Journal of Pediatrics and Neonatology

ISSN 2688-5573

Research Article

Association of Lactic Acid Concentration with Severity and In-Hospital Mortality in Neonatal Sepsis

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Abstract

Background: Sepsis is a major cause of neonatal mortality in developing countries. However, with current severity scores and laboratory parameters, early diagnosis and predicting outcomes of neonatal sepsis is a serious challenge. Lactic acid concentration is a readily available pragmatic means to predict outcomes of various comorbidities. However, its utility in neonates remains unexplored.

Objective of the study: The objective of this study was to observe the association of lactic acid level with severity and in-hospital mortality in neonatal sepsis.

Methodology: This prospective observational study was conducted on 151 neonates with sepsis, in the Department of Neonatology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, from June, 2021 to May, 2022. Written informed consent was taken and confidentiality was assured. Neonates with sepsis that fulfill the inclusion criteria were enrolled in this study. Lactic acid concentration was sent along with septic work up. The primary outcome was severity of sepsis and in-hospital mortality. Patient's demographic, clinical, and laboratory data including lactic acid were compared between survivors and no survivors and also between normal and high lactic acid groups. All data were recorded in a preformed questionnaire and were analyzed by Statistical Package for Social Sciences (SPSS) version 20.0. A cut-off value of >3.5 mmol/L was predetermined to level as high lactic acid group.

Results: A total of 151 neonates with sepsis were studied, the mean lactic acid (mmol/L) was found 2.12 ± 0.72, 5.08 ± 1.08, and 6.01 ± 3.51 in sepsis, septic shock, and severe sepsis respectively and p-value (<0.001) was statistically significant with regard to severity of sepsis. The mean lactic acid level was significantly higher in non-survivors compared with survivors (P< 0.001) with a value of 2.40 ± 1.08 and 5.13 ± 3.40 respectively. The power of lactic acid level for prediction of mortality was seen by result of logistic regression analysis evidenced by Odd Ratio of 2.46 (95% CI, 1.630-3.723, p value <0.001).

Conclusion: Lactic acid concentration has statistically significant association with disease severity and in-hospital mortality in neonatal sepsis.

Keywords: Neonatal sepsis; Lactic acid concentration; Severity of sepsis

Introduction

Neonatal period is the most unguarded time for a child's survival. The risk of children death elevated in their first month of life at a worldwide rate of 19 per 1,000 live births and 30 per 1000 live birth in Bangladesh [1,2]. Neonatal sepsis is one of the foremost common causes of neonatal mortality. It accounts for nearly 3 million neonatal deaths per year and an estimated neonatal mortality rate of 23.9 per 1000 live birth globally [3]. Mortality related to neonatal sepsis is more common in developing countries compared with developed countries accounting for 30% to 50% of total deaths per year [4]. In Bangladesh neonatal sepsis contributes 19.9% to neonatal mortality per year [5]. Neonatal sepsis can advance quickly to septic shock take place in 1.3% of neonates hospitalized in Neonatal Intensive Care Unit (NICU) with a general mortality of 40% [6].

Neonatal sepsis is a clinical syndrome that will identify by signs and symptoms of infection that will happen with or without accompanying bacteremia in the first month of Child life [7]. It has been classified as either early onset (within first 72 hours of life) or late onset sepsis (occurring after 72 hours of age) i.e. infections occurring before and after 72 hours of life [7]. Septic shock is a condition of deficient tissue perfusion secondary to cardiovascular dysfunction

Citation: Nasrin UT, Abdul Mannan Md, Moni SC, Kamrul Hasan Shabuj Md, Perveen J, Karmaker P, et al. Association of Lactic Acid Concentration with Severity and In-Hospital Mortality in Neonatal Sepsis. J Pediatr Neonatol. 2023;4(3):1036.

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Publisher Name: Medtext Publications LLC

Manuscript compiled: Sep 13th, 2023

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take place in the course of suspected or certain systemic infection, indispensable fluid resuscitation or inotropic support [8].

Early diagnosis, timely administration of appropriate antibiotics and a proper supportive therapy are crucial to improve survival and to reduce long-term sequel [9]. The early symptoms and signs of neonatal sepsis are usually mild and nonspecific but can rapidly progress to septic shock, disseminated intravascular coagulation, and death. It is therefore of subsequent significances to find a tool for prediction of infants who are more likely to experience a dreadful clinical outcome so that closer observation and more aggressive treatment would be offered to [10].

