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Original Article

Cerebral Hemodynamics in Late Onset Neonatal Sepsis in Preterm Neonates: A Prospective Observation Study

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Abstract

Introduction: Late onset neonatal sepsis (LONS) is one of the most prevalent conditions in neonates in developing countries. The aim of this study was to assess the changes in cerebral hemodynamics in neonates with LONS.

Methods: Preterm neonates (N = 60) with suspected LONS were enrolled over a period of 21 months and divided into three cohorts: Group A with clinical sepsis but with negative septic markers and culture report, group B, where septic markers were positive, but cultures were sterile and group C, where either blood or CSF culture was positive. Ultrasound doppler of the anterior cerebral artery was done at 0 hrs, 48 hrs and 5th day after suspecting sepsis. Peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistive index (RI) were measured and compared in three groups and sequentially at specific time points.

Results: A total of 60 neonates with a median gestational age of 30.5 [IQR (28 - 32.6)] weeks were enrolled: 21 in group A, 20 in group B and 19 in group C. RI was lowest in Group C at zero hours with a mean of 0.72 (SD ± 0.09) [$p < 0.05$], which gradually improved after starting antibiotics. Klebsiella sp. was the most common organism isolated.

Conclusion: Neonates with culture-positive LONS had the least resistive index. This parameter may have diagnostic implications and significance on the hemodynamic management in LONS.

Introduction

Neonatal sepsis is defined as systemic signs of infection attributed to a pathogen in the bloodstream in a neonate less than or equal to 28 days of life.[1] It is classified as early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS). Infection occurring within 72 hours of life is termed as EONS and is generally transmitted from the mother during the peripartum period. LONS occurs after 72 hours of life and is transmitted horizontally from the environment and health care providers.[2] It is one of the major causes of morbidity and mortality in preterm neonates globally, with most of the brunt taken by developing countries like India.[3-5] In a hospital-based study in a tertiary care setup in India, the incidence of sepsis was between 11.9% to 18.9% of all the hospital admissions, whereas in a rural community setting, there were 67 suspected cases of sepsis per 1000 live births.[6,7]

Neonates with sepsis have three-fold more chances of neuromotor and cognitive

development impairment at 12 months of corrected gestational age.[8] In sepsis, complex cerebrovascular hemodynamic changes take place, which have been investigated in various studies.[9-12] Most of the studies have been conducted in EONS and not in neonates with LONS.

This evaluation is important as the changes in cerebrovascular resistance and flow may provide diagnostic assistance where even the gold-standard test of blood culture may be falsely negative in 30 - 40% of cases due to various reasons such as antecedent antibiotic use, low-level bacteraemia, low blood volume and variable laboratory capabilities.[13,14] It can help in targeting management based on altered hemodynamic pathophysiology and may also potentially assist in prognostication.[9]

Methods

A prospective observational study was conducted from April 2019 to December 2020, in a tertiary level neonatal intensive care unit (NICU) in India. Approval was obtained from the Institutional Ethics Committee before starting the study. During the study procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000. All preterm (< 37 weeks) neonates admitted in NICU, who were clinically suspected to have LONS were enrolled after taking written informed consent from their parents. Baseline demographic data was noted. Preterm neonates with major congenital malformations and genetic syndromes were excluded. These enrolled neonates were divided into three groups – those with clinical sepsis but with negative septic markers [CRP < 10 mg / L, total leucocyte count > 5000 / mm^3, absolute neutrophil count in normal range according to Mouzinho's chart, I:T raio < 0.2] and sterile culture report (Group A), the second group, whose blood septic markers were positive (Any one or more of the specified markers positive), but cultures were sterile (Group B) and the third group who had a positive blood and / or CSF culture with a known pathogen (Group C).[15] All the neonates within the specified time period were considered for enrolment. We aimed to enroll a sample size of 60 patients based on likely enrollment rates in our nursery over the 20 months period as a pilot trial. Transcranial colour doppler ultrasonography was done by a single neonatologist trained in cranial ultrasonography using a SIEMENS machine (Acuson X 300, SIEMENS Medical Solution, USA) with a neonatal probe (5 - 10 MHz transducer). Doppler imaging of the anterior cerebral artery (ACA) was done through the anterior fontanelle in the sagittal plane at the place where the artery curves at the level of the genu of the corpus callosum. Pulse doppler was done to measure Peak Systolic Velocity (PSV) and End diastolic Velocity (EDV) (Figure 1). The resistive index (RI) was then calculated using the formula: RI= (PSV - EDV) / PSV.[16] Ultrasound Doppler was done in these neonates when starting antibiotics (PSV1, EDV1, RI1), then at 48 hours (PSV2, EDV2, RI2), and the third evaluation was done on day 5 (PSV3, EDV3, RI3). All the measurements were done in a thermo-neutral environment ensuring normal body temperature without any pressure provocation in quiet neonates, using oral sucrose as a pacifier with continuous monitoring of oxygen saturation and vitals. Three measurements were recorded at each time point and their mean was calculated. Blinding could not be done as the treating clinicians and investigators were the same. Data was analysed with IBM SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, N.Y., USA). Continuous variables were summarized with standard descriptive statistics including means and standard deviations for normally distributed data and median and inter-quartile (IQR) values for skewed data. Categorical variables were summarized using frequencies, and percentages. ANOVA and repeated ANOVA tests were used to compare the three groups. The chi-square test was used to assess associations between the categorical variables. Fisher's exact test was used to find out the association between two categorical variables when the observed frequency was less than five in at least one cell.

