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Original Research Article

Evaluation of hypoglycemic status and causative factors in neonatal sepsis

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ABSTRACT

Background: Very few studies have been reported on hypoglycemic status, hematological parameters and causative organisms of neonatal sepsis in different regions of Bangladesh. Hence, present study was conducted in the Chittagong city of Bangladesh.
Methods: The study was conducted on 106 neonates (0 to 28 days of age) in Chattagam Maa-Shishu O General Hospital, Bangladesh. The questionnaire was developed to get relevant information of the neonates. Blood from neonates were subjected to routine investigations like blood glucose, CRP, hematological parameters, blood culture and bacterial identification.
Results: Among 106 neonates with sepsis, 68 presented early onset neonatal sepsis (EONS) and 38 presented late onset neonatal sepsis (LONS). Fifty-one neonates had low birth weight (2500 g or less), 18 had very low birth weight (1500 g or less) and 22 were preterm. The most prevalent clinical features were reluctant to feed (56), hyperthermia (31) and hypotonia (22). Thirty-three neonates had neutropenia (<54%) and 62 had higher neutrophil count (>62%). Biochemical analysis showed 52 had higher C-reactive protein levels. Investigation of hypoglycemic status revealed that there were different types of neonatal sepsis, i.e. 77 neonates were hypoglycemic (<45 gm/dl), and among them EONS and LONS were 59 and 18, respectively. Thirty-three neonates had positive blood culture for bacteria. Among them, *Klebsiella* spp. accounted for 10 of the total isolates followed by *Acinetobacter* spp. 8. The Gram-positive and negative bacteria were found in 7 and 26, respectively.
Conclusions: Hypoglycemia was associated with neonatal sepsis as an exacerbating factor.

Keywords: Chittagong, Hypoglycemia, Neonates, Sepsis

INTRODUCTION

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection accompanying bacteremia occurring in the first month of newborn. It includes various infections such as meningitis, pneumonia, osteomyelitis arthritis, and urinary tract infections and septicemia. Neonatal sepsis is an important cause of death among infants in developing countries, and accounting 30-50% of total deaths each year.[1] It has classified into either early onset sepsis (EOS) (0-7 day of age) or late onset sepsis (LOS) (7-28 days of age).[2,3] Very few reports differentiate sepsis with early onset (within 24 hours), EOS and LOS.[4,5] EOS is due to vertical transmission during birth, and it involves bacteremia, meningitis and pneumonia. LOS is due to horizontal and /

or vertical infection. Clinical manifestations of LOS are meningitis (30-40%), septic arthritis (5% to 10%), bacteremia (40%), omphalitis and osteomyelitis.

The reported incidence of neonatal sepsis varies from 7 to 38 per 1000 live births in Asia, from 6.5 to 23 per 1000 live births in Africa, and from 3.5 to 8.9 per 1000 live births in South America and the Caribbean.[6-11] By comparison, rates reported in the United States and Australasia range from 1.5 to 3.5 per 1000 for EOS sepsis and up to 6 per 1000 live births for LOS sepsis, a total of 6-9 per 1000 for neonatal sepsis, and 0.3-3 per 1000 live births in Europe.[12-16] A number of organisms are associated with neonatal sepsis such as *Klebsiella pneumoniae*, *Staphylococcus aureus*, Group B *Streptococcus* (GBS), *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter spp* and *Enterobacter spp* etc.[17] Gram-negative bacteria remain to be the major cause of neonatal sepsis in developing countries.[18,19] Increased drug resistances have developed by these organisms over the last two decades and become a major problem to manage of neonatal sepsis.[20,21] Besides, frequent used of group B *Streptococcus* (GBS) as ethological agent of neonatal sepsis in developed countries, being responsible for high morbidity and death rates.[22]

Recent advances in molecular biology have contributed to the tremendous progress in understanding the pathophysiology of sepsis. Now it is accepted that the features of sepsis are the overwhelming activation of not only pro-inflammatory, but also anti-inflammatory responses, because of vast production of pro-inflammatory and anti-inflammatory mediators.[23-25] Such vast production of mediators triggers many pathological changes in vital organs and systems including metabolic changes.[26]

In neonatal sepsis, hypoglycemia and hyperglycemia are found as common metabolic changes. Hypoglycemia is the common blood glucose abnormality seen early in the course of bacterial sepsis. In general, hypoglycemia can be defined as any plasma glucose levels less than 50 mg/dl with symptoms that are improved with glucose treatment. In pre-terminal sepsis, profound hypoglycemia may occur because of increased tissue uptake of glucose and the failure of hepatic glucose production.[27] Hypothermia may result in hypoglycemia because the infants rapidly deplete body stores of brown fat to maintain heat production. Sepsis-related hypoglycemia is a manifestation of high levels of cytokines including tumor necrosis factor and interleukin-6.

