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Detection of Neurological Complications by Cranial Ultrasound in Neonatal Sepsis: A Cross-sectional Study

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Abstract

Neonates with sepsis are at risk of neurological complications. Cranial ultrasound (CUS) has been widely used in neonates for early detection of these intra-cranial abnormalities. It is a convenient, non-invasive, safe with no radiation exposure and quick imaging technique to visualize the neonatal brain parenchyma and ventricular system. To detect neurological complications in neonates with sepsis by CUS. This cross-sectional study was conducted in Department of Neonatology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from June 2019 to September 2020. Inborn neonates with sepsis and inborn preterm neonates without sepsis satisfying the inclusion and exclusion criteria who were admitted into neonatal intensive care unit (NICU), BSMMU during study period were the study population. Among 110 neonates, 75 neonates with sepsis and 35 pre-term neonates without sepsis were assessed for eligibility. Among these 75 septic neonates 19 were excluded. Finally,56 septic neonates were analyzed. Out of them 21 (37.5%) neonates had abnormal neurological findings in CUS. Distribution of abnormal CUS findings were intraventricular hemorrhage (33%), features of meningitis (24%), hydrocephalus (14%), prominent lateral and third ventricles (10%), intracerebral hemorrhage (5%), features of ventriculitis (5%). Among 35 non-septic pre-term neonates, 5 were excluded due to guardians did not give consent to perform CUS. So, 30 non-septic pre-term neonates were analyzed, among them, 2 neonates (7%) had feature of intraventricular hemorrhage in CUS. Septic neonates with abnormal CUS findings, most of the neonates were male (71%), gestational age (34.57±3.043) weeks and birth weight (1985.2±684.132) gm. In babies with abnormal CUS, convulsion

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was significantly associated (p value 0.01). This study showed proven sepsis was significantly associated with abnormal CUS findings. The abnormal CUS findings in newborn with sepsis was 37.5%. So CUS may be an important investigatory modality in NICU for early detection of intracranial complications.

Keywords: Neonatal sepsis, cranial ultrasound, neurological complications

Introduction

Sepsis is the most common cause of neonatal mortality that causes 30-50% of all neonatal deaths annually in developing countries.[1] It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis-related causes.[2] The most commonly implicated bacteria are *Staphylococcus aureus*, coagulase negative staphylococci (CONS), *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella* species, and Group B *Streptococcus*.[3] In the early-onset type, the patient may have a history of fetal distress, including fetal tachycardia during the peripartum period. Soon after delivery, other clinical signs, such as meconium-stained amniotic fluid and low Apgar scores, may be present. Vital sign derangements include both hypothermia and fever, tachycardia or bradycardia, signs of poor perfusion, and signs of respiratory distress, which are common in neonatal sepsis. Gastrointestinal signs include decreased feeding, vomiting, jaundice, abdominal distension, and hepatosplenomegaly, while neurological signs include lethargy, seizures, irregular respiration, and high-pitched cry, which may present in sepsis. Sepsis often presents as neonatal meningitis, which is inflammatory response of cerebrospinal fluid (CSF) and pia-arachnoid infection, and other neurological complications, including intraventricular hemorrhage, hydrocephalus, encephalomalacia, cerebral infarction, subdural empyema, ventriculitis, and abscess. The outcome of sepsis with central nervous system involvement should be considered. Various cranial sonographic findings, including echogenic and widened sulci, ventriculomegaly, ventriculitis, hydrocephalus, extra-axial fluid collections, cerebritis, and brain abscesses, may be observed in sepsis.[4]

Cranial ultrasound (CUS) has become an essential diagnostic tool in modern neonatology for observing normal anatomy and pathological changes in neonates. In the neonate, many sutures and fontanels are still open, and these can be used as acoustic windows to "look" into the brain.[5]

In Bangladesh, the neonatal health status is still not satisfactory, despite recent advances in biophysical and biochemical monitoring of the fetus during labor and delivery. One of the major causes of neonatal death is sepsis. Sepsis with abnormal ultrasonographic findings is associated with an increased risk of death and neuro-developmental disability in the future.

This objective CUS was performed to assess intracranial abnormalities in newborn babies with sepsis, and prompt action can be taken in time as it is a non-invasive, portable, real multi-planner imaging modality.

