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The Efficacy of Serum Procalcitonin as A Reliable Marker for Diagnosis of Neonatal Sepsis

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ABSTRACT

Background: Newborn sepsis (NS) is a major cause of neonatal morbidity and mortality, and it has become a serious global public health issue. Because the clinical appearance of NS can be confounded with non-infectious conditions, the onset of sepsis might be fast, and the clinical process can swiftly subside. Early recognition and diagnosis of neonatal sepsis are difficult because of the variable and non-specific clinical presentation of this condition. **Objective:** To evaluate the efficacy of serum procalcitonin as a reliable marker in diagnosis of neonatal sepsis. **Methods:** This cross sectional analytical study was carried out in the Department of Pediatric, Mugda Medical College Hospital, Dhaka, Bangladesh from March to May 2020. Total 55 new-borns with suspected sepsis were included in the study. Specimens of blood were obtained from each neonate prior to commencement of antibiotic for sepsis work up. Serum CRP and procalcitonin levels were measured. Data analysis was performed by using SPSS for windows version 21. Chi-square test, Mann- Whitney U test and Validity test was done to measure the level of significance. Area under the ROC (Receiver operating characteristics) was evaluated. A p value ≤0.05 was considered level of significance. **Results:** Among total 55 new-borns included in this study, 27(49.09%) new-born were diagnosed as proven sepsis and 28(50.9%) new-born as clinical sepsis. A statistical significant difference was observed between the mean of birth weight in septic and suspected groups. The mean of gestational age (GA) in proved sepsis infants was 31.9 weeks that was lower than two other groups (P< 0.05). The procalcitonin (PCT) was high in 58.2% (500-<2000 pg/ml) new-born and remarkably high (2000-<10000) in 36.4% new-born with sepsis. At a cut-off value > 500pg/ml, the sensitivity of

PCT in detecting sepsis was 46.4% its specificity 75%, positive predictive value was 67.9%, and negative predictive value was 60.7% whereas the sensitivity of CRP for predicting sepsis was 33.3%, specificity 77.8%, positive predictive value 62.9% and negative predictive value was 55.6%. The area under the ROC curve for procalcitonin (0.653) was significantly higher than CRP (0.571). **Conclusion:** In conclusion, the serum levels of PCT is a more reliable marker than the serum levels of CRP or the WBC counts in the early diagnosis of neonatal sepsis and in the evaluation of the response of the disease to the antibiotic therapy. The benefit of measuring serum PCT routinely in the diagnosis and follow-up of neonatal sepsis, is that it reduces the hospital costs.

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INTRODUCTION

New-born sepsis (NS) is a major cause of neonatal morbidity and mortality, and it has become a serious global public health issue [1, 2]. Because the clinical appearance of NS can be confounded with non-infectious conditions, the onset of sepsis might be fast, and the clinical process can swiftly subside. The timely and correct diagnosis of NS is typically challenging in everyday clinical practice. Improving diagnostic testing accuracy may improve outcomes in people with actual sepsis and reduce the indiscriminate administration of antibiotics in those who do not have sepsis [3]. Neonatal sepsis is the commonest cause of neonatal mortality and it is responsible for 30-50% of the total neonatal death in developing countries [4,5]. It is estimated that 20% of all neonates develops sepsis and approximately 1% die of sepsis related causes [5]. Neonatal septicemia is a clinical syndrome of systemic illness accompanied by bacterium occurring in the 1st 28 days of life [6]. Neonatal sepsis may be categorized as early onset and late onset sepsis. While many impoverished countries still use a substandard approach to diagnose NS, the disease's non-specific signs and symptoms have made it even more difficult for most modern medical settings to make a precise clinical diagnosis [7]. Definitive diagnosis of neonatal sepsis is based on blood culture which take at least 48-72 hours and yields a positive result in only 10- 60% of cases.6 It is also possible that a pseudo negative result may be obtained in some cases.7In addition to the blood culture, other tests that are usually used for the diagnosis of neonatal sepsis include estimations of the white blood cell count, the absolute neutrophil count (ANC), micro ESR and I/T ratio. Unfortunately, these tests do not have a high sensitivity and specificity in diagnosing neonatal sepsis. 8 C-reactive protein (CRP) is a good marker for diagnosis of neonatal sepsis. CRP is the most extensively used and investigated acute phase reactant [8,9,10,11] and synthesized by the liver. Microbial cultures can aid in diagnosing serious bacterial infections. However, they frequently produce false-negative results, particularly after maternal antibiotic usage, and may also produce false-positive results due to sample contamination. Furthermore, microbial cultures have a time lag (two-three days) in generating results. As a result, new-borns with clinical signs of sepsis or risk factors for serious bacterial infections are typically treated with antibiotics while microbiology testing results are awaited [12]. This eventually leads to antibiotic overuse, resulting in the growth of numerous drug-resistant bacteria in the neonatal intensive care unit (NICU) [13,14]. The most reliable test for diagnosing sepsis is a blood culture;

