ORIGINAL ARTICLE

HEMATOLOGICAL AND BIOCHEMICAL PREDICTORS OF MORTALITY IN NEONATAL SEPSIS

Asif Ahmed[1], Ikhlas Ahmad[1], Sheeraz Ahmad[2], Javeed Iqbal[3], Nayeem-u-din Wani[4], Yasir Bashir[5], Syed Wajid Ali[6]

Author's Affiliations: [1]Senior Resident; [2]Resident; [3]Asisstant Professor; [6]Professor, Department of Pediatrics & Neonatology, [4]Resident, Dept. of Microbiology; [5]Senior Resident, Department of Critical Care Medicine, SKIMS, Soura, Srinagar, India.
Correspondence: Dr Ikhlas Ahmad Email: ikhlas.paeds@gmail.com

ABSTRACT

Introduction: This study was conducted to study the factors predicting mortality in neonatal sepsis, so that focused attention is paid to them, with an aim to bring down the mortality rates in neonates admitted with sepsis.

Methods: This study was a prospective observational study. Neonates who were admitted with a suspicion of sepsis or in whom sepsis was suspected anytime during hospital stay were evaluated and included in study when sepsis was confirmed. Complete blood counts (CBC), C-reactive protein (CRP) levels, chest X-ray and cultures of blood, urine and CSF were collected. Additional data like blood sugar, serum calcium, serum creatinine, serum electrolytes and coagulogram were also collected. Different haematological and biochemical parameters were compared between septic babies who survived and those who expired. GraphPad Instat statistical software was used for analysis.

Results: Over the study period, 196 patients were evaluated for sepsis on the basis of clinical features. 120 patients satisfied our case definition and were allotted to the sepsis group and included in the study. Out of these 120 patients, 28 patients expired. Blood cultures were positive in 76 babies. Thirty six babies had meningitis and 22 babies had pneumonia. Thrombocytopenia, leucopenia, neutropenia, coagulopathy and hyponatremia had a statistically significant relationship with mortality. There was no statistically significant difference in mortality of patients with or without hypernatremia. Similar insignificant difference was seen with other parameters like acute kidney injury (AKI), seizures, meningitis, hypoglycemia and high CRP titers. On logistic regression analysis, birth weight < 2500 gm, neutropenia and coagulopathy were significant independent predictors of mortality in neonates with sepsis.

Key words: Neonatal sepsis, mortality, predictors

INTRODUCTION

In spite of the advances in diagnostic and therapeutic modalities, neonatal sepsis continues to be a challenge faced by neonatologists as well as neonates in neonatal care units across hospitals. According to World Health Organization (WHO) estimates, neonatal sepsis remains the major cause of mortality among the five million neonatal deaths per year.[1] As many as 2% of fetuses are infected in utero, and up to 10% of infants have infections in the 1st month of life.[2]

Morbidity and mortality in a neonatal intensive care unit (NICU) can be reduced by knowledge of epidemiology of sepsis, microbiology, infection rate profile and antibiotic sensitivity, and by introducing practices that are based on clinical evidence.[3,4]

This study was conducted to study the factors predicting mortality in neonatal sepsis, so that focused attention is paid to them, with an aim to bring down the mortality rates in neonates admitted with sepsis.