Highlights

- Sepsis is the commonest cause of neonatal mortality and is responsible for 30-50% of total neonatal deaths each year in developing countries.
- It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis.
- The most commonly implicated bacteria include *Staphylococcus aureus*, coagulase negative staphylococci, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella* species, and Group B *Streptococcus*.
- Cranial ultrasound has become an essential diagnostic tool in modern neonatology for depicting normal anatomy and pathological changes in neonatal brain.
- It can easily be performed, cost-effective, no risk of radiation exposure, it can be repeated whenever needed, enabling visualization of ongoing brain maturation and the evolution of lesions and it can be performed without sedation.

Material and Method

This cross-sectional study was conducted at the Department of Neonatology Bangabandhu Sheikh Mujib Medical University (BSMMU) from June 2019 to September 2020. Inborn neonates with sepsis and inborn pre-term neonates without sepsis satisfying the inclusion and exclusion criteria who were admitted to the neonatal intensive care unit (NICU), BSMMU during the study period were the study population. Thorough histories of these newborns, including demographic and socioeconomic information, clinical features, sepsis workup including blood culture, and CSF study reports, were enrolled in the data sheet. After obtaining written informed consent from the parents/guardians, CUS was performed in all enrolled neonates. CUS was performed using a Philips Affiniti 30 ultrasound machine (manufactured in USA). Sonologists performed a 2D ultrasonogram of the brain, real time B mode gray scale brain scan was performed through anterior fontanels (both sagittal and coronal view) with 3.5 to 12 MHz transducer. Normal blood flow within the brain parenchyma was seen by color doppler application. All findings were included in the data sheet.

Inclusion Criteria

- Inborn neonates with probable or proven sepsis.
- Inborn pre-term neonates without sepsis.

Exclusion Criteria

- Known case of congenital anomaly or infection.
- Unwillingness to participate the study.

Ethical Consideration

Minimum physical, psychological, social, and legal risk during history, physical examination and investigations. Proper safety measures were taken in every step of the study. Only the researcher was allowed to access the collected data. Ethical clearance was obtained from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (decision no: BSMMU/2019/7052, date: 25.06.2019) for the current study. According to the Declaration of Helsinki 1964, parents of all neonates were informed about the study design. The underlying hypothesis and the right of the participants to withdraw from the study at any time and for any reason. Informed written consent was obtained from parents or guardians who voluntarily provided consent to participate in this study.

The Following Ethical Issues were Addressed

- Strict confidentiality and security of patient data were maintained.
- The presentation of data and information related to patient were documented anonymously.
- The data analysis was completed for subjects who completed the study according to the protocol after recruitment of subjects with valid informed consent.
- There were no additional risks or safety concerns due to the research process for either the patient or researcher.
- There were no potential conflicts of interest in this study and the entire academic research project.
- Financial issues related to this research were managed by the principal investigator when parents did not make an effort.

Statistical Analysis

After collection, data were entered into a computer and edited, analyzed, and plotted in graphs and tables. Data were analyzed using the Statistical Package for Social Sciences version 20. All data were calculated and presented as proportions. All quantitative variables (between septic neonates with abnormal and normal CUS findings) were compared using the independent t-test, and categorical variables were compared using the chi-squared test. A p value <0.05 was considered significant.

Results

During the study period, 110 neonates were assessed, among whom 75 neonates were septic and 35 preterm neonates were non-septic. Of the 75 septic neonates, 19 were excluded, so 56 neonates were analyzed. Out of them 21 (37.5%) neonates had abnormal neurological findings in CUS. Among 56 neonates, 42 were preterm with sepsis. Of 35 nonseptic pre-term neonates, 5 were excluded because the guardians did not give consent to perform CUS; thus, 30 nonseptic preterm neonates were analyzed.

The baseline characteristics of the infants are presented in **Table 1**. According to gestational age range 28-<34 weeks reflected (52%) more predominance, gender distribution reflected male predominance (63%) and common mode of delivery was lower segment cesarean section (80%) (**Table 1**).

Data are presented as number (percentage) unless otherwise indicated. Among 56 neonates with sepsis, the common maternal characteristics were irregular antenatal care 36 (64%), pregnancy induced hypertension 32 (57%).

