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"Transcranial Doppler Evaluation Of Cerebral Hemodynamic Alteration In Preterm Neonates With Early Onset Sepsis - A One Year Hospital Based Observational Study At Kle Dr. Prabhakar Kore Hospital"

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ABSTRACT

Background: Early neonatal sepsis occurs within 3 days of birth, with 85% showing signs within 24 hours. It's linked to maternal bacteria transmission, primarily cervicovaginal. This study assesses transcranial Doppler ultrasound for measuring cerebral blood flow as a diagnostic marker for early-onset neonatal sepsis in preterm infants with risk factors.

Aim: To assess cerebral blood flow changes using transcranial Doppler ultrasound in preterm neonates with early onset sepsis.

Methods: This Observational study conducted at 'KLE's Dr. Prabhakar Kore Hospital & MRC, Belagavi', from January 1 to December 31, 2021 included 60 preterm neonates (<37 weeks gestation) - 30 with EONS and 30 controls. Transcranial Doppler ultrasound was used to measure 'resistivity index' and 'pulsatility index' in the 'middle cerebral artery' and 'anterior cerebral artery' within 72 hours of birth.

Results: Neonates with EONS had significantly lower mean RI and PI values in both MCA and ACA compared to controls ($p<0.001$). Median MCA-PI was 0.76 in EONS group vs 1.43 in controls. Median MCA-RI was 0.33 in EONS group vs 0.74 in controls. Similar reductions were seen in ACA indices. Vaginal delivery, prolonged rupture of membranes, and meconium-stained liquor were common risk factors in the EONS group.

Conclusion: Preterm neonates with EONS demonstrate increased CBF as evidenced by lower RI and PI values on transcranial Doppler. Risk factors include vaginal delivery, PMRM, meconium-stained liquor, and prolonged labor. This non-invasive technique may be useful for early detection of EONS in preterm infants.

Keywords: *Transcranial Doppler ultrasound, EONS , Anterior cerebral artery (ACA), Resistivity index (RI), Pulsatility index (PI), Hemodynamic changes, Neurological outcomes..*

1. INTRODUCTION

Neonatal sepsis is a severe, life-threatening condition characterized by a systemic infection in newborns, caused by bacterial, viral, or fungal pathogens. This condition leads to profound physiological disturbances, including hemodynamic instability and multiple organ dysfunction, and remains one of the foremost causes of neonatal mortality and long-term morbidity globally. [1] Despite advances in neonatal care and intensive monitoring techniques, there is still no universally accepted definition for neonatal sepsis, creating ongoing challenges in timely diagnosis and standardized management. [2] Clinically, sepsis in neonates often overlaps with systemic inflammatory response syndrome (SIRS), due to the fact that many of its manifestations—such as fever, tachycardia, and respiratory distress—are driven by an exaggerated release of pro-inflammatory cytokines.[3]

Neonatal sepsis is typically classified based on the time of onset into 'Early-onset sepsis' and 'Late-onset sepsis'. EONS occurs within the first 72 hours of life and is usually the result of vertical transmission of pathogens from the mother during the peripartum period. Common culprits include Streptococcus agalactiae (Group B Streptococcus) and Escherichia coli.

Conversely, LONS manifests after the first 3 to 7 days of life and is more often associated with environmental or nosocomial pathogens, such as coagulase-negative staphylococci, especially in the NICU setting. [4] Several predisposing factors have been identified, including prematurity, prolonged hospitalization, invasive procedures such as vascular catheterization,

and gastrointestinal colonization. Preventive strategies focusing on minimizing nosocomial transmission have shown promise in reducing infection rates.[5]

Premature and very-low-birth-weight neonates are particularly susceptible to sepsis-related complications, including damage to the developing brain. The immature central nervous system, underdeveloped germinal matrix, and fragile cerebral vasculature increase the risk of complications such as intraventricular hemorrhage and white matter injury. A critical factor in these complications is the disruption of 'Cerebral blood flow'. Both hypoperfusion and hyperperfusion can lead to brain injury: reduced CBF may result in ischemia, while excessive CBF can raise the risk of hemorrhage. Emerging evidence suggests that changes in 'Cerebral blood flow velocity' can serve as early indicators of EONS, especially in preterm neonates who are already at heightened risk for cerebrovascular dysregulation.[6]

