

Utility of Doppler ultrasound in early-onset neonatal sepsis

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Abstract

Background: Neonatal sepsis is an important cause of morbidity and mortality among newborns. As there is paucity of literature regarding early alteration of the cerebral blood flow (CBF) in neonatal sepsis our study aims to evaluate the changes in the CBF velocities and Doppler indices in neonates with early-onset neonatal sepsis (EONS) and to evaluate the predictive accuracy of cerebral blood flow velocities (CBFV) by using ultrasound Doppler as a diagnostic marker of EONS. **Methods:** This cross-sectional analytical study was conducted over a period of 2 years with 123 neonates enrolled in the study. The neonates were divided into two groups: Group I (with 54 neonates) - neonates with EONS and group II (with 69 neonates) - age-matched neonates without any signs of sepsis. Ultrasound Doppler examination was performed and the cerebral hemodynamics assessed in neonates during the first seventy two hours of life. Doppler indices and CBFV were measured in the internal carotid artery (ICA), middle cerebral artery (MCA), and vertebral artery (VA) of either side. Data were analyzed using the statistical program SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated at different selected cutoff values for CBFV parameters. **Results:** Lower resistance and higher peak systolic velocity and end diastolic velocity have been documented in neonates with EONS. **Conclusion:** Our study shows that the cerebral hemodynamics in neonates with EONS is altered which can be assessed bedside by noninvasive ultrasound Doppler examination.

Key words: Doppler indices; early-onset neonatal sepsis; internal carotid artery; middle cerebral artery; transcranial Doppler; vertebral artery

Introduction

Annually, worldwide one million neonatal deaths are attributed to neonatal sepsis alone.^[1] Neonatal sepsis is an important cause of morbidity and mortality amongst newborns.^[2,3] Neonatal sepsis is defined classically as a clinical syndrome characterized by systemic signs of infection commonly accompanied by bacteremia. Two types of neonatal sepsis have been described: early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS).

When features of sepsis appear within the first 72 h of birth or when there is bacteremia or bacterial meningitis occurring at ≤ 72 h in infants it is described as EONS. On the contrary, when features of sepsis manifest beyond 72 h of birth it is termed as late-onset sepsis.^[2,4,5]

There is paucity of literature regarding early alteration of the cerebral blood flow (CBF) in neonatal sepsis. The brain of

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Cite this article as: Ratnaparkhi CR, Bayaskar MV, Dhok AP, Bhende V. Utility of Doppler ultrasound in early-onset neonatal sepsis. Indian J Radiol Imaging 2020;30:52-8.

Received: 19-Jun-2019
Accepted: 17-Dec-2019

Revised: 26-Aug-2019
Published: 30-Mar-2020

Access this article online

Quick Response Code:



Website:
www.ijri.org

DOI:
10.4103/ijri.IJRI_265_19

the neonates is highly susceptible to blood flow fluctuations such that moderately elevated CBF can increase the risk of cerebral hemorrhage, whereas moderate hypoperfusion can expose the brain to ischemic damage.^[4,6,7]

Changes in the CBF during early hours of life may play a pivotal role in perinatal brain damage and cause acute and long-term morbidity which can be assessed by ultrasound Doppler examination which is a real time, relatively safe, noninvasive, and sensitive method to evaluate these vascular changes.^[8] Our study aims to document these changes by ultrasound Doppler examination by studying changes in values of peak systolic velocity (PSV) and end diastolic velocity (EDV), resistivity index (RI), and pulsatility index (PI) in neonates with EONS compared to age-matched neonates without any signs of sepsis and to evaluate the predictive accuracy of CBFV by using ultrasound Doppler as a diagnostic marker of EONS.

Methods

This cross-sectional analytical study was conducted over a period of 2 years with 123 neonates enrolled in the study. The neonates were divided into two groups: Group I had 54 neonates - neonates with EONS and group II - gestational age-matched neonates without any signs of sepsis which comprised 69 neonates.

Ethical clearance was obtained from the institutional ethical clearance committee. Informed consent was obtained from the parents/guardians of the enrolled subjects.

