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Original Article

Microbiology Section

Early Diagnostic Markers for Neonatal Sepsis: Comparing Procalcitonin (PCT) and C-Reactive Protein (CRP)

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ABSTRACT

Background: Early recognition and diagnosis of neonatal sepsis are difficult because of the variable and non-specific clinical presentation of this condition. It is extremely important to make an early diagnosis of neonatal sepsis for the prompt institution of anti-microbial therapy, which improves outcomes.

Aims: The aim of this study is to determine the diagnostic performance of Procalcitonin (PCT) and C-Reactive Protein (CRP) as early diagnostic markers in detection of neonatal sepsis in intensive neonatal care unit in comparison to that of blood culture and haematological parameters like micro ESR and Total WBC count.

Methods and Materials: This prospective study was conducted on neonates admitted to neonatal intensive care unit (NICU) at Tirunelveli Medical College Hospital, Tirunelveli, Tamil Nadu, India from July' 2010 and August' 2010. Specimens of blood (n = 50) were obtained from each neonate prior to commencement of antibiotics for sepsis work up including haematological parameters like Erythrocyte sedimentation rate, Total laeukocyte count, absolute neutrophil count (ANC), immature neutrophils to total neutrophil count ratio (I/T ratio), platelet count, degenerative changes in the neutrophils. Blood culture and Antibiotic sensitivity test were carried out. Serum CRP level was measured using A-15 CRP Kit by immunoturbidimetric method. Serum PCT level was measured using quantitative immuno-luminometry method by Lumitest kit.

Statistical Analysis Used: Data were expressed as mean ± SD and statistical significance was assessed by the Chi-square test.

Results: 50% (7/14) of the neonates with sepsis had raised CRP levels > 6 mg/lit. About 43.7 % (7/16) of the neonates with suspected sepsis and 20 % (4/20) of the neonates with clinical sepsis had raised CRP levels. The sensitivity of CRP for predicting sepsis was 50.0 %, its specificity was 69.4 %, its positive predictive value was 38.8 % and its negative predictive value was 78.1 %. Most (64.3% or 9/14) of the infants with sepsis had PCT levels ≥ 10 ng/ml. Out of 50 cases, elevated PCT was detected in 22, whereas CRP was noticed only in 18 cases. Among the 14 culture positive cases, elevated serum PCT level was noticed in 13 (92.85 %) cases whereas CRP level was noticed in 7 (50 %) cases. The sensitivity of the PCT in detecting sepsis was 92.8 %, its specificity 75.0 %, its positive predictive value was 59.0 % and its negative predictive value was 96.0 %.The altered haematological parameters were only noticed in 7-14 % cases.

Conclusions: In this study serum procalcitonin level was superior to serum CRP level in terms of early diagnosis of neonatal sepsis, in detecting the severity of the illness and in evaluation of the response to antibiotic treatment. The PCT concentration in our study was elevated in culture positive neonates. In some cases of culture positive babies other sepsis screening tests were negative but the level of PCT was elevated. These findings support the usefulness of the PCT to establish an early diagnosis of neonatal sepsis.

Key Words: Neonatal sepsis, Early diagnostic markers, Procalcitonin (PCT), C-Reactive Protein (CRP), Blood Culture, Haematological parameters

INTRODUCTION

Neonatal sepsis is defined as an invasive bacterial infection which occurs in the first 4 weeks of life. The incidence of neonatal sepsis varies from 11-24.5 /1000 live births in India [1]. The clinical manifestation of sepsis in newborn infants is usually non-specific. Because of the high morbidity and mortality which is associated with neonatal sepsis [2,3], an antibiotic therapy is commenced soon after the onset of the symptoms before the diagnosis is confirmed by blood culture.

The diagnosis of neonatal sepsis on the basis of the clinical symptoms is not possible [4]. Although isolation of the causative microorganisms by using blood culture has been the golden standard method for its diagnosis [5], the result is ready only 24-72 hrs after the sampling and during this period, it is necessary to treat the suspicious infants for sepsis with antibiotics on the basis of the clinical symptoms and the risk factors. It is also possible that a pseudo-negative result may be obtained in some cases [5]. The present trend which is being applied for infants who are suspected to have neonatal sepsis may lead to unnecessary and increased antibiotic consumption, a higher incidence of the side-effects due to their use, increased resistance to the antibiotics, a long hospitalization, the separation of the infants from their mothers and increased health costs [6]. Therefore, using fast diagnostic methods including laboratory markers could be beneficial for the diagnosis of neonatal sepsis [7].