In Bangladesh, very few studies have been reported on the glucose status and causative organisms of neonatal sepsis in the different areas of the country. So, there is still lack of information about the actual conditions of neonatal sepsis in the different area of Bangladesh. To fill the knowledge gap, this study was performed to investigate conditions of neonatal sepsis in the Chittagong area of Bangladesh, and to search ways to reduce the neonatal mortality and morbidity rate. In order to understand the epidemiology of neonatal sepsis, a cross-sectional prospective study was carried out based on investigation of glucose status, hematological parameters and the etiologic agents of neonatal sepsis during the period of September 2011 to July 2012 in the neonatal unit of Chattagram Maa-O-Shishu General Hospital, Chittagong, Bangladesh.

METHODS

The study was conducted during September 2011 to June 2012 on 106 neonates of the neonatal unit of Chattagram Maa-Shishu O General Hospital, Chittagong, Bangladesh. Subjects were collected every day of the week from 9-00 am to 2-00 pm from patients in the pediatric unit who admitted into this hospital with the complaints of one or more clinical signs and symptoms. This study subjects comprised of the following two groups as i) 33 neonates with culture proven sepsis; and ii) 73 neonates with culture unproven sepsis. In all cases of suspected sepsis belonging the age group of 0-28 days. Cases with following items were excluded- i) Stay more than 28 days; ii) Incomplete medical records and self-discharge against medical advice; iii) Local infection at the puncture site; iv) Proteomic profiling, procalcitonin and other molecular diagnosis are excluded in this study; and v) Neonates who don't fulfill the clinical criteria described in literature were excluded from the study. A questionnaire was developed to obtain relevant information of demographic and socio-economic data, and also birth history, past medical history and clinical information.

Estimation of blood glucose

Blood glucose estimation was performed using serum sample with glucose oxidase method. Absorbances of samples and standard against blank were taken at 510 nm by Humalyzer^{TM} 2000 (German).

Complete blood count

Complete blood count was performed by the ABX PENTRA 60^{TM} automated hematology analyzer (Microprocessor controlled) (Horiba, France). Blood counting machines aspirate a very small amount of the specimen through narrow tube. Sensors count the number of cells passing through the tube. Peripheral blood smears were prepared and stained by Wright's stain. White blood cell count, differential count and immature neutrophil count were performed then Immature/ Total neutrophil count (I/T) ratio was calculated.

Blood culture and bacterial identification

Blood culture was incubated aerobically at 37°C and inspected daily for 7 days for presence of visible microbial growth by observing turbidity, haemolysis, gas

production and coagulation of broth. All positive blood cultures were identified by their characteristic appearance on their respective media.

Measurement of CRP

Measurement of CRP was performed by reagents manufacturer instruction (invitrigen). ELISA microwell plate was coated with 100 µl sample (1:4000 dilution) for 2 h, and wash 5 times with washing buffer (Tris). Diluted (1:100) horseradish peroxidase (HRP)-conjugated anti-human C-reactive protein antibody 100 µl was added to each well and incubated for 1 h. After being washed with washing buffer, 100 µl TMB substrate solution was added to each well of the plate and incubate until color develop, then absorbance was taken using ELISA plate reader at 570 nm.

Statistical analysis

Collected data was checked for its completeness and correctness. Editing was done by employing Statistical Package for Social Science (SPSS version 11.5) software package.