however, false-positive results often occur due to contamination or no culture growth. Although neutrophil, total white blood cell (WBC), absolute neutrophil count (ANC), and platelet counts and blood culture are ordered to screen for suspected sepsis, these values are ineligible as infection markers due to insufficient sensitivity and specificity [15]. Thus, most hospitals commonly use C-reactive protein (CRP) levels as markers. It can be considered as a specific but late marker of neonatal infection [11]. CRP level rises 12-24 hours of infection and remain elevated for 3-7 days. Elevated CRP levels are seen in infection, in autoimmune disease, in surgery, meconium aspiration syndrome and recent vaccination [16,17]. Several serum biomarkers have been identified in recent years with potential uses to help diagnose local and systemic infections; differentiate bacterial from viral or fungal infections and guide antibiotic therapy. The serum biomarker that has been most extensively studied recently is procalcitonin [18,19]. Macrophage and monocyte cells of various organs such as the liver, lungs, kidney, adipocytes and muscle cells are the potential sources of procalcitonin in severe bacterial infection [20,21]. Serum procalcitonin levels appeared to correlate with the severity of microbial invasion.18The increase level of procalcitonin (PCT) has been observed before the rise in CRP [22]. However, some studies have shown a decrease in PCT specificity associated with an increase in uninfected preterm babies, hypoxia, neonatal respiratory distress syndrome (RDS), and hematologic failure [23,24, 25].

MATERIALS AND METHODS

This cross sectional analytical study was carried out in the Department of Paediatric, Mugda Medical College Hospital, Dhaka, Bangladesh from March to May 2020. Fifty-five (55) patients were included. The inclusion criteria were neonate who admitted into SCABU with clinical signs and symptoms of sepsis or who had maternal risk factors such as prolonged labour, PROM >18 hour, maternal fever, urinary tract infection, chorioamnionitis and neonatal risk factors such as prematurity, low birth weight. The exclusion criteria were neonates with congenital malformation, severe jaundice due to blood group incompatibilities, antibiotic therapy prior to admission. Before initiation of antibiotic therapy, blood sample was taken for total leucocyte count, absolute neutrophil count, blood culture, CRP and serum procalcitonin. The newborns under study were classified into two groups – group I as proven sepsis (who had clinical sign and symptom and positive blood culture) and group II clinical sepsis (who had clinical sign and symptom of sepsis but negative blood culture). Normal serum level of PCT are less than procalcitonin 500 pg/ml, test result interpretation is procalcitonin <500 pg/ml- normal, 500-<2000 pg/ml progress to sepsis, 2000- < 10000 pg/ml – sepsis and > 10000 septic shock. PCT level is compared between the categories of infection.

Specimens and Tests Which Were Performed: The specimens of blood were obtained from each neonate prior to the commencement of the antibiotics for the sepsis work up, which included haematological parameters like the erythrocyte sedimentation rate, total laeukocyte count, the absolute neutrophil count (ANC), the immature neutrophils to total neutrophil count ratio (I/T ratio), platelet count, degenerative changes in the neutrophils, blood culture and antibiotic sensitivity, PCT and C-reactive protein (CRP) estimation.

Serum CRP: The serum CRP level was measured by using the A-15 CRP Kit (Bio-system, Costa Brava, Barcelona, Spain). The quantitative measurement of CRP from the serum was done by an immunoturbidimetric method in the laboratory according to the manufacturer's instructions.

The reagent was linear up to 150 mg/L. The reference value was up to 6 mg/L.

