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ORIGINAL ARTICLE

Outcome Of Sepsis Evaluations In Very-Low-Birth-Weight Premature Neonates

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ABSTRACT

Objective: We aimed to evaluate the outcome of early onset-sepsis (EOS) workups in very low birth weight (VLBW) premature neonates

Methods: Premature neonates weighing less than 1500g were evaluated for EOS. Haematological screening parameters, CRP and blood cultures were obtained in all. EOS (occurring at <72 hours of life) was the primary outcome. We analyzed the relationship between various maternal and neonatal characteristics, screening parameters, CRP and EOS.

Results: The present study included 36 premature VLBW neonates. The mean (SD) gestational age and birth weight were 31.2(2.5) weeks and 1252.9(199.9) gms, respectively. Obstetric risk factors were present in 12 (33.3%) neonates. Twenty (55.6%) neonates had EOS, 2 (5.6%) grew organisms in their blood culture and 5 (13.9%) died. EOS was slightly, but not significantly higher in neonates who were born with obstetric risk factors as compared to those who were not born without the risk factors (OR 1.18; 95%CI: 0.29-8.46; p=0.27). Choreoamnionitis, decreasing gestational age and birth weight were associated positively. Asymptomatic newborns were at a lower risk than their critically illcounterparts (33.3% Vs 62.9%; OR 0.29). The sensitivity of the haematological screening parameters and CRP varied from 10%-35%. Combination of any two parameters had a sensitivity of 40% and a negative predictive value of 50%. Neonates with EOS had a significantly longer duration of mechanical ventilation (p=0.03) and higher mortality than those without EOS (25% Vs 6.3%).

Conclusions: Blood culture proven EOS is uncommon among VLBW premature neonates, but clinical sepsis continues to be a significant problem. Infection rate in asymptomatic neonates is low. Haematological screening parameters and CRP have limited roles in distinguishing the infected neonates from the uninfected ones.

Key words: Very low birth weight neonates, early onset sepsis, prematurity

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Introduction

Bacterial infections are an important cause of morbidity and mortality among very low birth weight (VLBW) preterm neonates [1],[2]. Higher rates of early-onset sepsis (EOS occurring in the first 72 hours of life) and mortality among these neonates have been described[1],[3,[4],[5],[6]The suspicion of EOS is almost universal in VLBW preterm infants and the initiation of antibiotic therapy at birth is a common practice[1]. The decision to discontinue antibiotic therapy in these fragile neonates is often difficult. There are limitations to blood culture methods and it is possible for a single blood culture result to be negative when

a neonate has bacterial sepsis. The reported rate of infection and treatment vary widely. About 4.4% to 10.5% of all infants born in United States were said to receive systemic antibiotics although the frequency of neonatal bacterial infections ranges from 1 to 5 per 1000 livebirths. A treatment rate of 10.9% was identified when the infection rate was 1% among asymptomatic infants [7]. A study involving a large cohort of VLBW infant population reported that almost half of the VLBW neonates received antibiotic therapy for 5 or more days, despite negative blood culture results in 98% of the patients [1],[4]. These findings underscored the difficulty of ruling out bacterial sepsis in sick immature neonates and the concern for possible culture-negative clinical sepsis. However, unnecessary and prolonged antibiotic therapy in VLBW neonates increases both risk and cost. In this context, we aimed to evaluate the outcome of sepsis workups in VLBW premature neonates. We examined the first evaluations performed for bacterial infection, the risk factors of the disease and its impact on the subsequent hospital course.

Material And Methods

This study was conducted prospectively in the neonatal intensive care unit of a teaching hospital between January and August 2005. The neonates were included if they were premature and weighed <1500 gms at birth. Those neonates who expired in less than 12 hours following birth and those with major congenital anomalies were excluded. The demographic data, maternal risk factors and treatment, delivery details, gestational age and birth weight were recorded. Gestational age was determined by obstetric measures and by the Ballard score. Neonatal and outcome data were collected until the discharge or death of the neonates. All neonates were subjected to haematological screening for sepsis which included the total leukocyte count (TLC), platelet count (PLT), micro ESR, C-reactive protein(CRP), band to total neutrophil ratio (B:N),cytoplasmic vaccuolations (CV) and/or toxic granulation (TG) in peripheral smears. The semi quantitative measurement of CRP was done in all. Blood culture samples included a single sample from a peripheral vein taken under aseptic conditions before commencing antibiotics. Chest X-ray and other investigations were performed whenever indicated.