Among 56 neonates, regarding age at onset of sepsis, early onset sepsis 42 (75%) and late onset sepsis 14 (25%) (**Figure 1**). Among 56 neonates with sepsis, 22 (39%) had proven sepsis and 34 (61%) had proven sepsis and probable sepsis (**Figure 2**). Among 22 cases of proven sepsis, 12 neonates had early-onset neonatal sepsis (EONS) (**Figure 3**). Regarding the septic screening result, total count of white blood counts was <5000/cumm in 10 (18%) neonates and >25000/cumm in 14 (25%) neonates. Twelve (21%) neonates had an absolute neutrophil count <1500/cumm, IT ratio was >0.2 in 40 (71%) neonates, positive C-reactive protein (CRP) was found in 39 (70%) and platelet count <150000 in 42 (75%) neonates.

Table 1.
Baseline characteristics of the study group, n=56

Characteristics	Frequency	Percentage
Gestational age		
28-<34 weeks	29	52
34-<37 weeks	13	23
≥37 weeks	14	25
Sex		
Male	35	63
Female	21	37
Mode of delivery		
LUCS	45	80
NVD	11	20

Data are presented as number (percentage) unless otherwise indicated, LUCS; Lower segment caesarean section, NVD; Normal vaginal delivery

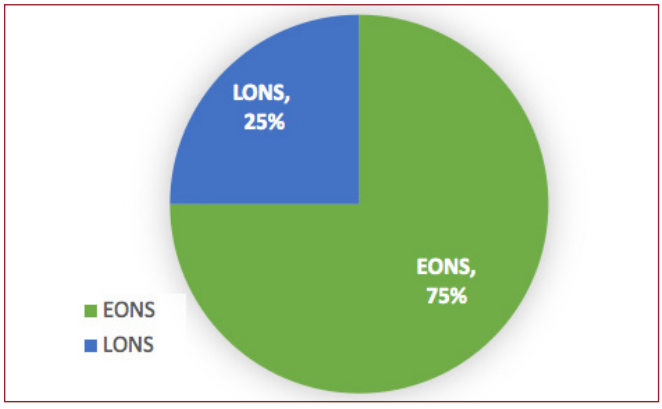

Figure 1. Distribution of age of onset of sepsis among study group, n=56
EONS; Early onset neonatal sepsis, LONS; Late onset neonatal sepsis

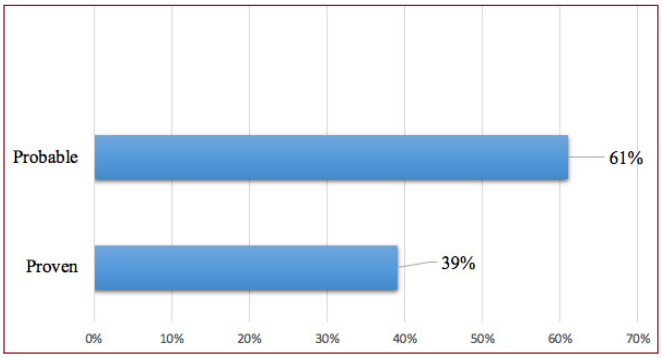

Figure 2. Types of sepsis of study group according to culture, n=56

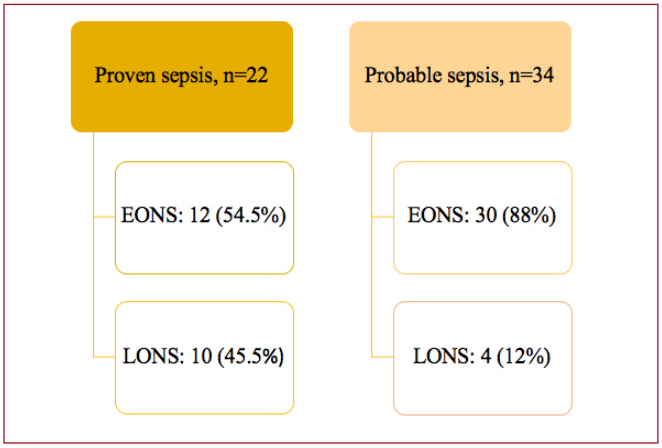

Figure 3. Flow chart of EONS and LONS between proven and probable sepsis, n=56

EONS; Early onset neonatal sepsis, LONS; Late onset neonatal sepsis

Among the 22 culture-positive neonates, *Acinetobacter* was found in 10 (45.5%) cases, *Klebsiella* in 7 (31.8%) neonates, *Salmonella* in 2 (9.1%), *Escherichia coli* in 2 (9.1%), and *Pseudomonas* in 1 (4.5%).

Out of 56, 46 neonates underwent lumber puncture among them 14 (30%) had positive CSF findings.