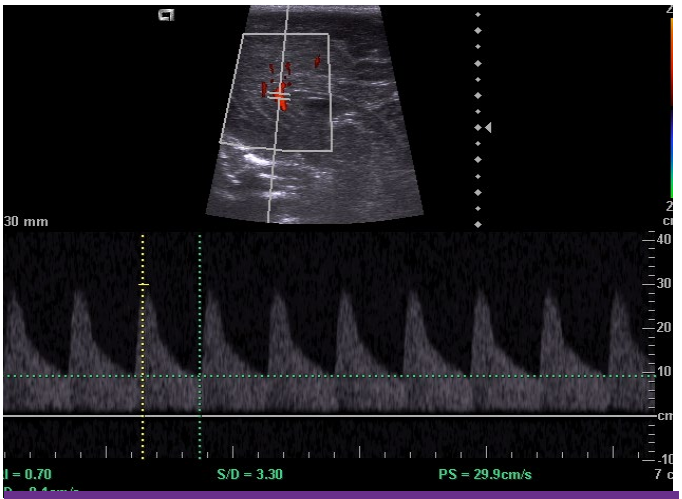

Fig 1: Doppler image of the anterior cerebral artery through anterior fontanelle in the sagittal plane

Results

We included total 60 neonates with 21 in group A, 20 in group B, and 19 in group C (Figure 2). The median birth weight of the cohort was 1207.5 gm [IQR (1000-1560)] grams and the median gestation age was 30.5 [IQR (28 - 32.6)] weeks. Eighty percent were male. Out of the 60, 10 (16.7%) neonates were small for gestational age. Just over two-thirds (71.7%) were delivered by Caesarean section. The median age at enrolment was 7.5 [IQR (5-23)] days. The baseline characteristics of the three subgroups are summarized in Table 1. The subgroups were similar in all studied parameters except for SGA which was less prevalent in group A. Culture-proven sepsis was found in 19 neonates and the most common organism was Klebsiella sp. (Table 2).

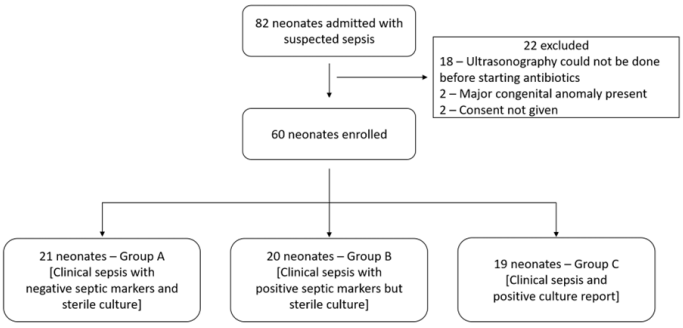

Fig 2: Study flow diagram

Table 1: Baseline characteristic of the neonates (N = 60)