Serum PCT: The serum PCT level was measured by using a quantitative immunoluminometry method and the Lumitest kit. In this assay, a PCT level of ≥0.5 ng/ ml was considered as pathological. PCT levels of 0.5-2 ng/ml, 2-10 ng/ml and >10 ng/ml were considered as weakly positive, positive, and strongly positive, respectively.

Statistical Analysis: Data analysis was performed by using SPSS for windows version 21. Chi-square test, Mann- Whitney U test and Validity test was done to measure the level of significance. Area under the ROC (Receiver operating characteristics) was evaluated. A p value ≤0.05 was considered level of significance.

RESULTS

Table-1: The characteristics of studied groups include the mean of birth weight, gestational age (GA), Apgar score (N=55)

Features	Proved sepsis	Suspected sepsis	p-value
Nu. of neonates	27	28	55
Birth weight (g)	2098±621	2313±826	0.002
GA (week)	31.94±4.2	33.9 ±3.5	0.04
Apgar scor-1	6.29±2.3	6.70±2.75	0.189
Apgar scor-5*	7.8±1.57	8.4±1.84	0.157

*The Apgar score is used as an indicator of the infant's condition in the first and fifth minutes after birth that include: appearance, heart rate, muscle tone, respiratory effort.

Total 55 new-born were included. Table-1 shows that the demographic data of the proven and suspected sepsis. A statistical significant difference was observed between the mean of birth weight in septic and suspected groups ($P< 0.05$). The mean of gestational age (GA) in proved sepsis infants was 31.9 weeks that was lower than two other groups ($P< 0.05$).

Table-2: Type of sepsis, pattern in new-born with sepsis and Proven Sepsis (N=55)

Type Of Sepsis	N	Percentage
Clinical	28	50.90%
Proven	27	49.09%
New-Born With Sepsis		
Bacterial	12	21.80%
Fungal	16	29.09%
No Growth	27	49.90%
Proven Sepsis		
ACINO	7	12.70%
KLEB	5	9.09%
NONALBCANS	15	27.30%
PSUEDO	1	1.80%

The study subject divided into two group- proven sepsis group and clinical sepsis group. 50.9% new-born were diagnosed as clinical sepsis and (49.09%) as proven sepsis. In proven sepsis group, bacterial growth was found in 21.3%, fungal growth in 28% and no growth observed in 50.9% new-born with sepsis. Among the bacterial growth, commonest organism was acinobactor (12.7%) followed by klebsiella (9.09%), pseudomonas (1.8%) and 27.3% new born had fungal growth (Table-2).

Table-3: Distribution of procalcitonin level in new-born with sepsis (N=55)

Procalcitonin cat	Frequency	Percentage
Normal (<500 pg/ml)	3	5.50%
Progress to sepsis (500-<2000 pg/ml)	32	58.20%
Sepsis (2000-<10000 pg/ml)	20	36.40%
Total	55	100.00%

The serum level of procalcitonin was high (500-d" 2000 pg/ml) in 58.2% new-born with sepsis and remarkably high (2000-d" 10000 pg/ml) in 36.4% new-born with sepsis and only 5.5% new born had normal procalcitonin level (Table-3).

Table-4: Comparison of mean of WBC count, ANC count, platelet count, CRP and procalcitonin in proven sepsis and clinical sepsis group (N=55)

Variable	**Proven Sepsis, N=27, mean± SD**	**Clinical Sepsis, N=28 mean± SD**	**p-value**
WBC count	15880.14±13986.30	13952.95±9160.11	0.874
Absolute neutrophil count	6980.24±5460.92	6675.24±4706.64	0.853
Platelet count	123786.49±96747.07	162307.89±90971.67	0.057
CRP	11.35±7.97	9.16±6.65	0.177*
PCT	2451.00±1938.95	1529.55±1168.37	0.023*

*Mann-Whitney U test

There was no significant difference of mean WBC count, ANC platelet count and CRP between two groups of patients and only mean of procalcitonin was significantly high in proven sepsis group p-0.023 (Table-4).