Among the 56 neonates, 21 (37.50%) had abnormal ultrasound findings (**Figure 4**). Among the abnormal findings of CUS, intraventricular hemorrhage (IVH) 7 (33%), most common (**Table 2**). Among 56 neonates with sepsis, the most common abnormal CUS finding was IVH in pre-term than term neonates (**Table 3**).

Among 42 pre-term neonates with sepsis, 6 (14%) and 30 pre-term neonates without sepsis, 2 (6.7%) had IVH in CUS finding. Among 42 pre-term neonates with sepsis, 1 (2.4%) had periventricular leukomalacia (PVL), whereas 30 preterm neonates without sepsis did not have PVL on CUS. Among the 21 neonates with abnormal CUS

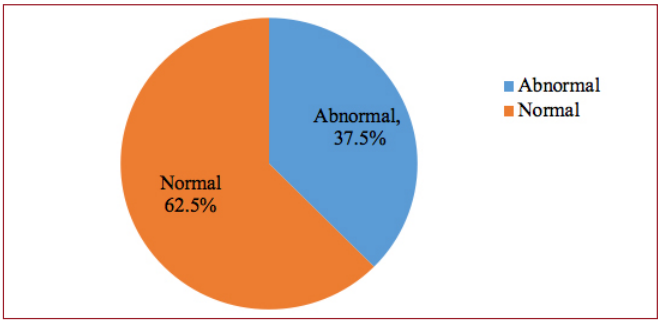

Figure 4. Distribution of CUS results among study neonates, n=56

CUS; Cranial ultrasound

Table 2.
Abnormal CUS findings, n=21

Abnormal ultrasound findings	Frequency	Percentage
Prominent echogenic sulci and gyri with increased vascularity of brain parenchyma-suggestive meningitis	5	24
Echogenic area with ventricular dilatation-suggestive of IVH	7	33
Hydrocephalus	3	14
Intracerebral hemorrhage	1	5
Hyperechoic periventricular area suggestive PVL	1	5
Increased periventricular echogenicity with irregular margin suggestive ventriculitis	1	5
Persistent cavum septum pellucidum	1	5
Prominent both lateral and third ventricles	2	10

IVH; Intraventricular hemorrhage, PVL; Periventricular leukomalacia, CUS; Cranial ultrasound

Table 3.
Comparison of abnormal CUS findings between pre-term and term neonates with sepsis, n=56

Abnormal CUS findings	Pre-term neonates with sepsis, n=42	Term neonates with sepsis, n=14	P value
IVH	6 (14%)	1 (7.1%)	0.484
Features of meningitis	2 (4.8%)	3 (21.4%)	0.058
Hydrocephalus	1 (2.4%)	2 (14.2%)	0.732
Intracerebral hemorrhage	1 (2.4%)	0	0.560
PVL	1 (2.4%)	0	0.560
Prominent ventricles	2 (4.8%)	0	0.406
Ventriculitis	1 (2.4%)	0	0.08
Persistent cavum septum pellucidum	1 (2.4%)	0	0.560

Statistical test; Chi-square test, IVH; Intraventricular hemorrhage, PVL; Periventricular leukomalacia, CUS; Cranial ultrasound

Table 4.
Maternal and neonatal characteristics in septic neonates with abnormal and normal CUS findings, n=56

Characteristics	Sepsis with abnormal CUS, n=21	Sepsis with normal CUS, n=35	P value
Maternal			
HTN	15 (71%)	21 (60%)	0.39
GDM	4 (19%)	3 (8.6%)	0.25
PROM	7 (33%)	19 (54.3%)	0.13
Neonatal			
Lethargy	12 (57%)	22 (63%)	0.67
Respiratory distress	15 (71%)	18 (51.4%)	0.14
Convulsion	8 (38%)	3 (8.6%)	**0.01**
Temperature instability	4 (19%)	8 (23%)	0.74
Feeding problem	6 (28.6%)	6 (17%)	0.31

Statistical test; Chi-square test, CUS; Cranial ultrasound, HTN; Hypertension, GDM; Gestational diabetes mellitus, PROM; Prelabor rupture of membranes

Table 5.
Abnormal CUS findings among neonates with probable and proven sepsis, n=21