Parameters	Group A (N = 21)	Group B (N = 20)	Group C (N = 19)	p-value
Birth weight (Gms) Median (IQR)	1130.0 (990.0 - 1632.5)	1077.5 (956.3 - 1558.8)	1300.0 (1100.0- 1635.0)	.54
Gestation (Weeks) Median (IQR)	29.7 (27. 5 - 32.8)	30.0 (27.5 - 32.5)	31.3 (29.0 - 35.0)	.31
SGA (%)	0 (0%)	6 (30%)	4 (21.1%)	.03
Male (%)	19 (90.5%)	14 (70%)	15 (79%)	.26
LSCS (%)	18 (85.7%)	12 (60%)	13 (68.4%)	.18
DOL at which deteriorated Median (IQR)	15.0 (6.0- 24.0)	12.5 (4.0- 32.0)	7.0 (5.0 - 15.0)	.20
No. of days of antibiotics Median (IQR)	7.0 (5.0- 10.0)	7.0 (5.0- 10.0)	14.0 (10.0-14.0)	.00
Hemoglobin (g/dl) Median (IQR)	12 (11-16.6)	11.15 (10.08-15.2)	13 (11.05-15.75)	0.48

DOL – day of life, IQR -interquartile range, LSCS - lower segment caesarean section, SGA – small for gestation

Table 2: Organisms isolated in culture (N = 19)

Organism	N
Blood	
Klebsiella pneumoniae	10
Enterobacter cloacae	3
Acinetobacter baumanii	2
Staphylococcal epidermidis	2
Escherichia coli	1
Elizabethkingia meningoseptica	1
CSF	
Staphylococcal epidermidis	1*

*Had also grown Staphylococcal epidermidis in blood
CSF – cerebral spinal fluid

USG Doppler done at zero hours, when starting antibiotics, showed significantly lower RI in group C as compared to groups A and B (P = 0.049). This lower RI persisted through follow-up at 48 hours and day 5 but lost its statistical significance at these time points when antibiotics had been introduced. EDV at zero hours and 48 hours was higher in group C than in the other two groups, but the difference was not statistically significant (Table 3). Changes in RI in three groups after starting antibiotics are depicted in Figure 3.

Table 3: PSV, EDV, RI in three groups at 0 hrs, 48 hrs and 5th day of suspecting sepsis

	Group A (N = 21)	Group B (N = 20)	Group C (N = 19)	P-value
0 hours				
PSV 1 Mean (SD)	42.64 (13.89)	47.01 (15.50)	44.70 (17.16)	0.668
EDV 1 Mean (SD)	9.36 (3.80)	10.68 (8.01)	12.96 (7.82)	.248
RI 1 Mean (SD)	0.78 (0.07)	0.79 (0.12)	0.72 (.09)	.049
48 hours				
PSV 2 Mean (SD)	45.64 (14.96)	47.74 (16.04)	44.39 (13.22)	.780
EDV 2 Mean (SD)	9.67 (3.30)	10.41 (5.12)	12.15 (6.11)	.309
RI 2 Mean (SD)	0.78 (0.05)	0.79 (0.09)	0.73 (0.09)	.081
Day 5				
PSV 3 Mean (SD)	48.71 (17.04)	48.61 (13.85)	42.91 (16.60)	.444
EDV 3 Mean (SD)	11.17 (7.13)	10.17 (5.68)	11.11 (7.63)	.886
RI 3 Mean (SD)	0.77 (0.08)	0.79 (0.09)	0.75 (0.08)	.387

* EDV – end-diastolic velocity, PSV – peak systolic velocity, RI – resistive index, SD – standard deviation

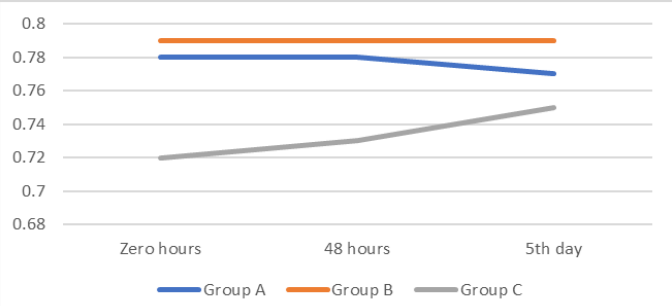

Fig 3: Change in RI in 3 groups at 0 hrs, 48 hrs, and 5th day of starting antibiotics