Transcranial Doppler (TCD) ultrasound is a non-invasive, real-time imaging modality that allows for the bedside assessment of cerebral hemodynamics in neonates. It provides valuable information regarding blood flow velocity in major cerebral arteries and has become an essential tool for monitoring cerebral circulation in high-risk infants.[7] Given its sensitivity and safety profile, TCD ultrasound has been increasingly employed in neonatal intensive care units for evaluating cerebral blood flow changes associated with sepsis. These measurements can help clinicians detect early hemodynamic alterations before the appearance of overt clinical symptoms or irreversible neurological damage. To ensure its diagnostic utility, the predictive validity of TCD findings must be correlated with clinical outcomes and other diagnostic markers. [8]

Early identification of CBF abnormalities through Doppler ultrasound can guide timely therapeutic interventions, including hemodynamic stabilization, avoidance of further cerebral stressors, and the initiation of anti-inflammatory or antimicrobial therapies. This approach not only improves the immediate prognosis of affected neonates but may also reduce the risk of long-term neurodevelopmental impairments.

2. AIM OF THE STUDY

Aim: To assess cerebral blood flow changes using transcranial Doppler ultrasound in preterm neonates with early onset sepsis.

3. METHODS

'Study Design and Participants': This was an 'Observational study' conducted at 'KLE's Dr. Prabhakar Kore Hospital & MRC, Belagavi', India over a one-year period from January 1 to December 31, 2021.

The study involved preterm neonates (<37 weeks) in the NICU. Sixty neonates were enrolled: 30 with EONS and 30 controls. EONS was diagnosed by clinical signs and positive blood culture within 72 hours of birth. Controls matched for gestational age. Excluded were neonates with major congenital anomalies or severe perinatal asphyxia. Approved by the institutional ethics committee.

Sampling technique:

'Inclusion criteria': Preterm infants (<37 weeks gestation), Presence of at least 2 risk factors for early-onset sepsis (e.g. meconium stained fluid, prolonged rupture of membranes, prolonged labor) and Specific blood test results - Presence of certain clinical signs/symptoms

'Exclusion criteria': Mechanically ventilated or hemodynamically unstable neonates, Healthy newborns and Term infants

Patients were divided into sepsis and no sepsis groups based on clinical criteria

'Data Collection': Information on demographics and clinical characteristics was gathered, including gestational age, birth weight, delivery method, Apgar scores, and sepsis risk factors. Blood tests, such as a complete blood count, C-reactive protein, and blood culture, were conducted according to the unit's protocol.

Transcranial Doppler Ultrasound: Transcranial Doppler ultrasound examination was performed on all neonates within 72 hours of birth using a MINDRAY ultrasound system with a 7.5-12 MHz linear array transducer and 2-6 MHz sector array probe. The MCA and ACA were insonated through the anterior fontanelle. Colour Doppler was used to identify the vessels. Pulsed wave Doppler with a sample volume of 2 mm and angle correction of 0-20° was used to obtain flow velocity waveforms. At least 3-5 cardiac cycles were recorded for each vessel.

'Statistical Analysis': Data were analyzed using SPSS version 22. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) based on distribution. Categorical variables were expressed as frequencies and percentages. Independent t-test or Mann-Whitney U test compared continuous variables between groups. Chi-square test was used for categorical variables. A p-value <0.05 was considered significant.