All newborn suspected to have sepsis should undergo a septic screen which include Total Leucocyte Count (TLC), Absolute Neutrophil Count (ANC), immature to mature neutrophil ratio (I:T ratio), micro Erythrocyte Sedimentation Rate (Micro ESR) and C-reactive protein [11]. These conventional screening tests may help in the diagnosis of septicaemias; however, they lack the capacity to predict the severity of sepsis [12]. Blood culture, though a gold standard test in the diagnosis of neonatal sepsis requires a long turnaround time and comes out positive in less than a third of suspected neonates. C-Reactive Protein in the sepsis screen begins to rise only after 6 to 8 hours of onset of infection [13].

It is high time to identify a test that is cheap, accurate, and easy to perform with quick availability of reports to enhance the early detection and prediction of neonatal sepsis as early diagnosis and treatment reduces the morbidity and mortality [14].

Materials and Methods

Study design

This prospective observational trial was done in the Department of Neonatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, from June 2021 to May 2022, after getting the approval from the Institutional Review Board.

Eligibility criteria

All neonates from birth to 28 days of age with suspected sepsis admitted in the Department of Neonatology, Bangabandhu Sheikh Mujib Medical University during the study period were eligible for enrolment. Neonates with Congenital anomalies (e.g., congenital diaphragmatic hernia, tracheo-oesophageal fistula), Surgical cases (e.g., omphalocele, choanal atresia, intestinal obstruction), Severe birth asphyxia, Meconium aspiration syndrome, suspected inborn error of metabolism, Parental refusal to go through the study, Suspected sepsis but septic screen negative were excluded from study.

Study procedure

This forthcoming observational study was regulate in the Department of Neonatology, BSMMU, Dhaka after confirmation by Institutional Review Board (IRB). All neonates with suspected early or late-onset sepsis satisfying the inclusion criteria were enrolled for the study. A written informed consent was obtained before enrollment in the study from the parents or guardians. Face-to-face interviews with the parents or caregivers were taken from all enrolled neonates.

Meticulous history regarding the demographic characteristics and clinical features such as hypothermia, fever, lethargy, refusal to suck, respiratory distress, irritability, high pitch cry, seizure, etc. were taken from the attendance/mother. In case of inborn babies besides this, information was also obtained from the attending doctor, birth record, and POMR (Patient Oriented Medical Record). Risk factors for sepsis such as prolonged rupture of membrane, prolonged labour, and meconium-stained liquor were evaluated and physical examination was done. All required information was recorded in a data collection form during hospital admission.

Gestational age was calculated from the 1st day of Last Menstrual Period (LMP) or early obstetric ultrasonography or New Ballard Score. Birth weight was recorded immediately after delivery using an electronic scale having a sensitivity of 5 gm in case of inborn babies. For outborn baby's birth weight was determined from previous documents. Lubchenco's intrauterine growth chart was used for classification as AGA/SGA/LGA.

Neonates with septic event were subjected to send septic work up along with lactic acid. For which at first cleansing of the skin site was done with 70% isopropyl alcohol for 30 seconds followed by povidone-iodine and isopropyl alcohol again [15]. A total of 4.5 ml venous blood was taken at a time for following purpose: 1.5 ml for CBC with PBF, 1 ml for blood C/S, 1ml for CRP and 1 ml for Serum Lactic acid. In EDTA tube blood was sent for sepsis screen which was done in Department of Laboratory medicine, BSMMU, by XT-4000I (Japan) or XN-2000 (Japan). If two or more of the following parameters were positive, it was considered as positive sepsis screen: (i) Total leukocyte count <5000/cu mm or >25,000/cu mm; (ii) Absolute neutrophil count: (<1500/cu mm); (iii) Immature/total neutrophil >0.2; (iv) C reactive protein ≥ 6 mg/L. (v) Micro ESR >15 mm in 1st hour.

Blood was sent to Department of Microbiology and Immunology, BSMMU for blood C/S. The sample was inoculated in the BD BACTEC Peds Plus/F Culture bottle containing 40 ml broth and culture was done by BD BACTEC FX40 (USA) fully automated system.