Inclusion criteria for neonates with early-onset neonatal sepsis

Neonates presenting within 72 h of birth with either clinical signs of sepsis or with positive septic screen and/or culture positive sepsis were included in group I.^[6-8]

Clinical signs of sepsis include features like hypothermia or fever, lethargy, poor cry, refusal to suck, poor perfusion, prolonged capillary refill time, hypotonia, absent neonatal reflexes, brady/tachycardia, respiratory distress, apnea and gasping respiration, hypoglycemia, hyperglycemia, metabolic acidosis, bulging anterior fontanelle, seizures, stupor/coma, vomiting, diarrhea, paralytic ileus, necrotizing enterocolitis, direct hyperbilirubinemia, acute renal failure, petechiae, purpura, bleeding, multiple pustules, umbilical redness and discharge, abscess.

Septic screen positive: When two or more of the following parameters are positive [Table 1].

Clinical workup

Detailed antenatal and intranatal history was taken. At birth, a thorough clinical examination was done to exclude any systemic or congenital malformation. Laboratory estimation

Table 1: Components of the septic screen

| Components | Abnormal value |
|-------------------------------------|--|
| Total leukocyte count | < 5000/mm ³ |
| Absolute neutrophil count | Low counts as per Manroe chart for the term and Mouzinho's chart for Very Low Birth Weight infants |
| Immature/total neutrophil | > 0.2 |
| Micro-Erthrocyte Sedimentation Rate | > 15 mm in the first hour |
| C reactive protein | > 1 mg/dl |

VLBW: Very Low Birth Weight, ESR: Erythrocyte Sedimentation Rate, AGA: Appropriate for Gestational Age

of liver and kidney function tests, serum electrolytes, blood glucose, coagulation profile, and arterial blood gas analysis was done to exclude inborn errors of metabolism on basis of clinical suspicion.

Exclusion criteria

- History of eclampsia or use of tocolytics or steroids in mothers
- Neonates with medical or surgical illnesses: Perinatal asphyxia, congenital infections, congenital heart disease, hemolytic anemia, metabolic disorders, surgical disorders gross congenital malformations and meconium aspiration syndrome
- Neonates with altered arterial blood gas analysis, with hemodynamic instability and those requiring vasopressor support and mechanical ventilation, receiving anticonvulsants or drugs like caffeine, theophylline at the time of Doppler examination.

Ultrasound Doppler examination of the neonate

Ultrasound Doppler examination was performed in neonates during the first 72 h of birth. The examination was carried out in a thermoneutral environment. All the babies were well fed before the examination. A total of 25% oral dextrose was used as a pacifier with continuous monitoring of vitals.

The Doppler examinations were performed by a single radiologist on MyLab50 esote ultrasonography with color Doppler ultrasound machine with curvilinear (3.5-5 MHz for ICA and MCA) and high frequency linear (7.5 MHz for VA) array transducer. PSV, EDV, RI, and PI were measured in the ICA, MCA, and VA of either side. Angle corrected velocities were taken. PI and RI were calculated as per formulae of the ultrasound blood flow imaging technique. The examination was carried out through the anterior fontanelle in the coronal plane [Figure 1]. The circle of Willis was located and the ICA and MCA were identified. The vertebral artery was assessed through either side of the neck of the neonate [Figure 2].

Statistical analysis

Data were analyzed using the statistical program SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Frequencies and proportions of the different variable were expressed in percentages. Comparison of numerical variables between the



Figure 1: Transcranial Doppler ultrasonography – examination of the neonate through the anterior fontanelle

study groups was done using Student *t*-test for independent samples in comparing two groups when normally distributed and Mann–Whitney U test for independent samples when not normally distributed. Chi-square test was used to compare proportions between the groups. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy were calculated at different selected cutoff values for cerebral blood flow velocity (CBFV) parameters. A *P* value of < 0.05 was considered statistically significant.