RESULTS

A total of 106 admitted neonates (0 to 28 days of age) with suspected sepsis were investigated for bacterial infection. Sixty-eight (64.2%) neonates were with EONS and 38 (35.8%) were LONS. Among the neonates with EONS, 41 (60.3%) were males and 27 (39.7%) were females. Among neonates with LONS, 21 (55.3%) were males and 17 (44.7%) were females (Table1). In terms of socio-economic status, 68 (64.2%) neonates were from lower class and 31 (29.2%) from middle class, indicating that the disease might affect people regardless of their socioeconomic status, while lower class peoples are more susceptible (data not shown).

Of the 106 neonates, 22 (20.8%) were preterm (gestational age less than 37 weeks) and 84 (79.2%) were term (Table 2). Twenty-three (21.7%) delivered by caesarian section/instrument and 83 (78.3%) by vaginal delivery. Approximately, 51 (48%) neonates with sepsis had low birth weight (<2500 g), 18 (17%) had very low birth weight (< 1500 g) (Table 3).

Table 1: Types of sepsis according to gender.

	Provisional diagnosis		Total no. (%)
	EONS no. (%)	LONS no. (%)	
Male	41(60.3)	21(55.3)	62(58.5)
Female	27(39.7)	17(44.7)	44(41.5)
Total	68(64.2)	38(35.8)	106(100)

The clinical features of EONS and LONS were summarized in Figure 1. The most prevalent clinical features were reluctant to feed (56, 52.8%), hyperthermia (31, 29.2%), hypotonia (22. 20.8%), jaundice (18, 17%), respiratory distress (17, 16%) and convulsion (14, 13.2%). Common clinical features observed in both EONS and LONS were hyperthermia, hypothermia, respiratory distress and reluctant to feed.

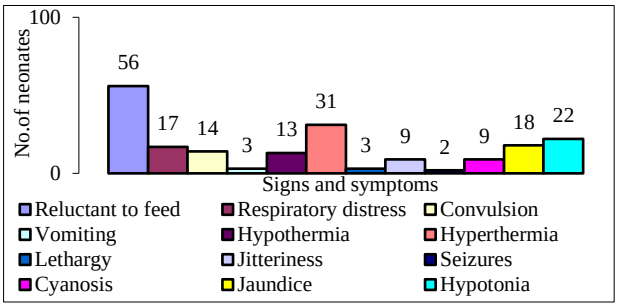

Figure 1: Distribution of neonates according to clinical symptoms.

Table 2: Distribution of neonates according to gestational age.

Gestational age (weeks)	Frequency	%
<37 Weeks (pre-term)	22	20.8
37-42 Weeks (term)	84	79.2
Total	106	100.0

Table 3: Distribution of neonates according to birth weight.

Birth weight	Frequency	%
<1500 gram (VLBW)	18	17
<2500 gram (LBW)	51	48
2500-4000 gram (Normal weight)	37	35
Total	106	100.0

Among the 106 neonates admitted with suspected sepsis, 101 (95.3%) had normal white blood cell count (5000-20,000/cmm), 3 (2.8%) high WBC count (>20,000/cm) and 2 (1.9%) low WBC count (<5000/cm) (Figure 2).

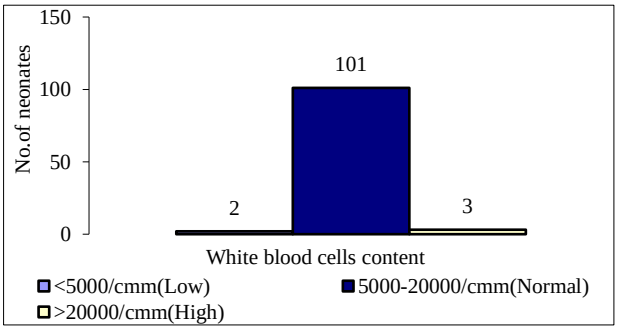

Figure 2: Distribution of neonates according to white blood cells.

Ratios of neutrophils (immature/ total) ≥0.2 and <0.2 were observed in 8 (7.5%) and 98 (92.5%) of peripheral

blood smear examined, respectively (Figure 3). Eleven (10.4%) had normal neutrophils, 33 (31.1%) had neutropenia (<54%), and 62 (58.5) had higher (>62%) neutrophils (Figure 4). Eighty-eight (83%) had higher, and 18 (17%) had normal C-reactive protein levels (Figure 5).