For C-Reactive Protein (CRP) estimation blood was sent in a clot activator tube in Biochemistry Department. Quantitative assay for the estimation of C-Reactive Protein (CRP) levels was done on an automated Biochemistry analyser (BECKMAN COULTER, USA) by using a commercially available particle enhanced turbidimetric assay.

One ml venous blood was collected for Lactic acid estimation in a fluoride containing tube and was sent to Department of Biochemistry. Enzymatic-colorimetric determination was done within 15 minutes by using automated analyzer (Thermo scientific, Indiko Plus, Finland). Results were expressed as mmol/L. A cut off value of >3.5 mmol/L was used to define high lactic acid.

The primary outcome measured in the study was in-hospital neonatal mortality and sepsis severity. Accordingly, patients were classified into survivors and nonsurvivors. The study patients were categorized according to severity of sepsis into 3 subgroup-Sepsis, Septic shock, Severe sepsis. The neonates who had 2 or more septic episodes were defined as multiple septic events and who had multiple episodes, most severe category was taken into consideration.

Data analysis

After collection data were entered into a personal computer and edited, analysed, and plotted in graphs and tables whenever necessary Information's were analysed using the statistical package for social sciences (SPSS) version 20. Quantitative data were expressed as mean and standard deviation and categorical data were presented as frequency and percentage. All quantitative variables were compared by independent t-test; categorical variables were compared by Chi-square test or Fisher's exact test. When more than 2 quantitative

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variables were compared, one-way ANOVA test was used. P-value <0.05 was considered as significant. Binary logistic regression analysis was used to assess the association of confounding variables with severity of sepsis and mortality.

Results

During the study period, a total of 208 neonates with suspected neonatal sepsis were assessed for eligibility. Among them, 57 were excluded as per exclusion criteria. Finally, 151 patients were included and analyzed in the study. The mortality rate was 26.5% in the study subjects (Figure 1).

Among the 151 enrolled neonates, 72% had sepsis, 9% had septic shock and 19% had severe sepsis (Figure 2).

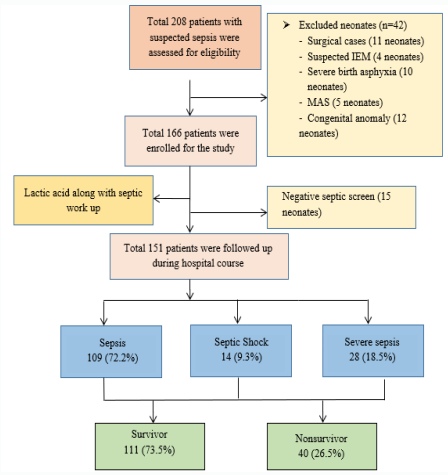

Figure 1: Inflammatory changes and bowel wall thickening centred.

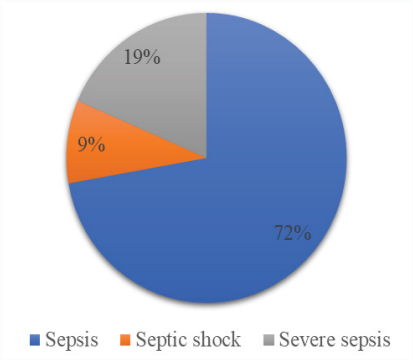

Figure 2: Distribution of severity of sepsis among enrolled neonates.

Standard characteristics of the examined neonates are displayed in Table 1 and 2. Mean gestational age was 34.22 ± 3.54 weeks and mean birth weight was 1960.5 g ± 800.34 g. Out of 151 enrolled patients, 122 (80.8%) were inborn. Male:Female distribution was 81 (53.6%) and 70 (46.4%) respectively. More than two-thirds of the enrolled patients (80.8%) were appropriate for gestational age. The predominant mode of delivery was LUCS (78.8%). About 66.9% & 68.9% of babies were born preterm and low birth weight respectively. Most of the patients (57.6%) had EONS.

According to Table 3, mean gestation age (33.60 ± 3.63) weeks and mean birth weight (1804.28 ± 751.25) g, was lower in high lactic acid group in comparison to normal lactic acid group which was

Table 1: Baseline characteristics of the enrolled neonates (N=151).