Results

- In our study out of total 123 neonates, 18% (22) were examined on day 1, i.e. within 24 h of life, 39% (48) were examined on day 2, i.e. within 24–48 h of life, and 43% (53) were examined on day three, i.e. within 48–72 h of birth
- Out of 69 neonates without sepsis, 29 were examined on day 2, 27 on day 3, and 13 on day one. Among neonates with sepsis 24 were examined on day 2, 21 on day 3, and 9 on day 1
- In the present study out of 123 neonates, 68 (55.3%) were preterm and 55 (44.7%) were term. Among neonates without sepsis there were 35 term and 34 preterm and in neonates with sepsis, there were 34 preterm and 20 term neonates. Thus, the percentage of preterm neonates (63%) was more as compared to term neonates (37%) in neonates with sepsis
- Out of total 123 neonates, 46% (57) were females and 54% (66) were males. Among neonates with sepsis there were 35 (64.8%) males and 19 (35.2) females. Among neonate without sepsis there were 31 (44.9%) male and 38 (55.1%) female. In neonates with sepsis, male patients were more as compared to females
- In neonates without sepsis, 30 (43.5%) were Appropriate for Gestational Age and 39 (56.5%) had low birth weight, whereas in neonates with sepsis 17 (31.5%) were Appropriate for Gestational Age and 37 (68.5%) had low birth weight. Thus, the percentage of low birth weight



Figure 2: Doppler ultrasonography – assessment of vertebral artery through the side of the neck

babies was more in neonates with early onset neonatal sepsis

- In the present study, we found there is statistically significant difference in Apgar score at 5 min among neonates with early onset neonatal sepsis [median (interquartile range)- 9 (8-9); min-max = 6-9] and neonates without early onset [median (interquartile range)- 9 (9-9); min-max = 8-9] neonatal sepsis
 - Statistically significant difference is noted between the median values of PSV, EDV, PI and RI of ICA, MCA and VA among neonates with sepsis and neonates without sepsis as *P* value is less than 0.05 The median and the range of PSV, EDV, RI, and PI of neonates with sepsis and of neonates without sepsis of ICA, MCA, and the VA is as shown in [Table 2 and Figures 3-8]
 - The predictive accuracy of measured parameters of ICA, MCA, and VA are as shown in Table 3
 - Among the various parameters measured the diagnostic accuracy was highest for PI in all the vessels
 - Sensitivity of the PI and the EDV of the ICA was 100%
 - The sensitivity of the PSV of the MCA was 100% and the diagnostic accuracy was 98.37% for the PI
 - The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of PI measured in VA was 100%
 - The positive likelihood ratio was highest for PSV of VA, i.e., 71.42
 - The negative likelihood ratio was highest for PSV of ICA, i.e., 0.44.

Discussion

In the present study, significantly lower resistance (PI and RI) and higher peak systolic velocity and end diastolic velocity in all the three major vessels ICA, MCA, and VA have been documented within 72 h of birth in

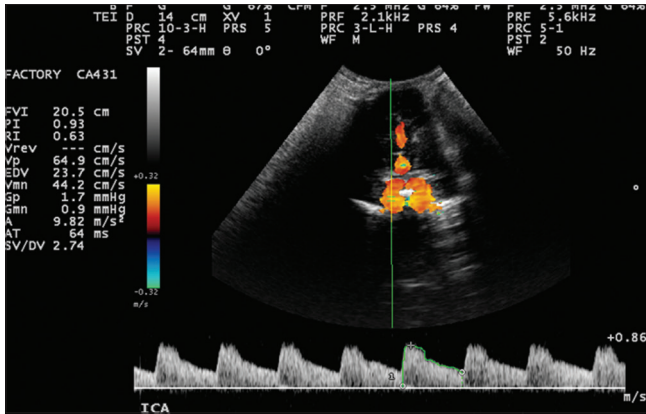


Figure 3: Transcranial Doppler ultrasound examination of internal carotid artery in a neonate with early-onset neonatal sepsis shows PSV-64.9 cm/s, EDV- 23.7 cm/s, RI- 0.63, PI- 0.93