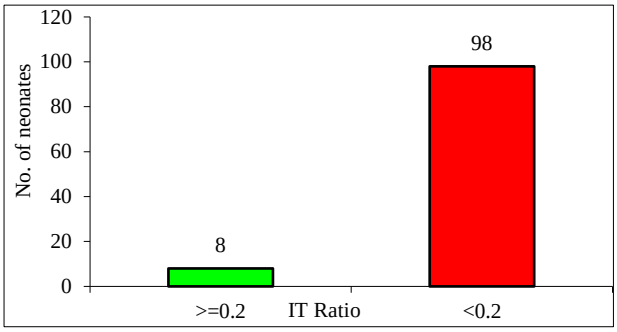

Figure 3: Distribution of neonates according to IT ratio (immature/ total neutrophils).

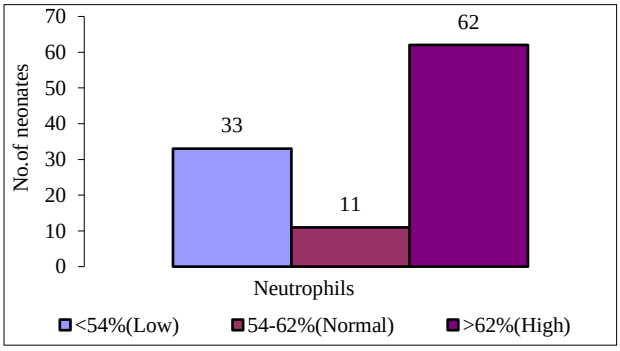

Figure 4: Distribution based on neutrophils.

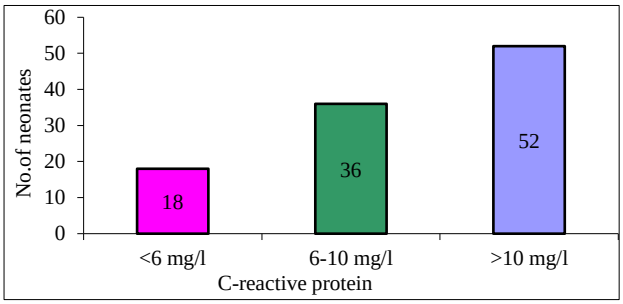

Figure 5: Distribution according to C-reactive protein.

Glucose status of EONS and LONS were summarized in Figure 6. Out of 106 neonates, 77 (72.6%) were hypoglycemic (<45 gm/dl) and 29 (27.4%) were normal. Among the neonates with EONS, 59 (88%) were hypoglycemic and 8 (12%) were normal. Among LONS, 18 (46.2%) were hypoglycemic and 21 (53.9%) were normal.

Among the neonates with suspected sepsis, 33 (31.1%) had positive blood culture for bacteria. *Klebsiella spp.* (*K. pneumoniae*) accounted for 10 (30.3%) of the total isolates followed by *Acinetobacter* 8 (24.2%), *Staphylococcus aureus* with prevalence of 7 (21.2%), *E. coli* 4 (12.1%) and *Pseudomonas spp* 4 (12.1%) (Figure 7). The Gram-positive and negative bacteria accounted for 7/33 (21.2%) and 26/33 (78.8%), respectively as shown in Figure 8.

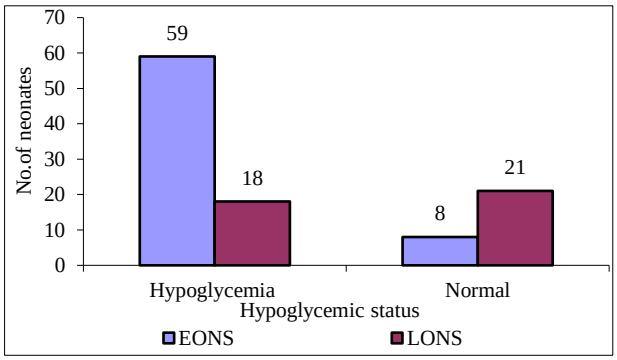

Figure 6: Blood sugar status in each group.