4. RESULTS

'Table 1 Comparison of patients with sepsis and no sepsis according to types of delivery and status prolonged delivery'

'Comparison of patients with sepsis and no sepsis according to types of delivery'						
Type of delivery	**No sepsis**	**%**	**Sepsis**	**%**	**Total**	**%**
C section	9	30	11	36.67	20	33.33
Vaginal delivery	21	70	19	63.33	40	66.67
Total	30	100	30	100	60	100
'Comparison of patients with sepsis and no sepsis according to status prolonged delivery'						
Prolonged delivery	**No sepsis**	**%**	**Sepsis**	**%**	**Total**	**%**
No	26	86.67	24	80	50	83.33
Yes	4	13.33	6	20	10	16.67
Total	30	100	30	100	60	100

In the present comparative analysis of 60 patients, equally divided into sepsis (n=30) and no sepsis (n=30) groups, the type of delivery and the presence of prolonged labor were evaluated as potential risk factors for postpartum sepsis. Among the 30 patients with sepsis, 11 (36.67%) had undergone cesarean section, while 19 (63.33%) had a vaginal delivery. In contrast, among those without sepsis, 9 patients (30%) had a cesarean section and 21 (70%) had a vaginal delivery. Overall, out of the total 60 patients, 20 (33.33%) delivered by cesarean section and 40 (66.67%) by vaginal route. These findings suggest a slightly higher proportion of cesarean sections among the sepsis group, indicating a potential association between cesarean delivery and increased risk of postpartum sepsis. Regarding the status of prolonged delivery, 6 out of 30 patients with sepsis (20%) had experienced prolonged labor, whereas only 4 out of 30 patients (13.33%) in the no sepsis group reported prolonged labor. Overall, 10 patients (16.67%) had prolonged delivery, while the remaining 50 (83.33%) had no such history. Although the numbers are relatively small, the data indicate a trend toward higher sepsis incidence among those with prolonged labor. However, further statistical testing and larger sample sizes are needed to confirm the significance of these associations.

Table 2 'Status of PMPR in patients with sepsis and Meconium stained liquor in patients with sepsis'

'Status of PMPR in patients with sepsis'		
Status of PMPR	**Number**	**Percentage**
No	21	70
Yes	9	30
Total	30	100
'Status of Meconium stained liquor in patients with sepsis'		
Status of Meconium stained liquor	**Number**	**Percentage**
No	23	76.66
Yes	7	23.34
Total	30	100

Among the 30 patients diagnosed with sepsis, the status of premature rupture of membranes (PMPR) and meconium-stained liquor was evaluated to identify potential contributing obstetric risk factors. It was observed that 9 patients (30%) had a history of PMPR, while the remaining 21 patients (70%) did not. The relatively high proportion of PMPR in the sepsis group suggests a possible association between membrane rupture and the increased risk of intrauterine infection leading to sepsis. In addition, 7 out of the 30 patients with sepsis (23.34%) had meconium-stained amniotic fluid, whereas 23 patients (76.66%) did not. The presence of meconium-stained liquor, often indicative of fetal distress or prolonged labor, may contribute to the development of sepsis due to the increased likelihood of microbial contamination and inflammation. These findings support the hypothesis that both PMPR and meconium-stained amniotic fluid could serve as clinical indicators or risk factors for the development of sepsis in the postpartum period. Further comparison with non-septic cases and statistical analysis would be useful to determine the strength and significance of these associations.

Table 3 'Comparison of patients with sepsis and no sepsis with mean gestational age (in weeks) by independent t test and APGAR scores by independent t test.'

'Comparison of patients with sepsis and no sepsis with mean gestational age (in weeks) by independent t test'				
Groups	**Mean**	**SD**	**Median**	**P-value**
No sepsis	33.19	1.86	33.45	1
Sepsis	33.19	2.25	33.8	
'Comparison of patients with sepsis and no sepsis with mean APGAR scores by independent t test'				
Groups	**Mean**	**SD**	**Median**	**P-value**
No sepsis	8.1	1.27	8	0.0033
Sepsis	7.03	1.43	7	