METHODOLOGY

This study was conducted in a tertiary care public referral hospital in northern India, which caters to a population of almost 5 million people, with almost 50000 yearly admissions. This study was a prospective observational study conducted in the neonatal unit of this institute. The study was approved by Ethical committee of the institute. All neonates admitted in the year 2013, who had features of sepsis at admission or during hospital stay, were evaluated and included in the study if confirmed to have sepsis. Informed consent was taken from parents/guardians of the included patients. Neonates with life-threatening congenital malformations, chromosomal disorders or who were extremely premature (<28 weeks gestation) were excluded. All neonates with positive blood culture or diagnosed with pneumonia, meningitis or urinary tract infection (UTI) were considered to have confirmed sepsis. Any organism, including *Coagulase-negative Staphylococcus* (CONS) was considered the causative agent of sepsis and not a contaminant if the criteria of the Vermont Oxford Network Database were present: clinical signs of sepsis, positive blood culture for CONS, and intravenous antibacterial therapy for at least five days after obtaining blood culture or until death, in case it occurs within five days after obtaining blood culture.[5] Complete blood counts (CBC) and C-reactive protein (CRP) levels were collected. Additional data like blood sugar, serum calcium, serum creatinine, serum electrolytes and coagulogram were also collected. Meningitis was defined when cerebrospinal fluid (CSF) culture was positive or when CSF analysis revealed pleocytosis, inappropriately low glucose or high protein content. Pneumonia was diagnosed by suggestive clinical signs and symptoms in addition to radiological evidence. UTI was confirmed by urine culture. Among investigations, leucopenia was defined as total leucocyte count < 5000/µl), neutropenia as absolute neutrophil count < 1500/µL and thrombocytopenia as platelet count < 150000/µl. CRP levels > 6 mg/dl were taken as positive. Hypoglycemia was defined as blood sugar < 50 mg/dl, hypocalcemia as serum calcium < 8 mg/dl, hyponatremia as serum sodium < 130mEq/l, hypernatremia as serum sodium > 150mEq/l. Data about various parameters like age at presentation, birth weight, mode of delivery, birth order, weight at time of presentation to hospital, maternal age, reason for seeking medical attention, was arranged in Microsoft Excel worksheet. Values of various analytes like serum sodium, serum potassium, serum bicarbonate, pH, serum creatinine, serum glucose, serum calcium, serum bilirubin, complete and differential leucocyte counts, platelet count, coagulogram etc were also recorded in the same. Different haematological and biochemical parameters were compared between septic babies who survived and those who expired. GraphPad statistical software was used for analysis. Comparisons were made by chi-square test and Fischers exact test.

RESULTS

Over the study period, 196 patients were evaluated for sepsis on the basis of clinical features. 120 patients satisfied our case definition and were included in the study. The baseline characteristics and presenting complaints of these neonates are as mentioned in tables 1 and 2.

Table 1: Characteristics of the study group

Indicator	Value
Mean Gestational age(weeks)	36.3(29-39)
Mean Birth weight (Kg)	2.6(0.9-4.5)
Mean Age at admission (days)	10(1-27)
Males	72(60%)
PROM in mother	5(4%)
Delivered by LSCS	48(40%)
Medical illness in mother	16(13%)
Obstetric problems in mother	14(12%)
Leaking>18 hours	6(5%)
UTI in mother	4(3%)

Table 2: Presenting complaints of patients

Presenting complaint	Patients (%)
Refusal of feeds	68(57)
Lethargy	60(50)
Respiratory difficulty	30(25)
Fever	22(18)
Oliguria	12(10)
Jaundice	10(8)
Irritability	6(5)
Skin abscess	6(5)
Loose stools	4(3)

Out of 120 patients, 28 (23.3%) patients expired. The mean birth weight of the babies who survived was 2.71±0.71kg (Range 2.45-2.97) and in case of babies who expired, it was 1.68±0.87kg (range 0.76-2.59). The difference in the mean birth weight of the two groups was statistically significant (p-value 0.0034).

Table 3: Organism isolated in blood culture in babies who survived

Organism isolated	Number (%)
Coagulase Negative Staph Aureus	16 (25.8)
Enterococcus	9 (14.5)
E.Coli	7 (11.29)
Candida	6 (9.67)
Methacillin Resistant Staph Aureus	6 (9.67)
Enterobacter	4 (6.45)
Morganella	4 (6.45)
Aerococcus	2 (3.22)
Klebsiella Pneumonae	2 (3.22)
Methacillin Sensitive Staph Aureus	2 (3.22)
Acinetobacter	2 (3.22)
Leuconostoc	1 (1.11)
Kukoria krusei	1 (1.11)