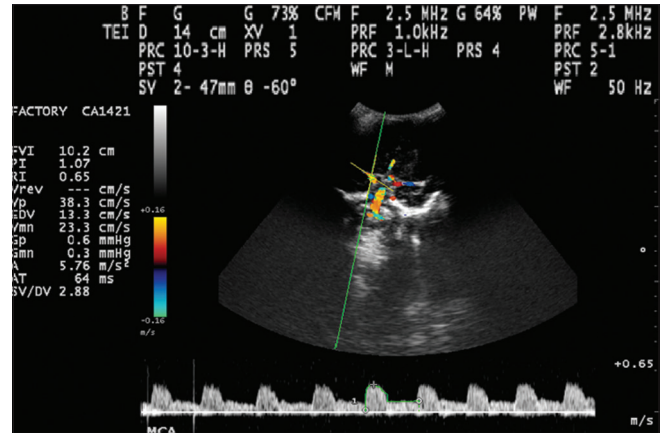


Figure 4: Transcranial Doppler ultrasound examination of middle cerebral artery in a neonate with early onset neonatal sepsis shows PSV- 38.3 cm/s, EDV-13.3 cm/s, RI- 0.65, PI- 1.07

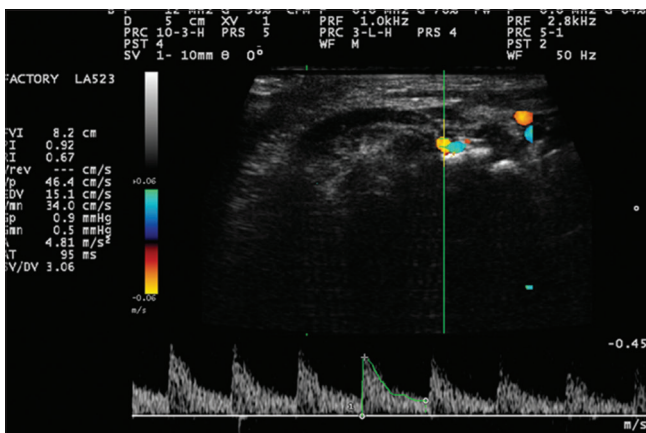


Figure 5: Doppler ultrasound examination of vertebral artery in a neonate with early-onset neonatal sepsis shows PSV- 46.4 cm/s, EDV- 15.1 cm/s, RI- 0.67, PI- 0.92

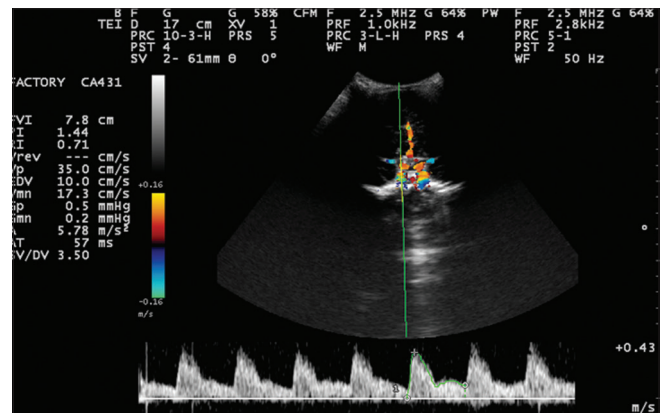


Figure 6: Transcranial Doppler ultrasound examination of internal carotid artery in a neonate without sepsis shows PSV-35 cm/s, EDV- 10 cm/s, RI-0.71, PI-1.44