Early-onset sepsis was the primary outcome. The outcome assignment was based on a positive result of the blood culture of the specimens drawn within the first 72 hours of life or on clinical sepsis. A culture proven infection is defined as an infection which is confirmed by a positive blood culture. A probable infection (clinical sepsis) is one in which the clinical course strongly suggested that infection was present, although the blood culture results were negative.

For analysis purposes, TLC [8],[9],[10] of <5000 or >20000/mm^3, PLT [10] of <150000/mm^3, CRP of >6mg/L, B: N ratios [9], [11] of ≥0.2 and the presence of CV or TG in the peripheral smear [12],[13], were considered abnormal. Micro ESR was considered to be positive if the readings were more than (age in days + 3) mm in the first hour [14]. A neonate was considered to be critically ill if assisted ventilation (nasal continuous positive airway pressure or intermittent mandatory ventilation) and/or vasoactive drugs were administered or if a thoracotomy tube was placed. Other neonates with no abnormalities were considered to be asymptomatic.

Statistical Analysis

Statistical analyses were performed by using the Statistical Package for Social Sciences for Windows version 11.5 software. χ^2 or Fisher's exact tests were used to compare categorical variables and Student's *t* tests were used to compare the mean differences of continuous variables. Multivariate analyses were performed using logistic regression. A *p*-value of <0.05 was considered to be significant.

Results

The present study consisted of 36 premature neonates weighing less than 1500 gms. Among them, 41.7% were born to primi mothers and 38.9% were born by Caesarean section. The

mean (SD) gestational age and birth weight were 31.2(2.5) weeks and 1252.9(199.9) gms, respectively. Five (13.9%) were extremely low birth weight infants. About two third of the infants were males and one third were 'small for gestational age (SGA) infants' [Table/Fig 1] .Obstetric risk factors were present in 12 neonates (33.3%), choreoamnionitis in 3 and rupture of membrane >18 hours prior to delivery in 9. Ventilator support was needed in 27; intermittent mandatory ventilation in 19 (52.8 %) and CPAP alone in 8 (22.2%) neonates. Surfactant was administered in 4 (11.1%) cases.

(Table/Fig 1) Description of study neonates

Maternal Parity	
Primipara (%)	15 (41.7)
Multipara (%)	21 (58.3)
Mode of delivery	
Cesarean (%)	14 (38.9)
Vaginal (%)	22 (61.1)
Gestational age (weeks)	
Median	31
Range	27-36
Mean (SD)	31.2 (2.5)
Birth weight (g)	
Median	1232
Range	850- 1495
Mean (SD)	1252 (199)
Appropriate/ small for gestational age	
AGA (%)	23(63.9)
SGA (%)	13(36.1)
Sex	
Male (%)	23 (63.9)
Female (%)	13 (36.1)

AGA, appropriate for gestational age; SGA, small for gestational age; SD, standard deviation

A total of 20 (55.6%) neonates met our criteria for infection. The blood culture grew organisms in 5.6% (2/36) cases. [Table/Fig 2] shows the relationship of the infection with various maternal and neonatal characteristics. Parity of the mother and the mode of delivery did not bear a positive relationship with sepsis. The early-onset of sepsis was slightly, but not significantly higher if the neonates were born with obstetric risk factors than without them (35% Vs 33.3%; OR 1.18; 95%CI: 0.29-8.46; p=0.27). The presence of choreoamnionitis was positively associated with neonatal sepsis. There was no association between the neonate's sex and the risk of early-onset sepsis. Decreasing gestational age and birth weight were positively but not significantly associated with EOS. Asymptomatic newborns were at a lower risk for early sepsis as compared to critically ill newborns (33.3% Vs 62.9%; OR of 0.29).

