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Procalcitonin (PCT) Concentration and Complete Blood Count (CBC) Values in Umbilical Cord Blood Samples in Detection of Neonatal Sepsis

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Abstract **Original Research Article**

This prospective study was conducted in the department of Obstetrics and Gynecology and Neonatology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh during the period from 1st April, 2013 to 31st July, 2014. Our study aim was to determine the usefulness of procalcitonin (PCT) concentration and complete blood count (CBC) values in umbilical cord blood samples in detection of neonatal sepsis. Mothers of both term and preterm having history of risk factor of sepsis were approached for enrolment in the study. After admission of such mother in the selected dept., obstetrician informed about the risk factor of sepsis and parents were approached for collecting cord blood. Analysis of correlation was done using Pearson's correlation coefficient and linear regression. Receiver operator characteristics (ROC) curves were used to determine the individual diagnostic performance of umbilical cord PCT and WBC count for detection of early onset neonatal sepsis. Mean gestational age and birth weight of enrolled infant were 34.89 ± 2.55 weeks and 2053.26 ± 503.75 grams respectively. Twenty-five (54.3%) of these newborns were male. Cesarean section was the mode of delivery for 39 (84.8%) of the enrolled infants. Low APGAR score at 1 min (<7) was documented only in one patient. Among the enrolled infants 6 (13%) were found to be small for gestational age. Common maternal risk factor for sepsis demonstrated during pregnancy were PROM in 71.7%, febrile illness with evidence of bacterial infection in 15.2%, foul smelling and/or meconium-stained liquor in 17.4%, chorioamnionitis in 4.3%, and Urinary tract infection in 4.3% of enrolled infants. The majority of the newborns had only one perinatal sepsis risk factor. More than 1 risk factor present in 6 (13%) mothers. Besides risk factors for sepsis, common maternal problems demonstrated during pregnancy were hypertension and diabetes mellitus in 20% and 17.5% of enrolled infants respectively. Forty-two (91.3%) of the mother received at least one dose of intrapartum antibiotic prophylaxis before 4 hours of delivery. Umbilical cord blood Procalcitonin concentration is a useful marker for early detection of neonatal sepsis. Complete blood count from umbilical cord is not useful in detecting early onset neonatal sepsis.

Keyword: Usefulness, Procalcitonin(PCT), Complete Blood Count (CBC), Receiver Operator Characteristics (ROC).

INTRODUCTION

Materno-fetal bacterial infection is one of the most common causes of neonatal morbidity and mortality. Neonatal septicemia is a clinical syndrome of systemic illness accompanied by bacterium occurring in the 1st 28 days of life [1]. Neonatal sepsis may be categorized as early onset and late onset sepsis. Eighty-five percent of newborns with early onset infection present within 24 hours and smaller percentage of patients present between 48 hours and 6 days of life [2]. These infants have a history of one or more significant

