

Original Research Article

DOI: <http://dx.doi.org/10.18203/2349-3291.ijcp20203088>

Role of procalcitonin in diagnosis of neonatal sepsis and procalcitonin guided duration of antibiotic therapy

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Received: 26 June 2020

Accepted: 07 July 2020

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ABSTRACT

Background: Neonatal sepsis is one of the important causes of neonatal morbidity and mortality particularly in the developing countries. Accurate and quick diagnosis is difficult because clinical presentation is non-specific, bacterial cultures are time-consuming and other laboratory tests lack sensitivity and specificity. Procalcitonin (PCT) is often reported to be more superior to C-reactive protein (CRP), being more sensitive and specific, starts to rise earlier and returns to normal concentration more rapidly than CRP.

Methods: It is a hospital based prospective observational study. Blood samples were obtained and analyzed for blood culture, septic screen including serum CRP and PCT. Neonates were categorized into proven sepsis (n=39), probable sepsis (n=21) and clinical sepsis (n=40) groups on the basis of laboratory findings and risk factors. Data was analyzed by using standard statistical tests using SPSS 16.

Results: Out of 100 cases, elevated PCT level >0.5 ng/dl was detected in 75 and >2 ng/dl was detected in 51 whereas CRP was positive only in 61 cases. Among the 39 culture positive cases, elevated serum PCT level was noticed in 39 (100%) cases whereas CRP level was noticed in 30 (76.9%) cases. Mean PCT levels were significantly high according to infection severity ($P<0.01$). Procalcitonin (sensitivity 87.2%, specificity 72.13%, positive predictive value 66.7% and negative predictive value 89.8% and with p value of <0.001) is more superior than CRP to predict sepsis in neonate. The mean duration of antibiotic therapy was 12.46 ± 4.62 days in definite sepsis, 4.53 ± 1.78 days in probable sepsis group and in clinical sepsis group 3.75 ± 1.33 days by serial PCT measurement.

Conclusions: Serum PCT levels >2 ng/dl has got a better sensitivity and NPV, which help us not only in the early diagnosis but also in the prognosis and duration of antibiotic therapy.

Keywords: C-reactive protein, Neonatal sepsis, Procalcitonin

INTRODUCTION

Neonatal sepsis (NS) is a clinical syndrome characterized by systemic signs and symptoms of infection with or without accompanying bacteremia in the first month of life. Early-onset sepsis (EOS) is defined as sepsis occurring in the first 72 h of life and that occurring beyond 72 h is defined as late-onset sepsis (LOS).¹ Its incidence varies from 25.3 per thousand live births in

Asia of which 22.2 per 1000 live birth is EOS and 2.9 per 1000 is LOS.² The incidence of NS according to the data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births.³ According to the Indian cohort study DeNIS, the incidence of total sepsis was found to be 14.3% with nearly two-thirds as EOS and quarter of neonatal death were attributable to neonatal sepsis.⁴ It is estimated that in India 56524 neonatal deaths each year are attributed to isolates

resistant to first-line antibiotics.⁵ Early accurate diagnosis using laboratory tests with higher diagnostic value and rationale targeted selection of a short course of antibiotics along with aggressive supportive care can prevent sepsis-related mortality and morbidity and unnecessary treatment of a non-infected neonate.²

The clinical manifestation of sepsis in newborns is usually non-specific and often confused with non-infectious disorders. Microbial culture is considered as an alleged gold standard and sensitive in detecting relatively low bacterial loads but these often produce false-negative results after maternal use of antibiotics and false-positive results due to sample contamination. Microbial culture result takes 2-3 day time and the result is positive in only 25% of cases. This leads to unnecessary starting of empirical antibiotics in sepsis suspect and also in the sick child with culture-negative reports leading to increased emergence of multiple drug-resistant bacteria, a long hospitalization, the separation of the infants from their mothers, and increased health costs.⁶ Among the "traditional" bio-markers, the readily available complete blood count and leukocyte differential assays have relatively poor specificity for diagnosing sepsis. Abnormal findings, such as neutropenia and elevated I: T ratio, may help confirm the decision to start antibiotics; however, normal values need to be viewed within the context of the clinical presentation of the patient.⁷