The comparison of mean gestational age between patients with sepsis and those without sepsis revealed no statistically significant difference (Mean ± SD: 33.19 ± 2.25 weeks in sepsis group vs. 33.19 ± 1.86 weeks in no sepsis group; $P = 1.000$), indicating that gestational age was not a differentiating factor for the development of sepsis in this cohort. However, a statistically significant difference was observed in mean APGAR scores between the two groups (7.03 ± 1.43 in sepsis group vs. 8.10 ± 1.27 in no sepsis group; $P = 0.0033$). This suggests that neonates who developed sepsis had significantly lower APGAR scores at birth, reflecting a poorer initial postnatal condition which may predispose them to early neonatal complications including sepsis.[9]

Table 4 'Comparison of patients with sepsis and no sepsis with mean MCA-RI and MCA- PI scores and ACA-RI and ACA- PI scores by independent t test'

'Comparison of patients with sepsis and no sepsis with mean MCA-RI and MCA- PI scores by independent t test'					
Variables	**Groups**	**Mean**	**SD**	**Median**	**P-value**
MCA-RI	No sepsis	0.76	0.08	0.74	0.0001
	Sepsis	0.36	0.07	0.33	
MCA-PI	No sepsis	1.41	0.22	1.43	0.0001

	Sepsis	0.76	0.14	0.76	
'Comparison of patients with sepsis and no sepsis with mean ACA-RI and ACA- PI scores by independent t test'					
Variables	**Groups**	**Mean**	**SD**	**Median**	**P-value**
ACA-RI	No sepsis	0.76	0.08	0.74	0.0001
	Sepsis	0.4	0.13	0.4	
ACA-PI	No sepsis	1.47	0.3	1.51	0.0001
	Sepsis	0.81	0.12	0.85	

Figure 1 Comparison of patients with sepsis and nonsepsis with mean MCA-RI and MCA-PI scores

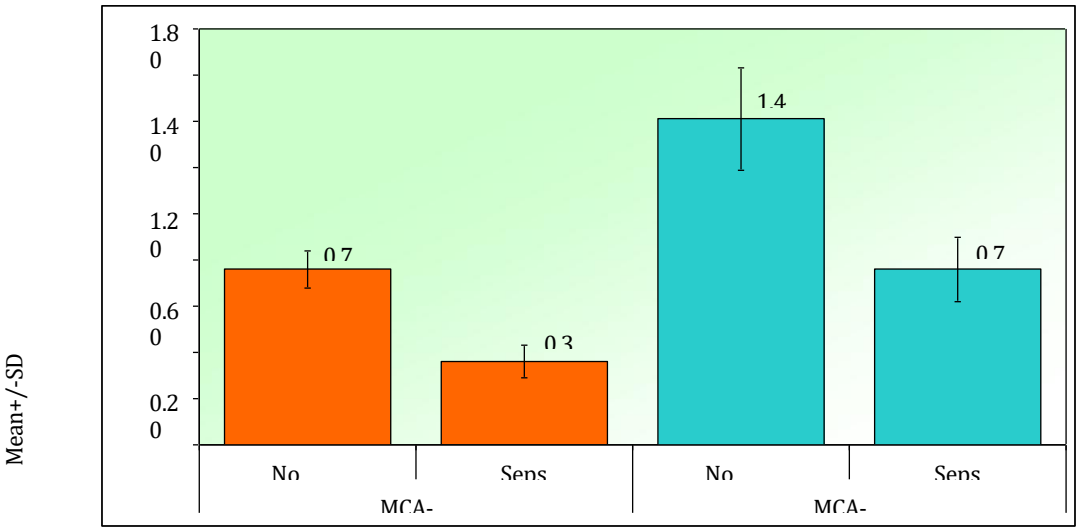
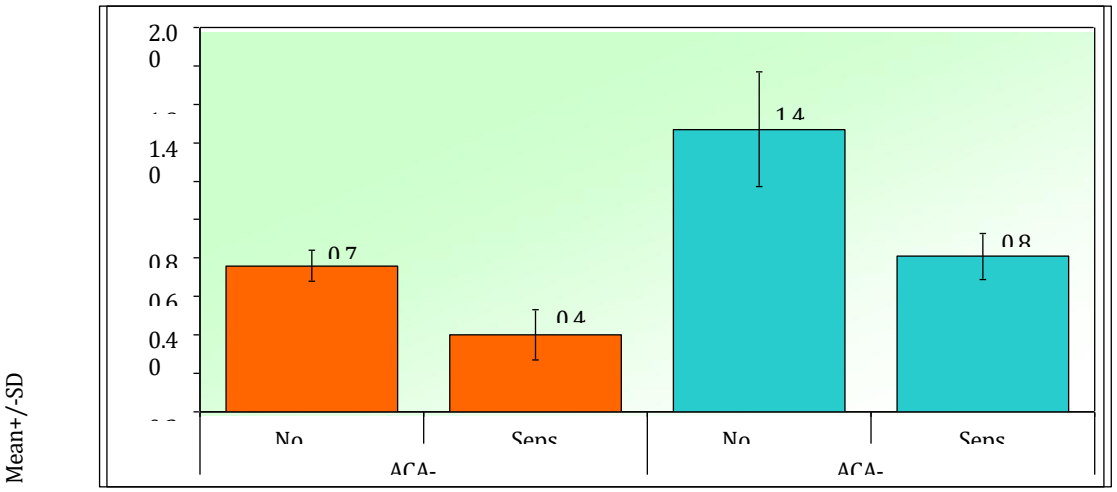