obstetric complications including premature rupture of membrane (PROM), prematurity, signs of chorioamnionitis, maternal fever. Bacteria responsible for early onset sepsis are acquired from infected amniotic fluid or from the birth canal during delivery and mortality rate is high. However, as the predictive value of these clinical risk factors is known to be limited, they are frequently supplemented by blood tests. Routinely, blood is drawn for the tests by venipuncture [3]. Early diagnosis and treatment are vital for better outcome. In the absence of reliable markers of infection during the first hours of life, pediatricians often start early antibiotic treatment in newborn infants with risk factors for infection, exposing a considerable number of patients to unnecessary treatment. Procalcitonin (PCT) has been implicated as a sensitive and specific marker of bacterial infection [4]. Early onset neonatal sepsis (EONS) suspicion is one of the most stressful situations for neonatologist [5]. Because clinical signs of EONS are known to be non-specific, pediatricians often start early empiric antibiotic treatment in newborns presenting few symptoms or some risk factors of infection before receiving results of bacteriologic cultures and inflammatory markers [6, 7] first demonstrated PCT level to increase at the onset of bacterial infection and sepsis. This acute phase reactant has the characteristics of acute phase proteins, hormones and cytokines. PCT is also the prohormone of calcitonin. It is a polypeptide with a molecular mass of 12,793 Da. The site of its production, the mechanism of its release and action, and the role it plays in man has still not been well established. PCT is not usually detectable in the serum of healthy adults, but the serum concentration rises markedly during bacterial infection [7] and therefore it may be a useful tool in the diagnosis of bacterial infections. A rapid increase in the concentration of the serum PCT (2 to 4 hours) occurs in response to the stimulation of endotoxin in healthy volunteers and reaches a plateau in 6 hours and decreases gradually to its initial level within 24 hoursn[6] but serum PCT has a long half-life in adults (25 to 30 hours). These characteristics suggest the possible utility of umbilical cord serum PCT concentration as a marker for perinatal bacterial sepsis [8]. Reference value in healthy neonates was established for the first time by time-resolved amplified crypt ate emission (TRACE) technology in 2007, ranging from 0.04 to 0.43 mg/L [9]. Considering that gestational age has a negative effect on PCT levels at delivery, clinical utility of PCT in the diagnosis of EONS requires the establishment of reference covering a range of both gestational and postnatal ages [10]. A complete blood count value in neonatal sepsis has relatively poor diagnostic ability as it may vary widely in the immediate newborn period. However, cord blood CBC and its relationship with newborn CBC has been questioned in very few studies so far. Therefore, cord blood CBC and its comparison with newborn blood CBC could reveal some interesting findings which may help in guiding in decision making whether cord blood CBC can be recommended in the setup of suspected neonatal sepsis. In an era of increased awareness of pain in neonates, there is a possibility of employing umbilical cord blood as the source for these tests, thereby obviating the need for venipuncture. Pathogenesis of Early onset neonatal sepsis starts in utero. Cord blood markers for sepsis are not a commonly practiced mode of investigations in most of the centers. Serum procalcitonin which is a proven marker in the diagnosis of sepsis and complete blood count (CBC) abnormality, if any, could help clinicians detecting sepsis early. The recommendations from the study would guide the neonatologist to start and continue the antibiotics in a setup of suspected sepsis instead of depending upon only on the risk factors. Moreover, if umbilical cord blood could be substituted for infants' blood without decreasing the accuracy of laboratory data, it would spare the infants the discomfort of an invasive procedure(s) and save both time and resources.

OBJECTIVES

General Objective:

- To determine the usefulness of procalcitonin (PCT) concentration and complete blood count (CBC) values in umbilical cord blood samples in detection of neonatal sepsis.

Specific Objectives:

- To estimate umbilical cord blood PCT and CBC values in newborn with risk factor of sepsis
- To compare PCT and CBC values of clinically septic and non-septic newborn
- To assess correlation of CBC results between umbilical cord and venous blood
- To establish a cut-off point of PCT to detect early onset sepsis

METHODOLOGY AND MATERIALS

We carried out a prospective study in the department of Neonatology and Department of Obstetrics and Gynecology Bangabandhu S heikh Mujib Medical University, Dhaka, Bangladesh during the period from 1st April, 2013 to 31st July, 2014. We used purposive sampling method. Our study populations were Newborns (Term and Preterm) delivered in the Department of Obstetrics and Gynecology of Bangabandhu Sheikh Mujib Medical University during the study period.

Inclusion criteria:

- Newborns delivered in the department of Obstetrics and Gynecology of Bangabandhu Sheikh Mujib Medical University having risk factors for sepsis.

Exclusion Criteria:

- Major congenital anomalies

- Baby of Rh negative mother
- Severe perinatal asphyxia

RESULTS

During the study period, after taking informed written consent from parents a total of 50 neonates were enrolled. Of 50 enrolled infants, 1 parent withdrew consent, 1 sample's volume was insufficient, 2 samples were clotted. The remaining 46 infants were ultimately retained for analysis. Demographic and perinatal characteristics of studied newborns are presented in table 1. Mean gestational age and birth weight of enrolled infant were 34.89 ± 2.55 weeks and 2053.26 ± 503.75 grams respectively. Twenty-five (54.3%) of these newborns were male. Cesarean section was the mode of delivery for 39 (84.8%) of the enrolled infants. Low APGAR score at 1 min (<7) was documented only in one patient. Among the enrolled infants 6 (13%) were found to be small for gestational age. Maternal characteristics are shown in table 2. Common maternal risk factor for sepsis demonstrated during pregnancy were PROM in 71.7%, febrile illness with evidence of bacterial infection in 15.2%, foul smelling and/or meconium-stained liquor in 17.4%, chorioamnionitis in 4.3%, and Urinary tract infection in 4.3% of enrolled infants. The majority of the newborns had only one perinatal sepsis risk factor. More than 1 risk factor present in 6 (13%) mothers. Besides risk factors for sepsis, common maternal problems demonstrated during pregnancy were hypertension and diabetes mellitus in 20% and 17.5% of enrolled infants respectively. Forty-two (91.3%) of the mother received at least one dose of intrapartum antibiotic prophylaxis before 4 hours of delivery.