Abnormal CUS findings	Probable sepsis, n=7	Proven sepsis, n=14	P value
IVH	1 (14.3%)	6 (43%)	**<0.001**
Features of meningitis	2 (28.5%)	3 (21.4%)	0.051
Hydrocephalus	2 (28.5%)	1 (7.1%)	0.828
Intracerebral hemorrhage	1 (14.3%)	0	0.417
Prominent ventricles	1 (14.3%)	1 (7.1%)	0.752
Ventriculitis	0	1 (7.1%)	0.210
Periventricular leukomalacia	1 (14.3%)	0	0.417
Persistent cavum septum pellucidum	1 (14.3%)	0	0.417

Statistical test; Chi-square test, CUS; Cranial ultrasound, IVH; Intraventricular hemorrhage

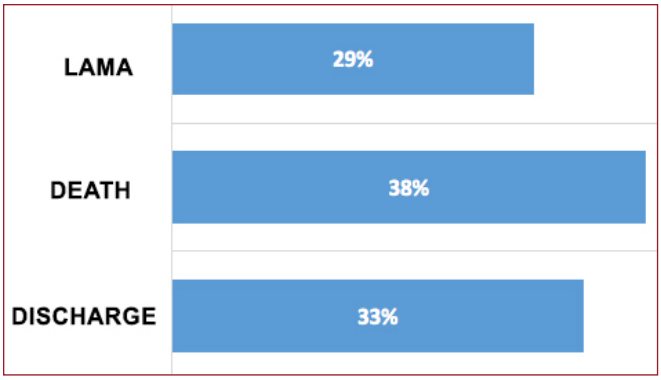

Figure 5. Outcome of the neonates with abnormal CUS, n=21
CUS; Cranial ultrasound, LAMA; Leave against medical advice

findings, those with low birth weight (1500-2499) gm and low gestational age (28-<34) weeks were more.

When comparing babies with abnormal CUS findings with septic babies without abnormalities, birth weight and gestational age were not significantly different. Comparison of septic neonates with abnormal and normal CUS findings showed that proven sepsis was found more frequently in septic neonates with abnormal CUS findings, which was statistically significant. The number of male babies, EONS, and negative CSF were higher in the abnormal CUS group, but the difference was not statistically significant. Comparison of septic neonates with abnormal and normal CUS findings and maternal conditions [hypertension, gestational diabetes mellitus (GDM), pre-labor rupture of membranes] were not statistically significant between the two groups. In terms of neonatal characteristics, convulsions were found more frequently in septic neonates with abnormal CUS, which was statistically significant (**Table 4**).

Abnormal CUS findings among neonates with probable and proven sepsis, IVH was more common in proven sepsis which was statistically significant (p<0.001) (**Table 5**). Among 21 neonates with abnormal CUS findings, 11 neonates (61%) stayed in hospital for (7-21) days. Among the 21 neonates with abnormal ultrasound 8 neonates (38%) were died, 6 neonates (29%) were taken leave against medical advice (LAMA) and 7 neonates (33%) were discharged with advice (**Figure 5**).

Discussion

Sepsis is a clinical syndrome of multiple involvement. Sepsis with neurological involvement is associated with increased morbidity and mortality. Probable sepsis as well as proven both can cause neurological complications. CUS is an important tool for early detection of intracranial complications and neurological outcomes in newborns with sepsis.

This cross-sectional study was conducted with the objective of identifying neurological complications of neonatal sepsis detected by CUS. In this study, 56 neonates with sepsis were analyzed, among whom abnormal CUS findings (approximately 37.5%). In one study, abnormal CUS findings were observed in approximately 38%.[6] In this study, premature babies mostly (28-<34) weeks and low birth weight babies

(1500-2499) gm were more in abnormal CUS group. Birth weight and gestational age between septic neonates with abnormal and normal CUS findings were approximately similar, p value not significant.

According to a previous report,[7] neurological complications on CUS had a high percentage (63.9%) in late pre-term (33-36) weeks. Among 56 neonates with sepsis, the most common abnormal CUS finding was IVH in pre-term than term neonates, but the p value was not significant (**Table 3**).

Among 42 pre-term neonates with sepsis, 6 (14%) and 30 pre-term neonates without sepsis, 2 (6.7%) had IVH in CUS finding. Among 42 pre-term neonates with sepsis, 1 (2.4%) had PVL, whereas 30 preterm neonates without sepsis did not. No neonate had PVL in CUS, but the p value was not significant. In one study, late-onset sepsis was more than early onset sepsis in terms of the cause of abnormal CUS.[8] In the present study, early-onset sepsis was more common in septic neonates with abnormal CUS, but the difference was not statistically significant.