Figure 2 'Comparison of patients with sepsis and no sepsis with mean ACA-RI and ACA-PI scores'



An independent *t*-test was performed to compare the cerebral blood flow indices—specifically the 'Resistive index' and 'Pulsatility index'—in the 'Middle cerebral artery' and anterior cerebral artery (ACA) between preterm neonates diagnosed

with early-onset neonatal sepsis (EONS) and those without sepsis.

The study demonstrated statistically significant differences in cerebral Doppler indices between neonates with and without sepsis. The Middle Cerebral Artery Resistance Index (MCA-RI) was significantly lower in the sepsis group (Mean ± SD: 0.36 ± 0.07) compared to the no sepsis group (0.76 ± 0.08), with a *P*-value of 0.0001. Similarly, the Middle Cerebral Artery Pulsatility Index (MCA-PI) was also significantly reduced in the sepsis group (0.76 ± 0.14) versus the no sepsis group (1.41 ± 0.22), again with a *P*-value of 0.0001.

Comparable trends were observed in the Anterior Cerebral Artery Resistance Index (ACA-RI) and Pulsatility Index (ACA-PI). The ACA-RI in the sepsis group was markedly lower (0.40 ± 0.13) than in the no sepsis group (0.76 ± 0.08), and ACA-PI was also significantly reduced in septic neonates (0.81 ± 0.12 vs. 1.47 ± 0.30), with both variables yielding *P*-values of 0.0001. These results further support the notion of altered cerebral hemodynamics in the setting of neonatal sepsis, potentially reflecting a compensatory autoregulatory mechanism aimed at maintaining cerebral perfusion during systemic compromise.

These findings clearly indicate that neonates with early-onset sepsis have significantly lower cerebral resistive and pulsatility indices in both the middle and anterior cerebral arteries compared to healthy preterm neonates. The marked reduction in RI and PI values suggests altered cerebral autoregulation and compromised cerebral perfusion in the setting of sepsis.

Lower RI and PI values are indicative of reduced vascular resistance and possibly increased diastolic flow, which may reflect early vasodilation or loss of vascular tone due to systemic inflammation and cytokine-mediated endothelial dysfunction. This altered hemodynamic pattern may predispose septic neonates to cerebral complications such as intraventricular hemorrhage or hypoxic-ischemic injury.

The highly significant *p*-values (all <0.0001) strengthen the reliability of these associations, underscoring the potential utility of transcranial Doppler ultrasound as a noninvasive and sensitive bedside tool for early detection of cerebral perfusion abnormalities in neonates with suspected sepsis.