In 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 (WBC), the absolute neutrophil count (ANC), micro ESR and the I/T ratio. Unfortunately, these tests do not have a high sensitivity and specificity in diagnosing neonatal sepsis.

Subsequent studies have suggested that additional markers such as C-reactive protein (CRP) and, more recently, procalcitonin (PCT) may be useful. CRP is an acute-phase reactant which is synthesized by the liver, which does not reliably differentiate between the systemic inflammatory response and sepsis. Meanwhile, some studies have shown that CRP has a limited use in the diagnosis of neonatal sepsis [7].

Recently, serum procalcitonin (PCT) has been reported as a measurable laboratory marker in the inflammatory response to the infection in some studies. Procalcitonin (PCT) is a 116-amino acid protein, a precursor of calcitonin which is produced by the thyroid. In sepsis, macrophages and the monocytic cells of the liver are involved in the synthesis of PCT. Several studies have reported on the usefulness of the quantitative measurement of PCT for an early diagnosis of sepsis in newborns [8]. Actually, definitive data are lacking, which can validate CRP and PCT as screening tools in the Emergency Department.

Clinicians are frustrated by the limitations in the diagnosis of neonatal sepsis and they would benefit from reliable tests in diagnosing sepsis early in its course. Currently, no single test fulfills the criteria of an ideal diagnostic test. In neonatology, tests which use haematological indices remain in widespread use, despite the continuing concerns about their reliability in diagnosing neonatal sepsis. These concerns largely stem from the demonstrated marked variations in the predictive accuracy of the haematological parameters.

The aim of this study was to determine the diagnostic performance of PCT and CRP as early diagnostic markers for the detection of neonatal sepsis in the intensive neonatal care unit in comparison to that of blood culture and haematological parameters like micro ESR and total WBC count.

MATERIALS AND METHODS

Study Design and Settings

This prospective study was conducted on neonates who were admitted to the neonatal intensive care unit (NICU) at Tirunelveli Medical College Hospital, Tirunelveli, Tamil Nadu over a 6 month period (April' 2010 to September' 2010).

This study was approved by the Institutional Scientific and Ethical Committee, and written informed consents were obtained from the parents. The inclusion criteria were infants who were admitted to this NICU with signs which is suggestive of sepsis, or those who developed signs of sepsis while they were in the ward. The exclusion criteria were infants who were on antibiotics or those who developed the signs of sepsis within 72 hours of discontinuation of the antibiotics and those who had birth asphyxia, aspiration syndromes, laboratory findings which were suggestive of the inborn errors of metabolism and congenital anomalies.

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 immuno-turbidimetric 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 immuno-luminometry method and the Lumitest kit (BRAHMS Diagnostic, Berlin, Germany). 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.

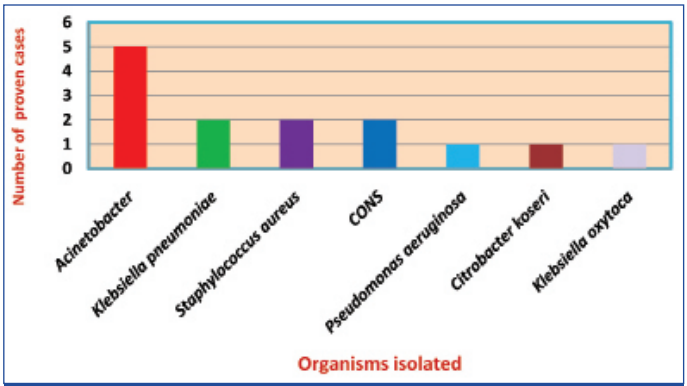
Statistical Analysis

The correlation of serum PCT and the CRP level with the haematological parameters (Total WBC count, Micro ESR and the I/T Ratio) and the blood culture for an early diagnosis of neonatal sepsis was compared statistically and the results were analyzed by using SPSS, version 12. P values of <0.05 were considered to be significant. By using the blood culture results as the gold standard, the sensitivity, specificity, positive predictive values and the negative predictive values of the PCT-Q and CRP for diagnosing sepsis were calculated. The sensitivity of a test was defined as the proportion of infants with sepsis and this was correctly identified by the test. The specificity of the test was defined as the proportion of infants without sepsis and this was correctly identified by the test. The positive predictive value of a test was defined as the proportion of infants with positive test results and who had sepsis. The negative predictive value of a test was defined as the proportion of infants with negative test results and who did not have sepsis.