In this study, proven sepsis was significantly more common in septic neonates with abnormal CUS, but a positive CSF study was not significant. In, proven sepsis was reported at approximately 73%, but in this study probable sepsis were more around 67%.[4] According to, newborn infants affected by group-B *Streptococcus*, *E. coli*, *Klebsiella*, *Listeria*, and *Citrobacter* have more devastating consequences in septic newborns.[9] In, *Staphylococcus aureus* and *E. coli* were shown to be coagulase-negative *Staphylococcus* responsible for abnormal neurosonogram findings in newborns with sepsis.[4] In, group B-*Streptococcus*, *E. coli*, *Klebsiella*, *Salmonella*, *Listeria* monocytogenes, and pseudomonas were common. In this study, *Acinetobacter*, *Klebsiella*, *Salmonella*, *E. coli*, and *Pseudomonas* were detected in blood cultures.[7]

This study showed that maternal hypertension, GDM, and premature rupture of membrane >18 h were common maternal characteristics in both septic neonates with abnormal and normal CUS groups (**Table 4**).

According to, maternal pre-eclampsia, premature prolonged rupture of membrane, maternal chorioamnionitis were common maternal characteristics.[4]

In this study, lethargy, signs of respiratory distress, convulsions, temperature instability, and poor feeding were common clinical presentations of septic neonates, and among these, 8 septic neonates with abnormal CUS had convulsions rather than 3 neonates with normal CUS, which was statistically significant (**Table 4**). In, respiratory distress, disseminated intravascular coagulation, coagulopathy, and gastrointestinal bleeding were common clinical manifestations of sepsis in newborns.[7]

In, a significant correlation was observed between a positive CRP level and a low platelet count with abnormal CUS findings. In this study, positive CRP levels, low platelet counts, and significant IT ratio were more common in septic neonates with abnormal CUS.[6]

In this study, abnormal CUS findings were increased periventricular echogenicity (ventriculitis), increased vascularity of brain parenchyma with prominent echogenic sulci and gyri (meningitis), intraventricular hemorrhage, prominent ventricles or ventricular dilatation (hydrocephalus), and hyperechoic areas in a distinctive fashion in the periventriculararea (periventricular leukomalacia) (**Table 2**). In pre-term babies, intraventricular hemorrhage and increased vascularity of brain parenchyma suggestive of meningitis were more common findings (**Table 3**).Features of meningitis and IVH in CUS findings were more common in proven sepsis, and IVH was significantly more common in proven sepsis (**Table 5**). In one study, IVH was a more common CUS finding in preterm babies.[4]

Among 21 neonates with abnormal CUS findings, 61% had a hospital stay (7-21) days, 28% had >28 days. Regarding the outcome of these babies with abnormal CUS findings, 38% died, 29% took LAMA, and 33% were discharged with advice.

Sepsis is a more common condition in the NICU, and sepsis-related neurological complications may occur in patients with probable and proven sepsis. Undetected and untreated neurological complications may cause neurodevelopmental sequelae. CUS can detect intracranial lesions earlier. After the detection of abnormalities, appropriate treatment duration and prompt management can reduce neurodevelopmental deficit in septic neonates.

Study Limitation

It was not possible to perform all CUS by the same radiologist. Unavailability of the bed side CUS in NICU, BSMMU. Scarcity of appropriate probe for newborn CUS in radiology department in BSMMU.

Conclusion

Abnormal CUS findings like IVH, features of meningitis, ventriculitis, hydrocephalus, and PVL were found in both preterm and term septic neonates. IVH was significantly more common in patients with proven sepsis.

Ethics

Ethical Approval: Ethical clearance was obtained from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (decision no: BSMMU/2019/7052, date: 25.06.2019) for the current study.

Informed Consent: Informed written consent was obtained from parents or guardians who voluntarily provided consent to participate in this study.

Footnotes

Author Contributions: Hossain N: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Rumman R: Data Collection or Processing, Literature Search.; Alam MS: Analysis or Interpretation, Literature Search.; Jahan A: Surgical and Medical Practices.; Mahmud R: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation.; Parajuli S: Data Collection or Processing,

Analysis or Interpretation.; Shahidullah M: Surgical and Medical Practices, Design, Analysis or Interpretation.; Mannan A: Data Collection or Processing, Analysis or Interpretation, Literature Search.

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