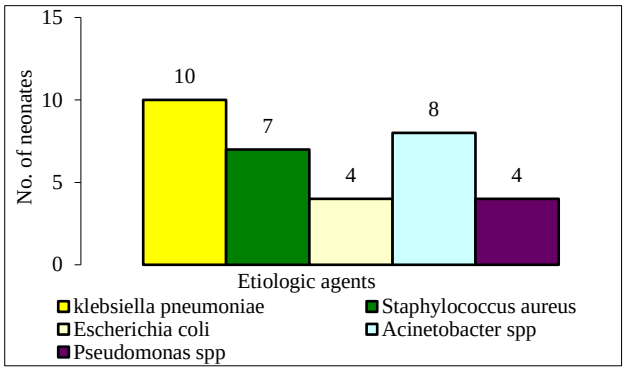

Figure 7: Bar diagram of distribution of neonates according to etiologic agent.

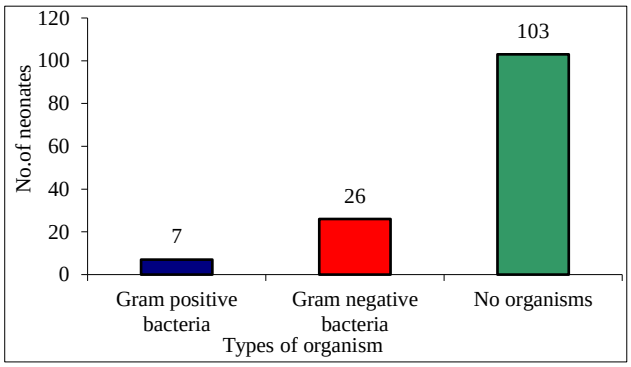

Figure 8: Distribution based on organisms.

Within the neonates with EONS, 25 (37.3%) had proven sepsis confirmed by positive blood culture (Figure 9). *K. pneumoniae* was the commonest isolates, showing 7 (28%) followed by *Acinetobacter*, 7 (28%) and *Staphylococcus aureus* 6 (24 %). Other bacteria were also isolated from EONS as shown in Figure 10. Eight neonates admitted with suspected LONS were positive

for bacterial culture. *Klebsiella Pneumoniae* accounted for 3 (37.5%), *Pseudomonas spp* accounted for 3 (37.5%), and 1 each of *Acinetobacter* and *Staphylococcus aureus.*

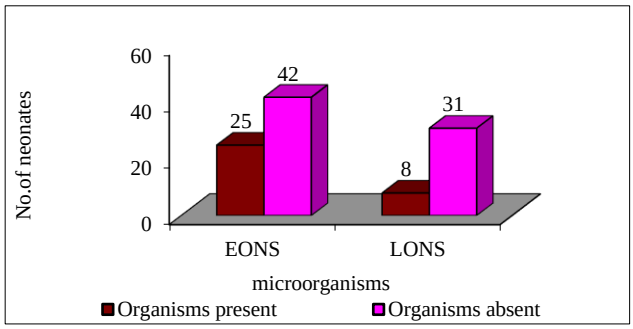

Figure 9: Distribution according to availability of microorganisms.

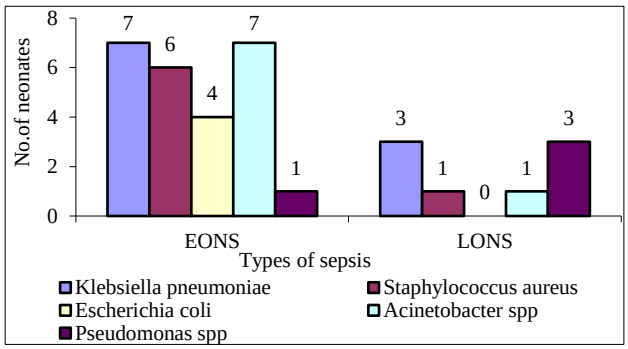

Figure 10: Based on types of microorganisms.

DISCUSSION

About five million deaths of neonates occur worldwide every year, and 98% of them occur in developing countries, mainly Asia and Africa. Neonatal sepsis generally refers to systemic symptomatic bacterial, fungal, and viral infections that may be associated with various gradation of symptoms, from subtle feeding disturbances to frank septic shock.[28] Neonatal sepsis due to the spectrum of organism's changes over time and varies from region to region.[29] Although extensive research information is available worldwide, very few reports are available on neonatal sepsis in Bangladesh.[30,31] The present study was undertaken to evaluate glucose status, hematological parameters and etiologic agents in neonates with clinical diagnosis of septicemia admitted at Chattagram Maa-Shishu O General Hospital from September 2011 to July 2012. An attempt has been also made to identify possible risk factors responsible for neonatal septicemia.