Table-5: Distribution of raised CRP and PCT in clinical sepsis and proven sepsis (N=55)

Variable	**Proven**	**Clinical**	**Total**	**p-value***
	Sepsis N=27(%)	**Sepsis N=28 (%)**	**N=55 (%)**	
CRP- Raised	9(33.3)	6(21.4)	15(27.3)	0.174
PCT-Raised	13(48.1)	7(25.0)	19(34.5)	0.024

*Chi-Square test was done, CRP- raised> 6 mg/L, PCT- raised > 500 pg/ml

The raised procalcitonin was observed in 48.1% new born with proven sepsis and 25% new born with clinical sepsis and it was statistically significant between two groups of new-born. On the other hand, raised CRP observed in 33.3% new born with proven sepsis and 21.4% (6) new born with clinical sepsis and it was not statistically significant in two groups (Table-5).

Table-6: Comparison of validity tests of procalcitonin (pg/ml) and CRP (mg/L) in sepsis (N=55)

Validity tests	CRP	PCT
Sensitivity	33.3% (23.6-45.2)	46.4% (36.3-59.1)
Specificity	77.8% (67.7-88.7)	75% (64.3-86.5)
PPV	62.9% (41.6-79.6)	67.9% (49.7-81.0)
NPV	55.6% (47.6-62.4)	60.7% (50.9-68.5)
Accuracy	59.2% (45.9-67.2)	64.3% (50.5-73.0)

The sensitivity of PCT in predicting sepsis was 46.4%, its specificity was 75%, positive predictive value (PPV) was 67.9% and negative predictive value (NPV) 60.7%. The sensitivity of CRP in predicting sepsis was 33.3%; its specificity was 77.8%. Its positive predictive was 62.9% and negative predictive value was 55.6%. The sensitivity, PPV, NPV were higher for procalcitonin whereas specificity was lower in comparison to CRP (Table 6).

Table-7: Area under curve.

Test Result Variable(s)	AUC	p-value	95% Confidence Interval	
			Upper Bound	Lower Bound
CRP	0.571	0.289	0.441	0.701
PCT	0.653	0.023	0.528	0.778

AUC (area under curve), Null hypothesis: true area= 0.5.

The area under the ROC curve for procalcitonin (median: 0.653, 95% confidence interval CI: 0.528 to 0.778) was significantly more (0.653) than CRP (median: 0.571, 95% CI: 0.441 to 0.528) on the ROC curve. P value 0.023 which was significant (Table-7).

DISCUSSION

Neonatal sepsis with its high mortality rate still remains a diagnostic and treatment challenge for the neonatal health care providers. An early diagnosis of neonatal septicaemia helps the clinician in instituting antibiotic therapy at the earliest, thereby reducing the mortality rates in the neonates. An early identification of an infected neonate also helps in avoiding the unnecessary treatment of a no infected neonate. In our study 55 new-born were included. A statistical significant difference was observed between the mean of birth weight in septic and suspected groups ($P< 0.05$). The mean of gestational age (GA) in proved sepsis infants was 31.9 weeks that was lower than two other groups ($P< 0.05$). There is no single reliable test for the early definite diagnosis of neonatal sepsis. The C-reactive protein has been the most analyzed parameter for the detection of bacterial infections for many years [26,27]. Procalcitonin (PCT) has been proposed as a marker of bacterial sepsis. In this present study, among 75 new-borns, 49.09% (27) new-born were diagnosed as proven sepsis and