RESULTS

Based on the clinical findings and the laboratory data, fifty neonates who were eligible for the study were classified into three groups viz., proven sepsis (14 neonates), suspected sepsis (16 neonates) and clinical sepsis (20 neonates). The age of onset of the sepsis ranged from day 1 to day 24. The commonest organism which was isolated was *Acinetobacter* (5/14), followed by *Klebsiella pneumoniae* (2/14), *Staphylococcus aureus* (2/14), *CONS* (2/14), *Klebsiella oxytoca* (1/14), *Citrobacter koseri* (1/14) and *Pseudomonas aeruginosa* (1/14) [Table/Fig-1].

The variables like maturity, birth weight and the sex of the patients were compared in the three sepsis groups [Table/Fig-2]. Early onset sepsis was confirmed in 29 (58 %) and late onset sepsis in



[Table/Fig-1]: Organisms isolated in Blood Culture

		Sex		Onset		Maturity		Birth weight		Mode of delivery	
Type of sepsis	No of cases	Male	Female	EOS	LOS	Preterm	Term	Low	Normal	Natural	LSCS
Clinical sepsis	20	13	7	10	10	6	14	9	11	12	8
Suspected sepsis	16	11	5	9	7	6	10	7	9	11	5
Proven sepsis	14	8	6	10	4	10	4	8	6	6	8
Total cases	50	32	18	29	21	22	28	24	26	29	21
Culture positive	14	8	6	10	4	10	4	8	6	6	8
Percentage %	28	25	33	34	19	45	14	33	23	21	38

[Table/Fig-2]: Comparison of variables between three sepsis groups

Sepsis Group TEST	Clinical sepsis (N =20)	Suspected sepsis (N = 16)	Proven sepsis (N =14)
Elevated Micro ESR	2	10	1
I:T ratio	4	9	2
Abnormal WBC Count	2	6	2

[Table/Fig-3]: Relation between haematological parameters with sepsis groups

WBC - White Blood Cell Count; I:Tratio – Immature and Total neutrophil ratio ; ESR- Erythrocyte sedimentation rate.

Group	PCT levels (ng/ml)	No of cases (n = 50)	Clinical sepsis (n = 20)	Suspected sepsis (n = 16)	Proven sepsis (n = 14)
Negative	< 0.5	28	20	7	1
Weakly positive	0.5-2	4	0	4	0
Positive	2-10	5	0	5	4
Strongly positive	> 10	13	0	0	9

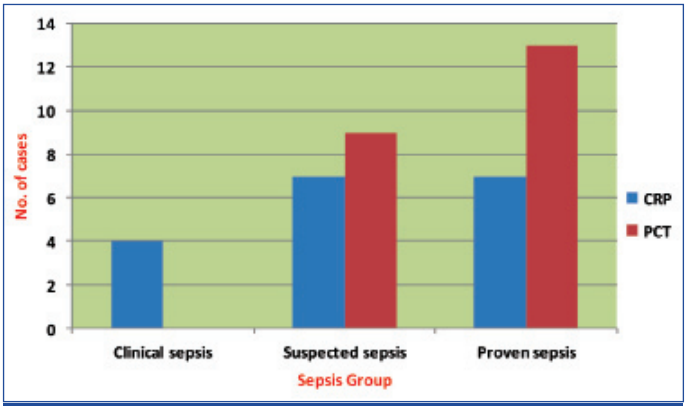
[Table/Fig-4]: Comparison of Serum procalcitonin level (ng/ml) between sepsis groups

21 (42 %) patients. Ten out of 14 neonatal sepsis patients were identified as of the early onset type and 4 were identified as of the late-onset type. Out of 14 infants, 8 were preterm and 6 were term babies. Out of 14 neonates, 8 were males and 6 were females. All the study neonates survived at discharge, except one, who died due to low birth weight and as it was preterm and it was one of twins.

The haematological parameters in the sepsis groups were compared and presented in [Table/Fig-3]. The total WBC count was normal in 12 out of 14 cultures in the proven sepsis cases. An elevated micro ESR level was observed in only one proven sepsis neonate. An abnormal I/T ratio was observed only in two cases.