C-reactive protein (CRP), an acute-phase reactant, is produced by the liver in response to inflammation and/or infectious stimuli.⁶ CRP is a late-rising diagnostic marker and is of limited use in the diagnosis of NS and in the initial decision to start antibiotics, particularly if the result obtained is within the equivocal 5–10 mg/L range.⁶ CRP cannot be used to differentiate between bacterial and other infections.⁸ Procalcitonin (PCT), another acute phase reactant, hormone, and cytokine, is normally synthesized by C cell of the thyroid gland. It is 116 amino acid glycoprotein also produced by hepatocytes and macrophages when encountered by bacterial toxins. PCT elevation is minimal in meconium aspiration syndrome (MAS), hypoxia and trauma in contrast to CRP.⁹ Its normal serum and plasma levels are less than 0.05 ng/ml and concentrations >0.5 ng/ml are interpreted as sepsis; more than 10 ng/ml are interpreted as severe sepsis or septic shock. The short half-life of PCT i.e. 20-24 hours enables not only rapid detection but also monitor response to treatment.² A second increase of PCT can be interpreted as the development of a new sepsis episode.² This favorable kinetic profile and its specificity and sensitivity for bacterial infection make it suitable for diagnosis, disease progression, and duration of antibiotics.

Aim and objective of the study were to determine the role of PCT in the diagnosis and treatment of neonatal sepsis and compare it with CRP along with other sepsis biochemical parameters and to determine the role of

quantitative serial PCT in guiding the duration of antibiotic therapy in neonatal sepsis.

METHODS

This prospective observational study was conducted on neonates admitted to Neonatal Intensive Care Unit (NICU), Department of Pediatrics, Bokaro General Hospital Jharkhand from 1st June 2014 to 1st May 2015 (1 year). The study was approved by the Institutional Scientific and Ethical Committee. Written valid and informed consent was obtained from the parents or caretakers.

Inclusion criteria

All the neonates up to 28 days age admitted in NICU during the study period with clinical features of sepsis as per Integrated Management of Childhood Illness (IMNCI) chart with gestational age (GA) more than 28 weeks including term, preterm, intrauterine growth restriction (IUGR) with early and late-onset sepsis both.

Exclusion criteria

All neonates greater than 28 days, birth weight less than 1000 grams, received any dose of prior antibiotic therapy, born to diabetic mother, hyaline membrane disease, birth asphyxia, laboratory findings suggestive of Inborn errors of metabolism, aspiration syndrome, major congenital anomalies, reinfection, who developed signs of sepsis within 72 hrs of discontinuation of antibiotics and refused consent by parents. The newborn that died and lost to follow-up were also excluded from the study.

Specimen and tests performed

The standard unit protocol for the management of infants with suspected sepsis was to obtain one ml blood within an hour of admission for total and differential white blood count (TLC, DC), absolute neutrophil count (ANC), I/T Ratio, micro ESR, peripheral smear and platelets, CRP, PCT and blood culture (1 ml) with strict aseptic and antiseptic precautions. Whole blood cell count was performed in an automated analyzer by 5-part analyzer Diacell-AD550. The sterile BACTEC system was used for blood cultures. Serum was separated from blood cells for measurement of PCT and CRP by centrifugation at 10000 rpm for 10 minutes. Qualitative Serum CRP was measured by using the BEACON kit (BEACON diagnostics Pvt. Ltd., 424, new GIDC, Navsari, India). The Quantitative measurement of CRP from serum was done by the Immunoturbidimetric method in the laboratory according to the manufacturer's instructions. The reagent was linear up to 150 mg/L. The reference value was 10 mg/L. Serum PCT was measured by using a Quantitative Immuno-luminometry method and B.R.A.H.M.N.S. Kit (previously known as LUMI Test R PCT) manufactured by Thermo Fisher, Hennigsdon, Germany. In this assay, a PCT level of >0.5 ng/ml was

considered as pathological. Chest x-ray and lumbar puncture were performed only if the clinical picture was suggestive of central nervous system and respiratory tract infection. All the tests were repeated in case of persistent sepsis on day 3rd, 7th, 10th, 14th, 18th, and 21st. Over-ruling of the algorithm was allowed for respiratory or hemodynamic instability. Compliance with algorithm was more than 90%.

Group stratification

All enrolled neonates were divided into three groups.

Group 1

Proven sepsis/Definite sepsis (clinical signs and symptoms as per IMNCI chart and positive blood culture).