Table 2: Comparison of cerebral blood flow velocities and Doppler indices measured in the internal carotid artery, middle cerebral artery, vertebral artery, on Doppler ultrasound among neonate without sepsis and neonate with sepsis

| Parameter | Neonate without sepsis [Median (range)] | Neonate with sepsis [Median (range)] | Statistical significance (P) |
|----------------|---|--------------------------------------|------------------------------|
| PSV (cm/s) ICA | 35.40 (27.5-45.0) | 54.00 (38.00-70.00) | 0.00 |
| EDV (cm/s) ICA | 7.60 (2.40-12.30) | 18.36 (8.64-31.4) | 0.00 |
| RI ICA | 0.80 (0.70-0.92) | 0.66 (0.50-0.84) | 0.00 |
| PI ICA | 1.4 (1.20-1.80) | 1.00 (0.60-1.24) | 0.00 |
| PSV (cm/s) MCA | 25.00 (17.00-33.3) | 45.00 (31.8-55.8) | 0.00 |
| EDV (cm/s) MCA | 5.42 (3.15-24.00) | 16.50 (7.60-24.00) | 0.00 |
| RI MCA | 0.79 (0.70-0.86) | 0.70 (0.40-0.82) | 0.00 |
| PI MCA | 1.35 (1.00-1.67) | 1.00 (0.55-1.20) | 0.00 |
| PSV (cm/s) VA | 21.00 (12.00-30.00) | 40.00 (30.00-55.00) | 0.00 |
| EDV (cm/s) VA | 3.60 (1.40-7.00) | 9.78 (4.10-19.20) | 0.00 |
| RI VA | 0.82 (0.70-0.92) | 0.73 (0.54-0.90) | 0.00 |
| PI VA | 1.51 (1.24-2.10) | 1.00 (0.89-1.20) | 0.00 |

neonates with EONS. This indicates a generalized increase in the CBF as an early response to sepsis with a decrease

in the blood flow resistance. As the earliest signs of sepsis are often subtle and nonspecific, a high index of suspicion is needed for early diagnosis.^[9]

In our study, we have examined the neonates within 72 h of birth as and when they presented with features of EONS as well as neonates without sepsis taken as controls.

Due to inflammatory challenges of chorioamnionitis, there is activation of the fetal immune system which is known as fetal inflammatory response syndrome (FIRS). FIRS is initially subclinical. Amplification of the inflammatory response in neonates after birth known as systemic inflammatory response syndrome (SIRS) due to chorioamnionitis is clinically diagnosed as EONS.^[10]

The pathophysiology of sepsis at the cellular and molecular level is unknown. Studies have stated that there occurs impairment of cerebral autoregulation due to cytokine response and lead to cerebral ischemia or overperfusion which is responsible for perinatal white matter injury and cerebral hemorrhage. Damage to blood-brain barrier (BBB)

Table 3: Predictive accuracy of different parameters of cerebral blood flow velocity in the internal carotid artery, middle cerebral artery, and vertebral artery

| Parameter | Area under the curve (AUC) | Cut-off | Sensitivity | Specificity | Positive predictive value | Negative predictive value | Diagnostic accuracy (%) | Likelihood ratio (LR) + | LR_ |
|-----------|----------------------------|---------|-------------|-------------|---------------------------|---------------------------|-------------------------|-------------------------|--------|
| PSV ICA | 0.967 | ≥ 39.5 | 98.1 | 68.1 | 70.7 | 97.9 | 81.30 | 3.07 | 0.44 |
| EDV ICA | 0.988 | ≥ 8.52 | 100 | 65.2 | 69.2 | 100 | 88.48 | 2.873 | -0.533 |
| RI ICA | 0.945 | ≤ 0.73 | 94.4 | 87 | 85 | 95.2 | 90.4 | 7.261 | -0.085 |
| PI ICA | 0.998 | ≤ 1.25 | 100 | 95.7 | 94.7 | 100 | 97.5 | 23.25 | -0.04 |
| PSV MCA | 0.994 | ≥ 31.4 | 100 | 91.3 | 90 | 100 | 95.12 | 11.49 | -0.095 |
| EDV MCA | 0.982 | ≥ 7.64 | 98.1 | 88.4 | 86.9 | 98.4 | 92.6 | 8.456 | -0.109 |
| RI MCA | 0.936 | ≤ 0.76 | 92.6 | 65.2 | 67.6 | 91.8 | 77.23 | 2.66 | -0.420 |
| PI MCA | 0.995 | ≤ 1.15 | 98.1 | 98.6 | 98.1 | 98.6 | 98.37 | 70.071 | 0.005 |
| PSV VA | 0.999 | ≥ 29 | 100 | 98.6 | 98.2 | 100 | 99.18 | 71.42 | 0 |
| EDV VA | 0.969 | ≥ 4.36 | 96.3 | 72.5 | 73.2 | 96.2 | 82.92 | 3.501 | -0.328 |
| RI VA | 0.802 | ≤ 0.80 | 81.5 | 66.7 | 65.7 | 82.1 | 73.17 | 2.44 | -0.221 |
| PI VA | 1.000 | ≤ 1.22 | 100 | 100 | 100 | 100 | 100 | | 0 |