50.9% (28) new-born as clinical sepsis. Almost half of the new-born were diagnosed as culture proven sepsis due to early arrival in hospital, sample collection before giving antibiotic and proper aseptic technique in collection procedure. Bacterial growth was found in 21.8% new-born with sepsis. Commonest bacteria were acinetobacter (12.7%) followed by klebsiella (9.09%) and pseudomonas (1.8%). This finding is similar with the study done by Sucilathangam et.al [28] and Begum S et al [27]. The blood culture not only takes time, but it is also complicated, with a low yield. The readily achievable complete blood count and the laeukocyte differential assays have a relatively poor specificity for diagnosing sepsis. The associated band count and a leftward shift of the myeloid immaturity measurements may improve the diagnostic yield, but their subjective measurement is problematic. Therefore, the need persists for improved diagnostic indicators of neonatal sepsis. In our study, acinetobactor was the leading cause of neonatal sepsis and non albicans candida was isolated in 27.3% cases. As most of the new-born were exposed to broad-spectrum antibiotics, especially third generation cephalosporins, mechanical ventilation and not receiving enteral feeds were the risk factor for non-albicans candidal growth [26]. In the present study, PCT was high (500-<2000) in 58.2% new-born with sepsis and remarkably high (2000- <10000) in 36.4%new-born with sepsis. Previous studies done by Chiesa C et al [29], Lapillonne A et al [30] and Monneret G et al [31] had shown high PCT levels in neonates with proven or clinically diagnosed neonatal sepsis. There was no significant difference of mean of WBC count, ANC count, platelet count and CRP in two groups patients but only mean of procalcitonin was significantly high in proven sepsis group and statistically significant, p- 0.02. This finding was similar study with Mohammed I A et al [32]. In our study, PCT was high in most new-born with proven sepsis (48.1%) and in clinical sepsis (23.7%) and it was statistically significant, p-0.024 in two group of patients and this finding was similar with Carol et al. study [26] Koksel et al [33], Kawezynski et al [34] and Lopez Sastre et al [35] studies. In the present study, the PCT levels were remarkably high in the neonates with proven sepsis (48.1%) and also in clinical sepsis cases (33.3%). This finding was comparable with that of the study which was conducted by Yadolla Zahadpasha et al [36]. There was a significant correlation between the serum PCT level and the proven sepsis (p-0.02) in our study which was comparable with Koksal et al. study [33]. In the present study, the sensitivity of PCT for detecting sepsis (more than 500 pg/ml) was 46.4%, its specificity 75%, its positive predictive value was 67.9% and negative predictive value was 60.7% and the sensitivity of CRP for predicting sepsis (more than 6mg/ L) was 33.3%, its specificity was 77.8%, its positive predictive value was 62.9% and negative predictive value was 55.6%. To evaluate the test performance ROC (receiver operating characteristic) curve using sensitivity and specificity of two test like PCT and CRP for cut off value of >500 pg/ml and >6mg/L respectively. The area under the ROC for PCT (median: 0.653, 95% confidence interval CI: 0.528 to 0.778) was significantly more (0.653) than CRP (median: 0.571, 95% CI: 0.441 to 0.528), p value 0.023 which was significant. Such finding are similar with the study done by Hatherill et al [37] and Sakha et al [38] studies. The present study confirmed the findings of other investigators that PCT was more sensitive than CRP in the detection of neonatal sepsis, earlier as the PCT level rose than the CRP level during sepsis. The raised procalcitonin was observed in 48.1% new born with proven sepsis and 25% new born with clinical sepsis and it was statistically significant between two groups of new-born. On the other hand, raised CRP observed in 33.3% new born with proven sepsis and 21.4%

(6) new born with clinical sepsis and it was not statistically significant in two groups. The sensitivity of PCT in predicting sepsis was 46.4%, its specificity was 75%, positive predictive value (PPV) was 67.9% and negative predictive value (NPV) 60.7%. The sensitivity of CRP in predicting sepsis was 33.3%; its specificity was 77.8%. Its positive predictive was 62.9% and negative predictive value was 55.6%. The sensitivity, PPV, NPV were higher for procalcitonin whereas specificity was lower in comparison to CRP. Since the serum PCT levels were elevated in almost all the culture proven sepsis cases, PCT can be used as a good tool for the diagnosis of neonatal sepsis and for treating the sepsis cases. PCT is highly specific for bacterial infection and it helps differentiating it from viral infection. It correlates well with the progression and the severity of the infection. PCT helps in an early diagnosis of the sepsis on the day of the admission itself, before the blood culture report is ready (usually after 3-5 days). PCT helps in avoiding antibiotic therapy where it is not required and thereby reducing the cost and the occurrence of bacterial resistance. PCT can also be employed for the prognosis of sepsis.

CONCLUSION

In conclusion, the serum levels of PCT is a more reliable marker than the serum levels of CRP or the WBC counts in the early diagnosis of neonatal sepsis and in the evaluation of the response of the disease to the antibiotic therapy. The benefit of measuring serum PCT routinely in the diagnosis and follow-up of neonatal sepsis, is that it reduces the hospital costs. The findings of the present study suggest that the serum levels of PCT is a more reliable marker than the CRP or WBC counts in the early diagnosis of neonatal sepsis. Such a benefit might support a wider acceptance of the test in the routine practice.

Conflict of Interest: None.

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