(Table/Fig 2) Maternal and neonatal characteristics Vs early onset sepsis

	Neonates with EOS	Odds ratio	95%CI	p value
Maternal variable				
Parity				
Primi	8	0.86	0.23-3.25	0.26
Multi	12			
Mode of delivery				
Vaginal	12	0.9	0.23-3.47	0.27
LSCS	8			
Choreoamnionitis	2	1.67	0.14-20.2	0.43
ROM length ≥ 18 hours	5	0.92	0.19-4.22	0.29
Neonatal variable				
Sex				
Male	12	0.68	0.17-2.72	0.24
Female	8			
Gestation (weeks)				
<28	1	1.13	0.06-21.09	0.53
28-32	8	0.48	0.12-1.92	0.16
32-36	11			
Birth weight (g)				
<1000	3	1.67	0.14-20.58	0.43
1000-1250	9	1.24	0.18-8.46	0.36
1250-1500	8			
Newborn examination				
Asymptomatic	9	0.29	0.06-1.44	0.09
Critically ill	17			

ROM, rupture of membrane.

[Table/Fig 3] shows the predictive values of haematological screening parameters and CRP. The sensitivity varied from 10%-35%. PLT and TG/CV had the best , but only 35%. Combination of any two parameters had a sensitivity of 40% and a negative predictive value of 50%.

(Table/Fig 3) Predictive values of sepsis screen parameters

	Sensitivity	Specificity	PPV	NPV
Total leukocyte count	10%	100%	100%	47%
Platelet count	35%	87%	78%	52%
MicroESR	10%	94%	67%	45%
CRP	20%	69%	44%	41%
B: N ratio	15%	94%	75%	47%
Toxic granules/ cytoplasmic vaccuolations	35%	63%	54%	43%
Any two parameters	40%	75%	67%	50%

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

[Table/Fig 4] shows the impact of EOS on the duration of mechanical ventilation and hospitalization. Neonates with early-onset sepsis had a significantly longer duration of mechanical ventilation than those who were not infected early. The mean duration of the hospital stay was not different in both groups. There was 13.9% (5/36) mortality among the

study population which was attributable mainly to infection. Neonates with EOS (5/20) were at an increased risk of death as compared to uninfected neonates (1/16).

(Table/Fig 4) Duration of hospitalization

Duration of parameters (days)	Early onset sepsis		p value
	Yes	No	
Mechanical ventilation	9.35±6.9	4.75±6.02	0.039
Length of hospital stay	19.6±10.9	20.25±11.3	0.86

Discussion

The incidence of the early onset of bacterial infections was higher in premature VLBW neonates than in term neonates [1],[2],[3],[15], [16]. A blood culture proven EOS rate of 19/ 1000 live births (or 1.9%) of VLBW infants has been reported from an analysis of 7606 infants [1]. The same analysis also described variations in the rate of 13-27 per 1000 live births among participating centers. We observed a higher blood culture proven sepsis rate of 8.3% (2/24). In contrast, Kuruvilla [6] et al reported a very low rate of 0.6%.

There were some limitations in our study. We used single blood culture samples. All mothers with risk factors for neonatal sepsis received antepartum /intrapartum antibiotics. It is possible that such treatment may partly suppress bacterial growth, leading to false negative results. Further, it is also likely that the clinician may either overestimate or underestimate the infant's risk for infection. Another possible reason for low culture yield could be the usage of conventional blood culture bottles rather than the usage of the BacT/Alert system.

The use of automated colorimetric blood culture (BacT/Alert) systems could confidently identify the presence or absence of bloodstream bacteria early and improve the positivity rate [17],[18],[19]. BacT/Alert automated microbial detection systems are based on the colorimetric detection of CO_2 produced by growing microorganisms. A CO_2 sensor separated from the broth by a semi-permeable membrane is bonded to the bottom of each bottle. CO_2 produced by growing microorganisms diffuses across the membrane into the sensor and dissolves in water, generating hydrogen ions. As the pH decreases, the blue to dark green sensor turns lighter green to yellow, which results in an increase of the reflected red light. The BacT/Alert system incubates, shakes, and scans CO_2 production every 10 minutes by using a computerized database management system to record and report results. The BacT/Alert system offers several significant advantages over manual blood cultures for microbial detection [18]. It is a fully automated system which eliminates repeated manipulations of bottles and consequently, reduces workload and errors. The system is non- radiometric, the detector is external to the bottles and hence, bottle cross-contamination during repeated aspirations is eliminated. The repeated automated testing of the culture bottles reduces the time needed to detect microbial growth. Shorter time to positivity[17],[19] decreases costs and medication errors. Further, the reports of Kumar et al [19] suggest that the administration of antibiotics before blood collection; including intrapartum maternal antibiotics, may not significantly compromise the growth in neonatal blood cultures.