Only 50% (7/14) of the neonates with sepsis had raised CRP levels of more than 6 mg/lit. About 43.7 % (7/16) of the neonates with suspected sepsis and 20 % (4/20) of the neonates with clinical sepsis had raised CRP levels. The serum PCT level in the different sepsis groups is presented in [Table/Fig-4].

The correlation between serum PCT and the CRP level is presented in [Table/Fig-5]. A higher proportion of the neonates with sepsis had raised PCT levels (26 % vs. 18 %) than those without sepsis, but raised CRP levels were seen in the suspected sepsis cases than in the proven sepsis cases (22% vs. 14%). However, a significantly higher proportion of the infants with sepsis, after 48 hours of age (11/12 or 91.6 %), had raised PCT levels ≥ 2 ng/ml and raised CRP levels (5/12 or 41.6%) than those without sepsis (PCT: 6/26 or 23.1%; CRP: 2/26 or 7.7%).



[Table/Fig-5]: Comparison of serum procalcitonin levels with CRP

Parameters	No. of + ve cases (Out of n = 50)	Culture positive (Out of 14)
PCT	22	13 (92.85 %)
CRP	18	7 (50 %)
Total WBC	10	2 (14.28 %)
Micro ESR	18	1 (7.14 %)
I:T ratio	15	2 (14.28 %)
Blood Culture	14	14

[Table/Fig-6]: Comparison of PCT, CRP, Haematological Sepsis Score and Blood culture

The sensitivity of PCT in detecting sepsis was 92.8 %, its specificity was 75.0 %, its positive predictive value was 59.0 % and its negative predictive value was 96.0 %. The sensitivity of CRP in predicting sepsis was 50.0 %, its specificity was 69.4 %, its positive predictive value was 38.8 % and its negative predictive value was 78.1 %.

22 of the 50 recruited neonates were preterm, and 45% (10/22) of this latter group had sepsis. When compared with the preterm infants without sepsis, a higher proportion of the preterms with sepsis were found to have raised PCT (90% sepsis vs. 33.3% no sepsis) and raised CRP levels (40% sepsis vs. 25% no sepsis).

Only 14.3% (4/28) of the term infants who were recruited had sepsis. When compared with the term infants without sepsis, the proportions of the term infants with sepsis who had raised PCT (100% sepsis vs. 20.8% no sepsis) and raised CRP levels (75% sepsis vs. 33.3% no sepsis).

The level of serum PCT was compared with the haematological parameters (total WBC and Micro ESR), the CRP level and the blood culture, which is given in [Table/Fig-6]. Among the 50 cases, an elevated PCT level was detected in 22 cases, whereas an elevated CRP level was noticed only in 18 cases. Among the 14 culture positive cases, an elevated serum PCT level was noticed in 13 (92.85 %) cases, whereas an elevated CRP level was noticed

only in 7 (50 %) cases. The altered haematological parameters were only noticed in 7-14 % of the cases.

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 non-infected neonate. 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.

There is no single reliable test for the early definite diagnosis of neonatal sepsis, and therefore, there is a continuing search for a new infection marker. The C-reactive protein has been the most analyzed parameter for the detection of bacterial infections for years [9,10]. This protein acts as a "scavenger" because it leads to the opsonization of bacteria and the activation of the complement system and thereby facilitates phagocytosis in the inflammatory response. Procalcitonin (PCT) has been proposed as a marker of bacterial sepsis. The advantage of PCT as compared to C-reactive protein is that the increase of the further in bacterial infection and its restoration to normal is more rapid [11].

In our study, the total WBC count was normal in 12 out of 13 cultures with proven sepsis. An elevated micro ESR level was not the reliable indicator of sepsis. An abnormal I/T ratio was observed only in two cases. This was contrary to the observations of Rodwell, Zipursky and Basu et al*.,* [12-14]. The degenerative changes in the neutrophils were not found to be a very sensitive indicator of sepsis.

In neonates, an elevated PCT level may help in predicting septicaemia; furthermore, low PCT levels were helpful in ruling out septicaemia as a diagnosis. Therefore, the PCT assessment could help the physicians in limiting the number of prescriptions for the antibiotics. In the present study, the PCT levels were remarkably high in the neonates with proven sepsis and also in the suspected sepsis cases. This finding was comparable with that of the study which was conducted by Yadolla Zahedpasha et al., [15] and Monneret et al., [16]. During the present study, the PCT test detected all the infants with gram-negative sepsis. There was a significant correlation between the serum PCT level and the type of sepsis ($p< 0.001$), which is comparable with Koksal et al., study findings [17]. Chiesa *et al.,* reported that the sensitivity of diagnosing late onset sepsis at an age after 48 hours of life in the neonates was 100% [18]. In the present study, the sensitivity of detecting the late onset sepsis was 92.8%.