Table 4: Organism isolated in blood culture in babies who died

Organism isolated	Frequency
Candida	6
Coagulase negative Staph aureus	2
Enterobacter	2
Enterococcus	2
Klebsiella pneumonae	2

Table 5: Relationship of various clinical, haematological and biochemical markers with mortality

Variable	OR	p-Value
Sex (m/f)	1.3	0.66
WBC	13.9	<0.0001
ANC	13.4	<0.0001
PLT	19	<0.0001
CRP	2.28	0.20
Meningitis	0.91	1.0
Hypernatremia	1.8	0.36
Hyponatremia	18.7	<0.0001
Coagulopathy	16.5	<0.0001
Hypoglycemia	0.6	0.59
AKI	2.8	0.09
Seizures	0.98	1.0

Table 6: Multiple Logistic Regression Analysis of Variables

Parameter	aOR (95% CI)	p-Value
Birthweight (<2500gm)	1.20 (0.94-1.45)	0.01
Neutropenia	1.03 (0.99-1.05)	0.025
Coagulopathy	0.98 (0.94-1.01)	0.044

aOR= Adjusted Odds Ratio

The mean gestational age of the babies who survived was 36.9±2 weeks (Range 36.1-37.5) and in case of babies who expired, it was 34.9±4.1 weeks (range 32.4-37.4). The difference in the mean gestational age of the two groups was statistically significant (p-value 0.036).

Blood cultures were positive in 76 babies. Out of these 76 babies, 62 survived and 14 expired. Coagulase negative Staph aureus was the most common organism in the surviving babies (see table 3). In the babies dying of sepsis, Candida was the most common organism isolated in blood culture (see table 4).

Thirty six babies had meningitis. Out of these, 28 survived and eight died. Twenty two babies had pneumonia and out of these, only 12 survived. Two patients had urinary tract infection and another two patients had extensive skin abscesses. All of these four patients survived. The effect of various clinical, hematological and biochemical markers on the mortality are depicted in table 5. There was no difference in mortality of male and female patients.

Thrombocytopenia, leucopenia, neutropenia, coagulopathy and hyponatremia had a statistically significant relationship with mortality. There was no statistically significant difference in mortality of patients with or without hypernatremia. Similar insignificant difference was seen with other parameters like acute kidney injury (AKI), seizures, meningitis, hypoglycemia and high CRP titers. Twenty five patients with confirmed sepsis had total leucocyte count less than 5000/µl and out of these, 16 (64%) died. In comparison, out of 88 patients with confirmed sepsis having a total leucocyte count more than 5000/µl, only 10 (11.36%) died (p<0.0001).

Seventeen patients with confirmed sepsis had an absolute neutrophil count less than 1500/ µl and out of these, 12 (70.58%) died. In comparison, out of 92 patients with an absolute neutrophil count more than 1500/ µl only 14(15.2%) patients died (p<0.0001). Forty two patients with confirmed sepsis had a platelet count less than 150000/ µl and out of these, 24 (57.1%) died. In comparison, 61 patients with confirmed sepsis had a platelet count more than 150000/ µl and out of these, only four (6.55%) died (p<0.0001).

Twenty two patients with confirmed sepsis had hyponatremia, out of which 16 (72.72%) died. In comparison, out of 96 patients with confirmed sepsis who did not have hyponatremia, only 12 (12.5%)

died (p<0.0001). Sixteen patients with confirmed sepsis had coagulopathy, out of which 12 (75%) died. In comparison, out of 104 patients with confirmed sepsis who did not have coagulopathy, only 16 (15.38%) died (p<0.0001).

Multiple regression analysis was done on data for 7 variables found significant on univariate analysis (Birth weight <2500 grams, gestational age <34 weeks, leucopenia, neutropenia, thrombocytopenia, hyponatremia and coagulopathy). These were put in stepwise backward model. On multiple regression analysis, insignificant variables were eliminated to give final results as shown in table 6. Birth weight <2500 grams, neutropenia and coagulopathy were found to be significant independent predictors of fatality in septic neonates.