Characteristics	Findings
Gestational age (wks), mean ± SD	34.22 ± 3.54
Gestational age category, n (%)	
<30 weeks	16 (10.6)
30- <35 weeks	64 (42.4)
35- <37 weeks	21 (13.9)
≥ 37 week	50 (33.1)
Birth weight (g), mean ± SD	1960.5 ± 800.34
Birth weight (g), n (%)	
<1000	15 (9.9)
100 - <1500	38 (25.2)
1500- <2500	51 (33.8)
≥ 2500	47 (31.1)
Sex, n (%)	
Male	81 (53.6)
Female	70 (46.4)
Place of birth, n (%)	
Inborn	122 (80.8)
Outborn	29 (19.2)
Mode of delivery, n (%)	
LUCS	119 (78.8)
NVD	32 (21.2)
Fetal growth at birth, n (%)	
SGA	27 (17.9)
AGA	121 (80.1)
LGA	3 (2.0)
Onset of sepsis, n (%)	
EONS	87 (57.6)
LONS	64 (42.4)

Continuous data are presented as mean ± SD and categorical data as number and percentage (%), LUCS: Lower segment Caesarean section; NVD: Normal vaginal delivery; SGA: Small for gestational age; AGA: Appropriate for gestational age; LGA: Large for Gestational Age

Table 2: Serum lactic acid among the studied neonates (N=151).

Serum lactic acid (mmol/L)	Findings
Mean lactic acid level, mean ± SD	3.12 ± 2.31
≤ 3.5 mmol/L, n (%)	111 (73.5)
>3.5 mmol/L, n (%)	40 (26.5)

statistically not significant. There was also no significant difference between the two groups with regard to sex and place of delivery. In high lactic acid most (70.0%) were LONS in comparison with normal lactic acid group, which was statistically significant (p value <0.001). Moreover, the neonates who had multiple septic events, had statistically significant high level of lactic acid (80.0%) and p value was <0.001.

Statistical test: Chi-square test and, for gestational age, birth weight-independent t test; s: significant, ns: not significant, p value <0.05 was considered significant.

According to Table 4, mean gestation age (32.65 ± 3.37) weeks and mean birth weight (1565.78 ± 604.31) g, was lower in non survivor group in comparison to survivor group and it was statically significant with a p-value of 0.001 and less than 0.001 respectively. Most of the infants (60%) in the non survivor group had LONS and was statistically significant. The majority of patients in the non survivor group had severe sepsis 52.5% followed by sepsis 25% and septic shock 22.5%, which were 6.3%, 89.2%, and 4.5% respectively in the survivor group and it was statistically significant. Moreover, most of the non survivor neonates (60%) had multiple septic event which had statistically significant difference and p value been <0.0001. There was no significant difference between the two groups with regard to place of delivery.

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Table 3: Comparison of demographic, clinical parameters of studied neonates with normal and high lactic acid (N=151).

Variable	Normal lactic acid group n=111 (%)		High lactic acid group n=40 (%)	p-value
Sex of the baby, n (%)				
Male	63 (56.8)		18 (45.0)	0.201[ns]
Female	48 (43.2)		22 (55.0)	
Birth weight (g) (mean ± SD)	2016.80 ± 813.20		1804.28 ± 751.25	0.151[ns]
Gestational age (weeks)(mean ± SD)	34.44 ± 3.49		33.60 ± 3.63	0.198[ns]
Place of delivery				
Inborn	89 (80.2)	33 (82.5)	0.749 [ns]	
Out born	22 (19.8)	7 (17.5)		
Onset of sepsis				
EONS<72 hours		75 (67.6)	12 (30.0)	<0.001[s]
LONS>72 hours		36 (32.4)	28 (70.0)	
Number of event, n (%)				
Single	96 (86.5)	8 (20.0)	<0.001[s]	
Multiple	15 (13.5)	32 (80.0)		
Blood C/S, n (%)				
Negative	89 (80.2)	18 (45.0)	<0.001[s]	
Positive	22 (19.8)	22 (55.0)		

Statistical test: Chi-square test and, for gestational age, birth weight -independent t test; s: significant, ns: not significant, p value <0.05 was considered significant. EONS: Early onset neonatal sepsis, LONS: Late onset neonatal sepsis, C/S: culture and sensitivity

As seen in Table 5, the mean lactic acid (mmol/L) was found 2.12 ± 0.72, 5.08 ± 1.08, and 6.01 ± 3.51 in sepsis, septic shock, and severe sepsis respectively and p-value was statistically significant.

