinatal asphyxia. J Paediatr Child Health. 2000;36:363-69.

[9] Younkin DP, Reivich M, Jaggi JL, Obrist WD, Delivoria-Papadopoulos M. The effect of hematocrit and systolic blood pressure on cerebral blood flow in newborn infants. J Cereb Blood Flow Metab. 1987;7(3):295-99.

[10] Daneman A, Hellmann J, Barks J, et al. Neuro-sonographic and Doppler studies in full term asphyxia. Presented at the 30th Annual Meeting of the Society for Pediatric Radiology, Toronto, Canada, June 1987.

[11] Jongeling BR, Badawi N, Kurinczuk JJ, Thonell S, Watson L, Dixon G, et al. Cranial ultrasound as a predictor of outcome in term newborn encephalopathy. Pediatr Neurol. 2002;26:37-42.

[12] Liu J, Cao HY, Huang XH, Wang Q. The pattern and early diagnostic value of Doppler ultrasound for neonatal hypoxic-ischaemic encephalopathy. J Trop Pediatr. 2007;53:351-54.

[13] Gray PH, Tudehope DI, Masel JP, Burns YR, Mohay HA, O'Callaghan MJ, et al. Perinatal hypoxic-ischaemic brain injury: prediction of outcome. Dev Med Child Neurol. 1993;35(11):965-73.

[14] Liao HT, Hung KL. Anterior cerebral artery Doppler ultrasonography for prediction of outcome after perinatal asphyxia. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi. 1997;38(3):208-12.

AUTHOR(S):

1. Dr. Pikala Tarakeswara Rao
2. Dr. Manem Saisunil Kishore
3. Dr. Gundapaneni Manasa
4. Dr. Chokkakula Sanyasi Naidu

PARTICULARS OF CONTRIBUTORS:

1. Professor, Department of Paediatrics, Maharaja Institute of Medical Sciences, Vizianagaram, Andhra Pradesh, India.
2. Associate Professor, Department of Paediatrics, Maharaja Institute of Medical Sciences, Vizianagaram, Andhra Pradesh, India.
3. Junior Resident, Department of Paediatrics, Maharaja Institute of Medical Sciences, Vizianagaram, Andhra Pradesh, India.
4. Senior Resident, Department of Paediatrics, Maharaja Institute of Medical Sciences, Vizianagaram, Andhra Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Manem Saisunil Kishore,
Associate Professor, Department of Paediatrics,
Maharaja Institute of Medical Sciences, Beside MDO Office,
Nellimarla, Vizianagaram-535217, Andhra Pradesh, India.
E-mail: ptrao1971@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS:

None.

Date of Publishing: **Jan 01, 2018**