DISCUSSION

Neonatologists have always been concerned about the mortality due to sepsis in neonates. Concerted efforts have been put in to bring down the neonatal mortality figures. The results have improved over the years, but more needs to be done to bring the mortality figures further down. Knowing the risk factors associated with higher mortality in neonatal sepsis is important as it will help in focusing on better management of these risk factors and hence decreasing the mortality. Out of 196 patients enrolled in the study, sepsis was confirmed in 120 patients. Only 15(12%) patients had antenatal risk factors for sepsis in form of PROM, UTI and prolonged leakage for more than 18 hours in the mother.

In our study, we saw that refusal of feeds was the most common presenting complaint seen in 57% of the patients, followed by lethargy (50%), respiratory difficulty (25%), fever (18%), oliguria (10%), jaundice (8%), irritability (5%), skin abscesses (5%) and loose stools (3%). CONS was the most common organism isolated in 25.8% of blood cultures in these babies. Almost similar results were found by Sylvia Maria Porto Pereira et al[6] in their study, where CONS was isolated in 35.5% of blood cultures. In babies dying of sepsis, candida was the most common organism isolated in blood culture. This indicates the serious nature of fungal sepsis and hence need for more aggressive preventive and curative measures in case of fungal sepsis. In case of babies with meningitis, 22.2% died. This all the more emphasizes the serious nature of meningitis in these neonates. Even the survivors have a high chance of complications and poor neurodevelopment, as was seen by Zhu M et al[7], who saw that four out seven cases of neonatal meningitis who were followed up had neurological impairment and delayed development.

Only 54.5% of babies with pneumonia survived. Throughout childhood, the greatest risk of death from pneumonia is in the neonatal period. In a field trial of community based management of childhood pneumonia in India, more than half of all child deaths from pneumonia occurred among neonates.[8] Thus contribution of pneumonia to neonatal deaths cannot be underestimated.

There was a statistically significant relation between leucopenia (total counts<5000/µl) and neonatal deaths. Similar results were seen with thrombocytopenia (platelet count <150000/µl) and neutropenia (absolute neutrophil count < 1500/ µl). Many studies have previously shown similar results.[9,10] Leucopenia, neutropenia and thrombocytopenia represent advanced sepsis in older children and adults and are taken as markers of systemic inflammatory response syndrome. Presence of these may represent advanced stages of sepsis in neonates as well and can thus, indicate poorer prognosis.

We saw that patients with coagulopathy had a higher mortality than those without coagulopathy. Disseminated intravascular coagulation (DIC) is a clinical syndrome with complex pathophysiology with varying etiological factors. Even though hemorrhage is more obvious, microvascular thrombosis induced end organ damage is responsible for most of the morbidity and mortality.[11] This associated microvascular thrombosis may be the cause of increased mortality in our patients having coagulopathy. We saw increased mortality in neonates with hyponatremia. Boehm G et al[12] in their study on Sodium homeostasis in neonatal infection of eutrophic premature infants have shown that the serum sodium concentration fell and urinary sodium concentration started to rise 24 hours before first clinical evidence of sepsis. Similarly in our study, the babies who had hyponatremia might have likewise progressed to clinical sepsis earlier than those babies who had normal serum sodium concentration. This may have lead to delayed start of treatment when the baby had already developed advanced clinical features of sepsis, leading to poor outcome in terms of mortality. In addition, hyponatremia is associated with many conditions like

syndrome of inappropriate anti diuretic hormone secretion and cerebral salt wasting, which may have been coexisting conditions in these babies.

CONCLUSIONS

Neonatal sepsis continues to be a persisting challenge despite advances in medical care. There is a significant relationship between neonatal mortality and parameters like leucopenia, thrombocytopenia, neutropenia, hyponatremia and coagulopathy. Appearance of any of these parameters in a neonate admitted in nursery or NICU should set the alarm bell ringing in the minds of treating neonatologists, so that the patients are managed aggressively and mortality is averted.

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