Table -1: Baseline characteristics of enrolled newborns (n= 46)

Variable	Newborns (n= 46)	
Birth weight (g)	2053.26	± 503.75
Gestational age (weeks)	34.89	± 2.55
Gender, Male	25 (54.3%)	
Cesarean section	39 (84.8%)	
Small for gestational age	06 (13%)	
Apgar score in 1 minute	7.33 ± 0.52	
Apgar score in 5 minutes	8.67 ± 0.67	

Numerical data are presented as mean ± SD and categorical data as percentage (%)

Table -2: Maternal Characteristics of enrolled newborns (n= 46)

Variable	Newborns (n= 46)
Maternal age (years)	25.10 ± 4.74
PROM (> 18 hours)	33 (71.7%)
Febrile illness in the mother	07 (15.2%)
Foul smelling and/or meconium-stained liquor	08 (17.4%)
Chorioamnionitis	02 (4.3%)
Urinary tract infection	02 (4.3%)
Single perinatal risk factor	40 (86.9%)
More than one perinatal risk factor	06 (13%)
Intrapartum antibiotic prophylaxis	42 (91.3%)
(Before 4 hours of delivery)	

Numerical data are presented as mean ± SD and categorical data as percentage (%)

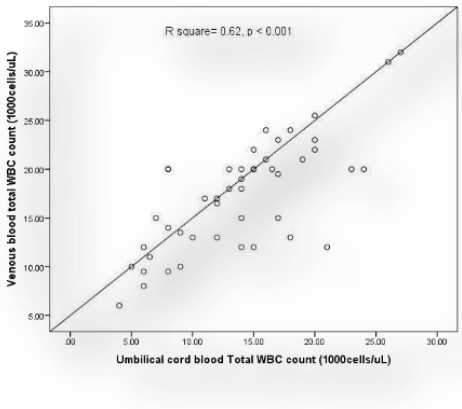

Fig-1: Linear regression plots of cord blood WBC vs venous blood WBC of the enrolled infants. (n= 46)

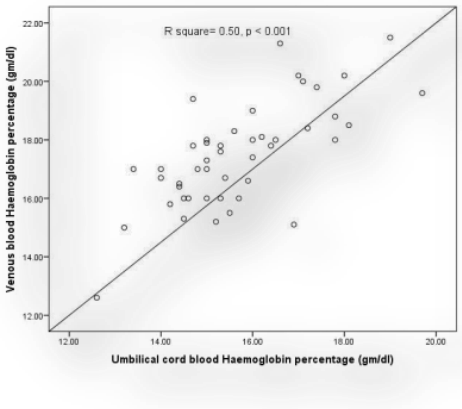

Fig-2: Linear regression plots of cord hemoglobin vs venous blood hemoglobin of the enrolled infants.(n= 46)

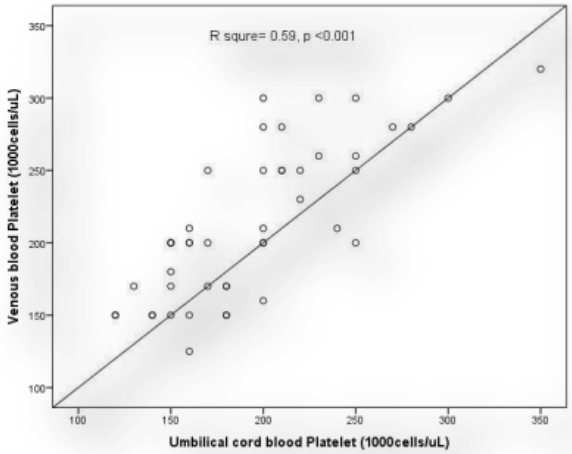

Fig-3: Linear regression plots of cord platelet count vs venous blood platelet count of the enrolled infants. (n= 46)

Table-3: Hematological indices in umbilical and peripheral venous blood in term and preterm infants. (n= 46)

Variable	Term(n=15)	Preterm (n =31)	P value
WBC	-	-	-
UC	15.67 ± 6.22	13.06 ± 5.44	0.160
VB	18.87 ± 6.71	16.58 ± 5.10	0.206
HB		-	-
UC	15.35 ± 1.95	14.71 ±1.50	0.271
VB	17.42 ± 2.94	17.31 ±1.57	0.889
HCT	-	-	-
UC	0.44 ± 0.05	0.43 ± 0.05	0.492
VB	0.53 ± 0.07	0.50 ± 0.05	0.381
PLT	-	-	-
UC	181.33 ± 47.34	200.97 ± 49.62	0.209
VB	196.00 ± 49.52	222.10 ± 53.51	0.129