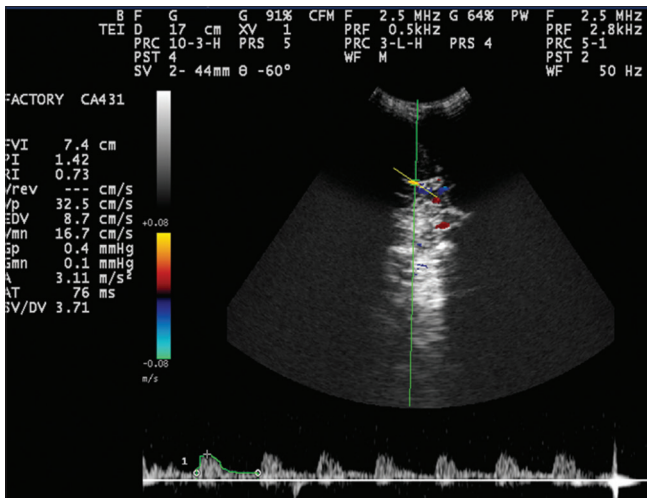


Figure 7: Transcranial Doppler ultrasound examination of middle cerebral artery in a neonate without early-onset neonatal sepsis shows PSV-32.5 cm/s, EDV- 8.7 cm/s, RI- 0.73, PI- 1.42

results in its increased permeability with the transfer of cytokines across the BBB with the direct inflammatory effects of free radicals, oxidative stress, and cytokines on glial cells.^[11-14]

It has also been shown that astrocytes and microglia are capable of producing proinflammatory cytokines during inflammation which can modify the re-uptake of glutamate and stimulate the release of free radicals or induce local production of nitric oxide which is a potent vasodilator.^[15-19]

As there has been a substantial improvement in the antenatal, perinatal care there has been an increase in the survival of the premature and the low-birth weight babies. Changes in CBFV may have a key role in perinatal brain damage, and both acute and long-term morbidity may be closely related to rapid vascular changes during the early hours of life.^[6]

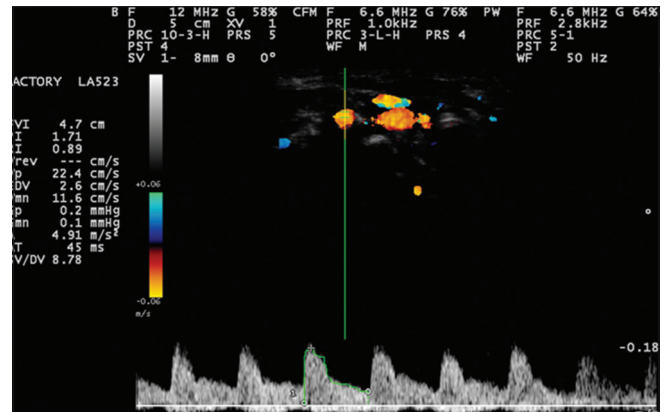


Figure 8: Doppler ultrasound examination of vertebral artery in a neonate without early onset neonatal sepsis shows PSV-22.4 cm/s, EDV-2.6 cm/s, RI- 0.89, PI- 1.71

We measured the parameters of the vessels on either side as there are studies which have shown that there is no significant difference in the values on both sides.^[6,7,20]

Our results agreed with the study conducted by Sriparna Basu *et al.* that detected significantly lower resistance, vasodilatation, and higher peak systolic velocity in the three major cerebral vessels (ICA, MCA, and VA) indicating generalized increase in CBF as an early response to sepsis.^[6]

Koch *et al.* also proved that their chorioamnionitis full terms had decreased resistance in most of the major cerebral vessels compared with controls.^[21]

Lower resistance and increased peak systolic velocity in neonates with EONS was also stated by Rania Hashem *et al.* by evaluating the ACA and MCA at day 3 of life by transcranial Doppler^[4] and by EL Shimmy^[3] *et al.* who concluded that CBF and cord blood neuron-specific enolase were elevated in the neonates with EONS.