In the present investigation, we found that EOS was more common than LOS (64.2 % versus. 35.8 %), which is in agreement with the reports from other developing countries e.g. Iran (77.5% versus 22.5%), but in contrast with reports from Saudi Arabia (39% versus. 61%) or Pakistan (42% versus 58%), where LOS is more common.[29,32,33] The possible explanation for a lower frequency of LOS in this study might be the early discharge policy in the hospital.

Early signs of neonatal sepsis are often non-specific, i.e. respiratory distress, temperature instability, difficulty in breathing, lethargy, reluctant to feed, and unexplained jaundice.[28] Clinical assessment by using signs and symptoms is a useful guide to provisional diagnosis of neonatal sepsis.[34] Reports from India showed that 50-60% of septic babies were premature neonates and very-low-birth-weight (VLBW) were more vulnerable. In our cases, 48.0% were low-birth-weight (LBW) babies and 20.8% were premature neonates.

Various hematological parameters, a complete blood count, total WBC and differential count (immature neutrophil, band form count), platelet count, ratios of immature/total neutrophil count and their combination have been evaluated for their ability to predict neonatal sepsis.[35] In the present study, neonates who were clinically suspected of sepsis, their WBC counts was normal, high or low as 95.3%, 2.8% or 1.9%, respectively. Among WBC count changes, neutropenia is the most reliable predictor of neonatal sepsis; it reflects the severity of sepsis and represents depletion of neutrophil reserves, and requires specific therapeutic measures for management.[36] In the present investigation, in neutrophil count ratios (immature/total) ≥0.2 and <0.2 was observed in 7.5% and 92.5%, respectively.

Our result showed that elevated CRP level is associated with sepsis, which is not surprising. Several previous studies have already shown that CRP is a sensitive marker of inflammation, but it responds with a lag time of 24-48 h. Repeated measurement of CRP levels has therefore been suggested as a method to rule out sepsis, rather than a method of detection.[37]

Most neonates in our samples had blood glucose changes, with hypoglycemia being most prevalent. Waeschle et al indicated the association between poor prognosis in septic patients and blood glucose changes, as well as the role of fluctuations between hypoglycemia and normal glucose during sepsis as predisposing factors for death.[38]

Isolation of the causative pathogens by blood culture remains to be the mainstay of diagnosis for neonatal sepsis. Among neonates with suspected sepsis, 31.1% were positive for bacterial culture. The isolation rate of bacteria in this study is comparable to rates reported in Nigeria (45.9%), India (52.6%), Pakistan (54.0%) and Uganda (37.5%).[34,33,39,40] Lower isolation rates were reported in Ethiopia (23.1%- 27.9%) and studies conducted in other developing countries e.g. in Iran (6.6%) (28), Bahrain (4.2%).[41,42] The frequency of isolation of gram-positive and -negative bacteria from blood culture was 21.2% and 78.8%, respectively. This result is similar to that of other studies that showed that

gram-negative bacteria were responsible in most cases of neonatal sepsis.[36,43,29,33] *Klebsiella spp* was the most common isolates (30.3%) causing neonatal sepsis in this study. Study report from Dhaka Shishu Hospital revealed that principal organisms are *klebsiella, acinatobactor, E coli,* coagulase negative *staphylococci* and *staphylococcus aureus*.[44] *Klebsiella* species have often been isolated in hospital setting and are often implicated in nursery outbreaks.[45] *Acinetobacter spp* was the second most common organism isolated in this study.

CONCLUSION

Neonatal sepsis patients are associated with hypoglycemia, and suggesting its role in neonatal sepsis as pathogenic basis. Findings from this study will help to assess changes in the pattern of etiologic agents and biochemical, hematological abnormalities in septic neonates by comparing the results of the previous studies of another region in Bangladesh and elsewhere in the world. Results from this study will also provide update information for appropriate management of neonatal sepsis.

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