UC- Umbilical cord, VB- Venous blood, Hb- Hemoglobin, Hct- Hematocrit, PLT-Platelet, Numerical data are, presented as mean ± SD, Statistical test: Independent Sample t- test

Table-4: Procalcitonin concentration in umbilical cord blood in term and preterm infants. (n= 46)

Variable	Term (n =15)	Preterm (n =31)	P value
UCB Procalcitonin	307.99 ± 390.26	366.37 ± 356.64	0.63

UCB- Umbilical cord blood, Numerical data are presented as mean ± SD, Statistical test: Independent Sample t- test.

Table-5: Correlation of umbilical cord and venous CBC. (n= 46)

Variable	UC blood	Venous blood Correlation	P value
WBC (cells/mm3)	13.89 ± 5.70	17.32 ± 5.70	0.75 < 0.001
ANC	7384.48 ± 4351.77	9420.66 ± 5474.04	0.53 < 0.001
Hemoglobin (gm/dl)	15.69 ± 1.51	17.48 ± 1.78	0.50 < 0.001
Platelets	194.57 ± 49.25	213.80 ± 53.07	0.77 < 0.001
UC- Umbilical cord			

Numerical data are presented as mean ± SD, Statistical test: Paired sample t test, r = correlation coefficients

Table -6: Complete blood count and clinical significance.(n= 10)

Variable	Cord	Neonatal	
	Blood; n (%)	Blood; n (%)	P value
WBC > 30 x 103	1 (2.2)	2 (4.3)	0.957
WBC < 5 x 103	2 (4.3)	0	0.978
Platelets < 150 x 103	4 (8.70)	1 (2.2)	0.913

Numerical data are presented as mean ± SD,

DISCUSSION

The aim of this study was to determine the usefulness of PCT and CBC from umbilical cord blood for early detection of neonatal sepsis. This was a prospective study with 46 newborns, both term and preterm. We analyzed the cord blood PCT and CBC for early detection of neonatal sepsis. In this study risk factor for sepsis was more common in male (54.3%) than female (45.7%), which is consistent with the findings of Naher, BS *et.al* (2011) [11]. In our study, percentage of caesarean section was 84.8%. The 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 often requiring caesarean section. Among the risk factors of sepsis premature rupture of the membrane which was more prevalent in 71.1% cases. This high percentage of PROM is not consistent with other studies; Naher, BS *et.al* (2011) [11] showed in their study, PROM was present only in 24% cases, though this study showed risk factors for sepsis in both early onset and late onset neonatal sepsis. The majority of the infants had only one perinatal risk factors which is consistent with the findings of Hansen, A *et.al* (2005) [12]. Recent study done by Steinberger, E *et.al* (2014) [13] showed that among the 218 preterm infants, 101 (46.3%) had PROM. In our study 91.3% of the mother having risk factors of sepsis is treated with at least 1 dose of antibiotics with Ceftriaxone before 4 hours of delivery [12] they showed in their study 84% of the mother got prophylactic antibiotic. This high rate of prophylactic antibiotic given to the mother is due to protocol that Department of Gynecology and Obstetrics of BSMMU follows. Procalcitonin concentration in preterm newborn (366.37± 356.64) was higher than term baby (307.99±390.26) which was not significant. These findings are consistent with the findings of Kordek, A *et.al* (2003) [14]. In our study the correlation of the WBC counts, ANC as well as the hemoglobin and platelets counts in cord blood and infant's venous blood were moderate to high as measured by Pearson's correlation coefficient ($r= 0.75$, $p<0.001$; $r= 0.53$, $p< 0.001$; $r= 0.50$; $p< 0.001$; $r= 0.77$, $p< 0.001$ receptively). Similar observation was also made by Stoll, BJ *et.al* (2003) [15] regarding correlation of hematological indices between umbilical cord and venous blood of the newborns [3] also found similar findings. The elevated values of WBC, neutrophil, hemoglobin, hematocrit and platelet in the venous blood in comparison to those found in the umbilical cord blood samples and the trend of elevated values of the CBC components in term versus preterm infants shown in this study is consistent with our knowledge of elevation in CBC components as gestational age progresses and in the first hours after birth. In this study there were 46 paired samples for CBC from the cord and from the neonates. WBC counts>30000/mm3, low WBC counts (<5000/mm3), Platelets counts were similar for clinical significance in both samples. Similar observation has been made by Beeram, MR *et.al* (2012) [16]. Total numbers of clinical sepsis were found in 9 patients in our study. Respiratory distress, poor perfusion and lethargy were the prominent clinical manifestation found in 66.7% of newborns each (6/9). [17] in their prospective study of 128 newborns (including septic and no septic) found 22 (17%) babies developed respiratory distress followed by poor perfusion (9%). The fact that we evaluated 46 patients for sepsis and did not have a single positive blood culture is not surprising since the rate of positive blood cultures in neonatal sepsis evaluations is reported to be 0.5 (14) to 0.8% [18,12] also observed no culture proven sepsis in their study of 113 newborns which is similar to our finding. Moreover 42 (91.3%) mothers with risk factor got at least one dose of prophylactic antibiotics. Perhaps the most reassuring result of this study was that essentially all of the infants who were diagnosed with clinical sepsis become ill early, within the usual newborn nursery admission time post-delivery. This finding is similar to that of Ascher, DP *et.al* (1993) [19] in their study of 30000 births at 5 medical centers reported that when intrapartum antibiotics failed, most infants were ill immediately after birth. A more recent study of 319 infants with group B streptococcal disease by Escobar, GJ *et.al* (2000) [18] indicated that exposure to intrapartum antibiotics had no effect on the timing of illness presentation, with > 95% of newborns demonstrating clinical signs of infection in the first 24 hours of life. The comparison of mean of WBC count, ANC count, platelet count from umbilical and venous blood in clinical sepsis and no sepsis. There was no significant difference of mean of WBC count, ANC count and platelet count in two group's patients. The comparison of Procalcitonin concentration from umbilical cord blood in clinical sepsis and no sepsis showed in table 8. Procalcitonin was significantly high in clinical sepsis group and statistically significant, p-0.001. A prospective study done by Kordek, A *et.al* (2003) [14] showed that there were no statistical differences in WBC count between clinical sepsis and no sepsis patients. But they found statistical significance in PCT concentration between clinical sepsis and no sepsis newborns. Present study aimed to determine the usefulness of cord blood PCT and CBC for early detection of neonatal sepsis. Receiver operator characteristic (ROC) curves were constructed to examine diagnostic performance of PCT and CBC from cord blood in predicting the occurrence of early onset neonatal sepsis. The area under the ROC curve for umbilical cord blood PCT was high and statistically significant in comparison to umbilical cord blood CBC (AUC of PCT 0.87, P value 0.001). Best cut-off value was obtained at 530.16 pg./ml yielded sensitivity 89% and specificity 92%. Our AUC are within the range of a commonly considered good (≥ 0.75) and excellent (≥ 0.90) biomarker [20]. Area under curve for umbilical cord blood WBC was 0.59 (p value 0.42). [21] chose