As seen in Table 6, the mean lactic acid (mmol/L) was found 2.40 ± 1.08, and 5.13 ± 3.40 in survivor and non survivor group respectively and p-value was statistically significant with regard to death.

Binary logistic regression analysis (Table 7) with survivor and non survivor as dependent variable and lactic acid and other factors as independent variables revealed that there was a significant association of lactic acid concentration with mortality (OR=2.46, 95% CI 1.630-3.723, p value <0.001). Here only sex and lactic acid had significant association with survivor and non survivor group but gestational age, birth weight, number of septic events had no significant association with survivor and non survivor groups [15].

Table 4: Comparison between survivor and non survivor of studied neonates regarding demographic and clinical parameters (N=151).

Variable	Survivor n=111 (%)	Non survivor n=40 (%)	p-value
Sex of the baby, n (%)			
Male	68 (61.3)	13 (32.5)	0.002[s]
Female	43 (38.7)	27 (67.5)	
Birth weight(gm) (mean ± SD)	2102.75 ± 816.65	1565.78 ± 604.31	<0.001[s]
Gestational age (weeks)(mean ± SD)	34.75 ± 3.44	32.65 ± 3.37	<0.001[s]
Place of delivery			
Inborn	88 (79.3)	34 (85.0)	0.431[ns]
Out born	23 (20.7)	6 (15.0)	
Onset of sepsis			
EONS<72 hours	71 (64.0)	16 (40.0)	0.009[s]
LONS>72 hours	40 (36.0)	24 (60.0)	
Number of event, n (%)			<0.001[s]
Single	88 (79.3)	16 (40.0)	
Multiple	23 (20.7)	24 (60.0)	
Blood C/S, n (%)			<0.001[s]
Negative	89 (80.2)	18 (45.0)	
Positive	22 (19.8)	22 (55.0)	
Severity of sepsis, n (%)			
Sepsis	99 (89.2)	10 (25.0)	<0.001[s]
Septic shock	5 (4.5)	9 (22.5)	
Severe sepsis	7 (6.3)	21 (52.5)	

Statistical test: Chi-square test and, for gestational age, birth weight -independent t test; s: significant, ns: not significant, p value <0.05 was considered significant. EONS: Early onset neonatal sepsis; LONS: Late onset neonatal sepsis; C/S: Culture and Sensitivity

Table 5: Comparison of mean lactic acid among the subgroups of neonatal sepsis of the study subjects (N=151).

	Sepsis	Septic shock	Severe Sepsis	p-value
	n-109	n-14	n-28	
Lactic acid, (mmol/L)				
Mean ± SD	2.12 ± 0.72	5.08 ± 1.08	6.01 ± 3.51	<0.001[s]

Statistical test: One way ANOVA test; s- significant

Table 6: Comparison of mean lactic acid among the survivor and non survivor groups of neonatal sepsis of the study subjects (N=151).

	Survivor	Non survivor	p-value
	n-111 (73.5%)	n-40 (26.5%)	
Lactic acid, (mmol/L)			
Mean ± SD	2.40 ± 1.08	5.13 ± 3.40	<0.001[s]

Statistical test: Independent t test; s- significant

Table 7: Logistic regression analysis for the mortality outcome of neonatal sepsis of the study subjects (N=151).

Factors	Odds ratio	95% Confidence interval		P-value
		Lower	Upper	
Sex (Female)	3.36	1.199	9.419	0.021[s]
Gestational age, wks	0.975	0.785	1.212	0.822[ns]
Birth weight, g	0.999	0.998	1	0.063[ns]
Multiple number of septic event	1.977	0.684	5.712	0.208[ns]
High lactic acid	2.464	1.63	3.723	<0.001[s]

Statistical test: Binary logistic regression; s: Significant; ns: Not Significant

Discussion

Sepsis is a common and serious neonatal illness with high morbidity and mortality particularly in resource-limited communities [16]. Extensive research efforts have yielded many biomarkers that are potentially useful, not only for the diagnosis of sepsis but also for the prediction of its outcome.