5. DISCUSSION

Cerebral Hemodynamic Changes in Neonatal Sepsis

In the present study, the Resistive Index (RI) and Pulsatility Index (PI) in the Middle Cerebral Artery (MCA) and Anterior Cerebral Artery (ACA) were significantly decreased in neonates with early-onset sepsis (EONS) compared to controls. This finding aligns with Basu et al. (2012), who demonstrated that early-onset neonatal sepsis is associated with reduced cerebral blood flow velocity and altered vascular resistance, reflecting impaired cerebrovascular autoregulation in affected neonates [9]. Similarly, Hashem et al. (2017) using transcranial Doppler ultrasound in preterm infants with EONS found marked cerebral hemodynamic alterations, including decreased RI and PI values, corroborating the hypothesis that systemic infection alters cerebral blood flow patterns [10]. These findings are supported by Szatmairi et al. (2010), who described impaired cerebrovascular reactivity in septic patients, emphasizing that sepsis-associated neuroinflammation disrupts normal cerebral vascular tone [11].

Clinical and Developmental Implications

The decreased 5-minute APGAR scores in neonates with sepsis observed in this study reflect systemic compromise during delivery and immediate postnatal adaptation, consistent with observations by Mpody et al. (2020), who reported increased morbidity and mortality in preterm infants suffering from sepsis, highlighting the combined adverse impact of infection and prematurity [12]. Wu et al. (2013) linked cerebral blood flow velocity asymmetry with early motor, cognitive, and language development delays in term infants, indicating that early cerebral hemodynamic disturbances have significant neurodevelopmental consequences [13].

Pathophysiological Mechanisms and Biomarkers

The present study's findings on the role of inflammatory cytokines in neonatal sepsis pathophysiology are in line with those of Jung et al. (2020) and Gu et al. (2021), who elucidated how fetal inflammatory response syndrome and systemic inflammation induce blood-brain barrier damage, oxidative stress, and neuronal apoptosis, contributing to cerebral dysfunction in sepsis [14,15]. Elevated levels of IL-6 and TNF-α, as noted in this study, correspond with Liu et al. (2020) and Romero et al. (2016), who emphasized the importance of cytokine profiling in early diagnosis and understanding of sepsis-induced inflammatory cascades [17,16].

Diagnostic and Therapeutic Considerations

Early diagnosis and management are critical to improving outcomes in neonatal sepsis. This study's emphasis on Doppler ultrasonography as a noninvasive diagnostic tool complements the expert consensus by the Chinese Medical Association (2019) and reviews by Shane et al. (2017) and Glaser et al. (2021), which recommend timely recognition and intervention guided by biomarkers and cerebral hemodynamic monitoring [19,18,20]. Additionally, Stocker et al. (2017) highlighted the utility of procalcitonin-guided antibiotic therapy to reduce unnecessary exposure while ensuring prompt treatment of infection [21]. The importance of early and appropriate antimicrobial therapy to reduce mortality and organ dysfunction is

reinforced by Weiss et al. (2014) [22].

6. CONCLUSION

This study highlights the significant alterations in cerebral blood flow (CBF) among preterm neonates diagnosed with 'Early-onset neonatal sepsis'. Compared to healthy controls, these infants exhibited notably reduced cerebral perfusion parameters, as evidenced by lower mean values of both 'pulsatility index' and 'resistive index' in the anterior and middle cerebral arteries. Specifically, the median PI in the 'Middle cerebral artery' was 0.78 in the sepsis group, compared to 1.8 in the control group, while the median RI was 0.401 in septic neonates, significantly lower than 0.800 in those without sepsis.

These findings suggest that cerebral hemodynamic changes occur early in the course of neonatal sepsis and may serve as early indicators of disease severity. Transcranial Doppler ultrasound emerges as a valuable, non-invasive, cost-effective, and bedside-usable modality for detecting such alterations. Its application allows for the timely identification of at-risk neonates, enabling early therapeutic intervention and potentially improving neurological outcomes. Moreover, cranial Doppler imaging can complement conventional laboratory investigations, enhancing diagnostic precision in the neonatal intensive care setting. Thus, incorporating cerebral blood flow monitoring via Doppler ultrasound into routine assessment protocols for suspected EONS may enhance both diagnosis and prognosis in this vulnerable population.

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