0.5 µg/L as the cut-off point that offered sensitivity 87.5%, specificity 98.7%, positive predictive values 87.5% and negative 98.7% in both term and preterm newborns. Some years later the same authors published an optimal cut-off value for PCT as 0.6 µg/L. This resulted in sensitivity and specificity being 92% and 97% respectively [21]. More recently a study on preterm newborn for prediction of sepsis was done which showed the optimal cut-off values for PCT was 0.235 µg/L (p value < 0.01, sensitivity 78.6% and specificity 86.3%) [22]. There are a lot of studies focusing on either cord blood PCT or CBC in the prediction of early onset sepsis, but none looked for the combined use of these investigations. Since different study groups determined or used different cut-off values in different populations, the diagnostic and/or predictive value of cord blood PCT and CBC values are difficult to analyze and to compare with our findings. For example, one study reported on cord blood PCT in neonates at risk for bacterial infection and found an optimal cut-off value of 0.6 µg/L [21] resulting in sensitivity and specificity of 92% and 97%, respectively. Some years later the same authors published an optimal cut-off value for PCT as 0.5 µg/L. This resulted in sensitivity and specificity being 87.5% and 98.7%, respectively. Thus, more well-designed and prospective investigations on the marker PCT for the use of the prediction of early-onset sepsis in preterm infants are needed.

Limitations of the study

It was a prospective study with small sample size. So, the study result may not reflect the scenario of the whole country.

CONCLUSION AND RECOMMENDATIONS

Umbilical cord blood Procalcitonin concentration is a useful marker for early detection of neonatal sepsis. Complete blood count from umbilical cord is not useful in detecting early onset neonatal sepsis. Venous complete blood count can be replaced by umbilical cord blood for septic screening in newborn having risk factor for sepsis. Further study is needed to detect cut off value of umbilical cord complete blood count to detect early onset sepsis.

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