Discussion

In this prospective study, we found that the cerebrovascular RI at the onset of LONS in preterm neonates is lower in culture-positive sepsis suggesting cerebral vasodilatation. This improves following the initiation of antimicrobial therapy. Various factors like meningitis, ventriculitis, shock, anemia, and raised intracranial pressure due to hydrocephalus or cerebral oedema can alter cerebral hemodynamics and affect cerebral perfusion. Cytokines and interleukins generated during systemic inflammatory response syndrome may affect the endothelin and endothelial nitric oxide synthase activity causing the impairment of the microcirculation of the brain.[17] The disrupted blood-brain barrier in sepsis may alter the internal milieu of brain cells with high levels of endogenous catecholamines to influence cerebrovascular resistance.[18] Autoregulation of blood-brain circulation, especially in preterm or sick neonates, has not been well studied. In neonates with sepsis, it has been postulated that with cerebral vasodilatation, there is an increase in cerebral blood flow, thus decreasing the RI.[11,19,20] Hashem et al in their study showed that neonates with EONS had lower RI and PI compared to the control cohort.[11] Basu et al also documented significantly lower resistance (RI and PI), vasodilatation, and higher peak systolic velocity in all three major cerebral vessels [internal carotid artery (ICA), middle cerebral artery (MCA), and vertebral artery) in neonates with EONS.[9] With sepsis, there may be cerebral vasoconstriction as well, with a decrease in blood flow resulting in increased

RI.[21] This might be explained by hemodynamic instability or due to cerebral oedema causing decreased compliance of the cerebral vasculature. Bowton et al demonstrated that CBF is reduced in patients with sepsis by using ^{133}Xe clearance technique to measure CBF in nine septic patients.[22] Similarly, in contrast to the finding in our study, Yengkhom et al did cerebral doppler in LONS and showed the association of LONS with high RI indicating decreased CBF.[12] This might be explained by different time points when USG doppler was done. Whether this occurs in sequential order with the first vasodilatation followed by vasoconstriction or whether it is due to different mechanism remain poorly understood.

In our study, most of the culture-proven sepsis was caused by gram-negative organisms, similar to previous studies reported from developing countries.[6,7] The most common organism was Klebsiella species, accounting for more than half of the cases of bacteraemia in the LONS cohort. This is in contrast with other developed countries where gram-positive organism predominates in neonates with LONS.[23]

For the assessment of suspected sepsis in neonates, investigations many times give inconclusive results. Even the gold standard of blood culture may be falsely negative in one-third cases.[13,14] Performing Doppler assessment of the ACA may be an additional tool in the assessment if other studies with larger sample sizes could corroborate our findings.

The strength of our study lies in the sequential observation using the cerebral doppler, which also demonstrated the response to the antibiotics. Also, the division of the cohort into the three groups mirrors the real-life scenario in the NICU. Since all the USG dopplers were done by a single person – there was no scope for inter-operator variability. The limitation of our study is being the pilot trial - small sample size was taken, which could have led to the small absolute difference in the numbers and lower but still normal RI values in group C. We plan to do similar study with larger sample size in the future. Also, the measurement of RI was done only in the ACA in view of its easier access and easy replicability in other settings. We acknowledge that the doppler of MCA or ICA could have given more clues about cerebrovascular changes during LONS. Also, because of the study design, treating clinician could not be blinded as he also performed the ultrasonography. The changes in doppler which might have occurred due to different respiratory support in the three groups was not evaluated.

Since it is known that high cerebral blood flow may lead to cerebral hemorrhage and low cerebral blood flow may lead to ischemic damage to the brain, both could cause poor long-term neurological outcomes in the child. Prospective studies are required to evaluate the effects of changes in cerebral hemodynamics on long-term outcomes.

Conclusion

To conclude, this observational study highlights the cerebral hemodynamic changes during LONS in preterm babies with the least RI in culture-positive cases. Further studies with a larger sample size are required to confirm the findings before this parameter is used in the clinical practice as a diagnostic or prognostic ultrasound marker in neonates with LONS, which remains a common and prevalent problem in most of the NICUs, especially in the developing countries.

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Conflict of Interest None

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