Many of these markers are expensive and not readily available, which is negatively reflected on their popularity. In this regard, the lactic acid concentration appears to have an advantage. It has emerged, in recent years, as a promising marker capable of predicting the prognosis in sepsis. However, data in pediatric and neonatal patients are very limited. Thus, this prospective observational study was conducted with an objective to see the association of lactic acid concentration in neonatal sepsis with regard to its severity and outcome i.e. mortality during hospital stay.

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In the present study, a total of 151 neonates with the diagnosis of sepsis were enrolled. Mean gestational age is close to a previous study done by Tomar et al., Sarkar et al., and Kalathia et al. [15,17,18]. In a different study mean gestational age was lower than the present study. Hansen et al. [19] in their study, the mean gestational age was much higher than our findings [20]. In the present study mean birth weight was lower than the previous study [15].

Most of the babies were delivered in our hospital which is more than the previous study done in BSMMU [21]. Male was predominant than female which is quite similar to a previous study done in Bangladesh [22]. In the current study, most of babies were low birth weight which was similar in a previous study [23]. About two third of babies were preterm which was higher than a previous study [24]. In this study, the percentage of caesarean section was more. This higher percentage of caesarean section may be explained by the fact; this study was conducted in a tertiary care as well as only university hospital in Bangladesh, where most of the complicated pregnancies are dealt with necessitating caesarean section.

In the present study, early onset sepsis constituted more, which is in agreement with the reports from other developing countries e.g., in Iran and in a study of Bangladesh but in contrast with reports from Saudi Arabia, Pakistan and Libya where late onset sepsis is more common [24]. The possible explanation for a higher frequency of EOS in this study might be the more referral of preterm labors and preterm newborns to our center.

More patients with LONS were found in the non-survivor group on in-hospital mortality analysis, which might be attributed to the colonization of NICU of BSMMU with pathogenic bacteria like Acinetobacter, Klebsiella, etc. and repeated episodes of the event during the hospital stay.

Among the study subjects less than one third neonates had high lactic acid with a higher mean value than the study conducted by Iskandar et al. [25] mostly due to relative larger sample size. In the present study, high lactic acid was found to be significantly associated with severity of sepsis. Mean value of lactic acid was higher in septic shock and severe sepsis when compared with sepsis. The results of one-way ANOVA test showed significant differences among the groups of sepsis severity degree which was similar as a previous observational study [25]. Categorization of lactic acid as normal and high revealed that lactic acid was always within normal limit in all neonates with sepsis, high in all with septic shock and majority of severe sepsis had high value which had statistically significant association.

Moreover, lactic acid was significantly elevated in nonsurvivors compared with survivors of neonatal sepsis. This suggests a potential value of lactic acid in the prediction of sepsis outcome, which has been demonstrated in previous studies. The durability of interrelation between the parameters was determined as the Odd Ratio (OR). High lactic acid had strong association with mortality than those neonates with normal lactic acid. Among the non survivors, females were predominant as their gestational age and birth weight were relatively lower than the male. Among neonates with lactic acid level of >3.5 mmol/L, majority died which was similar to a previous study [26]. In that study, had findings that the mortality rate was significantly higher for full-term infants in the severely-elevated lactic acid group than in the mildly elevated and the normal lactic acid group. Another study showed that the impoverished prognosis group had a significantly escalate lactic acid level on admission collated with the good prognosis group [26].

In this study serial measurement of lactic acid was not done and the time intervals from onset of sepsis to collection of blood samples were not same in all patients.

Conclusion

Lactic acid concentration has significant association with disease severity and in-hospital mortality in neonatal sepsis.

Recommendation

Further multicenter studies on a large scale are needed to fully evaluate and confirm the predictive role of lactic acid in severity and mortality in patients with neonatal sepsis. Follow up studies of the survivors with high lactic acid are warranted to assess their long-term neurodevelopmental outcome.

Acknowledgments

We are thankful to Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka for providing all types of logistic supports and the facilities for the conduction of this study. Our gratitude to all the nurses of NICU, BSMMU for their unconditional help in this research. This work was supported by the Department of Neonatology and Department of Biochemistry, BSMMU.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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