In the present study, the sensitivity of PCT for detecting sepsis (more than 0.5 ng /ml) was 92.8%, its specificity 75.0%, its positive predictive value was 59.0% and its negative predictive value was 96.0 % and the sensitivity of CRP for predicting sepsis (more than 6 mg/ L) was 50.0%, its specificity was 69.4%, its positive predictive value was 38.8% and its negative predictive value was 78.1%.

Sakha *et al*. investigated the role of procalcitonin (PCT) in the diagnosis of neonatal sepsis and its correlation with the C-Reactive Protein (CRP). The sensitivity, specificity, positive predictive value and the negative predictive value of PCT (more than 2 ng mL^{-1}) were 66.7, 50, 28.6, 83.3 and those of CRP (more than 3.5 mg L^{-1}) were 70.4, 72.2, 43.2 and 89%, respectively, in the diagnosis of neonatal sepsis [19]. Ballot *et al.,* studied 52 neonates with possible infections. Only 13 neonates had a definite infection, in whom the sensitivity and the negative predictive value of serum PCT was 89.5 and 95%, respectively. But they stated that although PCT was significantly related to the category of the infection, it was not sufficiently reliable to be the sole marker of neonatal sepsis. PCT would be useful as a part of the full sepsis evaluation, but it is relatively expensive. A negative PCT on presentation may rule out sepsis [20]. Vazzalwar et al*.,* assessed PCT for the diagnosis of late-onset sepsis in 67 neonates. At a PCT cutoff value of 1.0 ng mL^{-1} the sensitivity was found to be 97% and the specificity was 80%, while with CRP, sensitivity was 72% and the specificity was 93% [21]. Boo *et al*., showed in 18 neonates among 87 infants with confirmed sepsis, based on the positive blood culture results, at a PCT cut-off level of greater than or equal to 2 ng mL^{-1}, that the sensitivity and specificity, PPV and NPV were 88.9, 65.2, 40 and 95.7% and that for CRP, they were 55.6, 89.9, 58.8 and 88.6%, respectively [22]. Chiesa *et al.,* studied the reliability of the PCT concentration in 28 infants who had a severe early onset of neonatal sepsis. They found that the sensitivity, specificity, PPV and NPV were 92.6, 97.5, 94.3 and 96.8%, respectively. They also found that 24 infants had PCT levels which were higher than normal at the time of the diagnosis. However, at that time, only 13 of them had high CRP levels [18]. Hatherill *et al.*, in their study, showed that the sensitivity and specificity of the serum PCT level were 92.6 and 97.5%, respectively, in the diagnosis of early onset neonatal sepsis and that they were 100% in neonates with late onset sepsis [23].

Carol *et al.,* in their study, showed that procalcitonin was more sensitive than the CRP in the diagnosis of septicaemia, meningitis and urinary tract infections [24]. In our study, there were seven cases of culture positive sepsis which were accompanied by elevated levels of procalcitonin and CRP. In most of the culture positive cases, the other sepsis screening tests were negative, but the level of PCT was elevated. This was similar to Boo et al's findings [22]. These findings support the usefulness of PCT in establishing an early diagnosis of neonatal sepsis.

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. In a recent study, Koksal et al*.,* concluded that the serum procalcitonin level was superior to the serum CRP level in terms of an early diagnosis of neonatal sepsis, in detecting the severity of the illness and in the evaluation of the response to the antibiotic treatment [17].

However, when PCT is used together with CRP, a negative PCT test result may help in "ruling out", while a raised CRP result helps in "ruling in", the possibility of sepsis, particularly of the late onset type. Based on the results of the present study, we recommend that the commencement of antibiotics in newborn infants should be based on the PCT results on the day of their admission to the NICU.

Among the 50 cases, an elevated PCT level was detected in 22, whereas an elevated CRP level was noticed only in 18 cases. Among the 14 culture positive cases, an elevated serum PCT level was noticed in 13 (92.85 %) cases, whereas an elevated CRP level was noticed only in 7 (50 %) cases. The altered haematological parameters were only noticed in 7-14 % of the cases.

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 findings of the present study confirm that 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. Such a benefit might support a wider acceptance of the test in the routine practice.

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