The pathogens responsible for EOS generally reflect the predominant vaginal flora of the pregnant woman. Gram-positive organisms, especially group B streptococcus, were the most frequent pathogens identified for early-onset sepsis in many earlier studies [9],[10], [12],[15]. Reports from India identified gram negative organisms [6],[13]. Two blood culture isolates of the present study included pseudomonas and enterobacter species. Recent studies have reported a change in the distribution of pathogens from predominantly gram-positive to primarily gram-negative organisms [2],[20].

It was reported that the strong association of the mode of delivery with EOS significantly increased risk with vaginal delivery than in cesarean delivery [1]. On the contrary, we did not find the association of the risk with the parity of the mother and the mode of delivery. The time from the rupture of the membrane

(ROM) to birth, was identified as a strong risk factor for EOS [1]. The longer the time from ROM to birth, the greater is the risk of EOS. We did not find this association. This could be due to antibiotic administration to the mother. A similar observation was made by Escobar [7] et al. We observed an increased risk with the presence of choreoamnionitis, that was similar to the reports of many authors [1],[7],[15]. When the maternal variables were entered into a multivariate regression equation, none of the variables remained as statistically significant risk predictors.

We did not find increased risk in male infants unlike several studies that reported an increased risk of infection in male neonates. The equal risk of infection in VLBW male and female infants was earlier reported by Stoll BJ et al [1]. In very immature neonates, factors like pathogen exposure and immaturity of the immune system that influence early-onset sepsis, may be more important than sex. Decreasing gestational age and birth weight were positively but not significantly associated with EOS. Similar results and in neonates who were born at < 28 weeks' gestation twice the risk of EOS as those who were more mature were published by earlier reports[1]. The present study had only 2 neonates who were less than 28 weeks old. Asymptomatic newborns were at lower risk for early sepsis as compared to critically ill newborns (33.3% Vs 62.9%; OR of 0.29). Very low risk of bacterial infection in asymptomatic newborns was recognized [7].

The sensitivity of haematological screening parameters and CRP in the present study varied from 10%-35%. PLT and TG/CV had the best predictive value, but it was only 35%. Wide variations in the predictive ability of these parameters exist in literature [7],[8],[9],[10], [11],[12],[13],[14],[15] Kumar V [21] et al reported that none of screening parameters individually predicted the presence of bacteraemia satisfactorily. Similar observations were made earlier too [11]. Benitz WE [22] et al concluded that the positive predictive value of elevated CRP levels is low, especially for culture-proven early-onset infections. Further, they described that the sensitivity of a normal CRP at the initial evaluation is not sufficient to justify withholding antibiotic therapy and suggested serial CRP levels. Escobar [7]et al did not use CRP in their evaluation because of the lack of the full assessment of its utility. They also suggested the reassessment of the complete blood count. In our study, the combination of any two parameters had a sensitivity of 40% and a negative predictive value of 50%. This was in contrast to reports of better efficacy [9],[11],[13].

Neonates with EOS had a significantly longer duration of mechanical ventilation than those who were not infected early. The mortality was higher among neonates who were infected early than uninfected neonates (25% vs. 6.3%). A longer duration on the ventilator and significantly increased mortality in early infected neonates were recognized in studies done on a large population [1],[23].

Conclusion

Blood culture proven early onset sepsis among VLBW premature neonates is uncommon, but clinical sepsis continues to be a significant problem. An automated colorimetric blood culture system with improved positivity rate would probably narrow down this gap. The mortality among early infected neonates remains high. Increased rates of infection are likely to be associated with maternal risk factors, decreasing gestational age and birth weight. The rate of infection in asymptomatic neonates is low. However, screening, observation and rational antibiotics therapy is warranted to this group. Early identification of the truly infected neonates who require prompt antibiotic therapy remains challenging for a clinician. The sensitivity and negative predictive value of haematological screening parameters and CRP have limited roles in early-onset sepsis.

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