Among all the parameters studied in ICA, the sensitivity of pulsatility index was highest in the present study with sensitivity of 100% and with a diagnostic accuracy of 97.5%, whereas for MCA the diagnostic accuracy was highest for pulsatility index (98.37%) and the sensitivity was highest for peak systolic velocity (100%). The pulsatility index measured in vertebral artery had 100% sensitivity and diagnostic accuracy.

Blood culture is considered to be the gold standard for the diagnosis of neonatal sepsis.^[9] In our study, eight (14.8%) neonates had a positive blood culture.

Certain differences can be observed in the measurements of various parameters of the ICA, MCA, and VA among neonates with and without EONS in the different studies. These differences can be attributed to the time of performance of the Doppler measurements and the number of culture-positive cases which were different in all the studies.

It has been documented that there occurs increase in the CBF before the clinical appearance of the frank features of sepsis meaning that the inflammatory process first affected the cerebral circulation before it could affect any other body system, thereby further making the role of transcranial Doppler in assessment of EONS more important such that CBF can be used as an early marker of SIRS and to identify the neonates who are going to develop EONS.

There are contradictory reports regarding evidence of effect of sepsis on the CBF. Some state that there occurs vasodilatation and increased CBF,^[22-25] whereas others have demonstrated decreased CBFV along with higher PI in patients with sepsis.^[26-28] Reduced CBF is ascribed to the vasoconstriction of the resistance arterioles.^[28] Increased PI, a parameter for compliance of the vascular bed suggesting cerebral edema or venous congestion, has been found to correlate with poor neurological outcome.^[29]

Among the various demographic parameters and the clinical data, we found that the preterm and low-birth weight neonates were affected more as compared to term which are also the risk factors for EONS.^[30,31] Our study reveals male neonates to be more vulnerable to develop EONS as compared to females which was similar with the study by Basu *et al.*^[6] Studies have revealed that term male infants have higher incidence of sepsis than term female infants.^[31]

There are conflicting reports regarding the significance of low Apgar score at 5 min as risk factor in development of neonatal sepsis. In our study, we found statistically significant difference in Apgar score at 5 min among neonates with EONS and neonates without EONS. However in the study conducted by Basu *et al.* there was

no statistically significant difference in Apgar score at 5 min among neonates with EONS and neonates without EONS.^[6] However according to Kari Simonsen, low Apgar scores (score of 6 at 5 min) is a risk factor for EONS.^[2]

Our study was cross-sectional with single-time assessment of CBFV and therefore could not assess the fluctuation of CBFV over a period of time and correlate it with the adverse effect as studies have shown that children who developed neonatal sepsis were three times more likely to have neuromotor and cognitive development alterations at 12 months of corrected age.^[21] Therefore, the single-time assessment of the CBF velocity was one of the limitations of our study.

Conclusion

Our study shows that the cerebral hemodynamics in neonates with EONS is altered with an increase in the CBF and a decrease in the resistance.

Assessment of CBF at early hours of birth by Doppler ultrasound examination can be adopted as a bedside, noninvasive investigation with immediate diagnostic, and late prognostic significance. It can be considered as one of the complementary investigation to the various laboratory test that requires sufficient amount of blood sample requiring invasive procedure, which can be avoided by noninvasive Doppler examination. Apart from being noninvasive it is portable, uses nonionizing radiation, accurate, cost-effective, and allows simultaneous examination of cranial structures and measurement of absolute CBFV with the added benefit of serial and repetitive examination with early institution of treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) parents/guardian has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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