Group 2

Suspected sepsis/Probable sepsis (Clinical signs and symptoms as per IMNCI chart with negative blood culture but at least 2 out of 5 positive septic screen: TLC less than 5000 or more than 20000 per mm³, ANC as per Monroe curves, I/T ratio more than 0.2, micro ESR more than 15 mm in the first hour and CRP more than 10 mg/L).

Group 3

Clinical sepsis (Clinical signs and symptoms as per IMNCI chart with negative blood culture and negative septic screen).

Antibiotic was started initially in all 3 groups and the choice of antibiotic was decided as per unit protocol. The indications for starting antibiotics in neonates at risk of EOS include any one of the following: the presence of greater than or equal to three risk factors for EOS, presence of foul-smelling liquor, presence of less than or equal to two risk factor(s) and a positive septic screen, abnormal PCT and strong clinical suspicion of sepsis. The indications for starting antibiotics in LOS include the positive septic screen and/or strong clinical suspicion of sepsis. Guidelines for stopping antibiotics: When two serial CRP 24 hours apart less than 10 mg/L and/or when the serial two consecutive PCT values 24 hours apart less than 0.5 ng/ml and the child clinical condition improved. The child was kept under observation for 48 hours after the stoppage of antibiotics. The child was further followed up to 28 days of age for any morbidity or mortality.

Those with PCT less than 0.5 ng/ml and CRP less than 10 mg/L at presentation and 48 hours, antibiotic was stopped and were further kept under observation till final blood culture was available at 72 hours. If CRP and PCT levels were abnormal antibiotic therapy was continued and monitored by serial CRP and PCT levels. If the culture

was positive or baby condition deteriorated later antibiotic therapy was recommended otherwise discharged. Outcome includes, no. of days of antibiotic therapy based on PCT and Clinical recovery and length of hospitalization.

Statistical analysis

Data were analyzed by using SPSS (version16 software). The following statistical tests were used: Mean and standard deviation (SD) to describe quantitative data. Student t-test and chi-square test were used to compare between two groups as regard to parametric and non-parametric data. Recover operating character (ROC) analysis was obtained to evaluate sensitivity, specificity, positive and negative predictive values of procalcitonin and CRP levels as diagnostic tests. For all tests, a probability (p) <0.05 was considered significant, p <0.01 highly significant, and p<0.001 very highly significant.

RESULTS

A total of 1519 patients were admitted to NICU, out of which 123 were made the diagnosis of sepsis at the time of admission fulfilling the inclusion and exclusion criteria and divided into three groups (Figure 1).

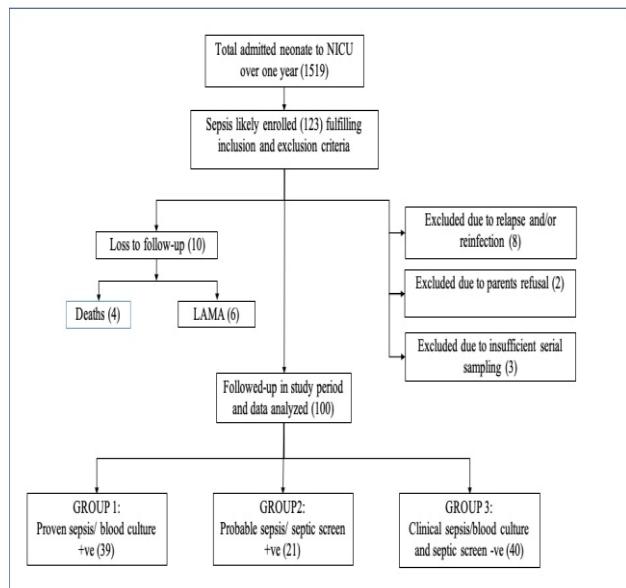


Figure 1: Work up a plan.

In this study, there were more males (73%) than female babies (27%); however, the difference was not significant (P>0.5). In preterm neonates, proven sepsis was more (66.7%), and in term neonates, probable and clinical sepsis (71.4% and 60% respectively) was more. The result was statistically significant in different groups (p<0.01). This study showed that neonates with birth weight between 1.5-2.5 Kg were most affected with sepsis (61.5% in proven sepsis group, 42.9% in probable sepsis group, and 50.0% in clinical sepsis group) but it was not statistically significant (p>0.5) (Table 1).

Totally sixteen babies were diagnosed to have early-onset sepsis and they all presented within 72 hours of life. Of these babies (EONS), 75% of mothers had h/o chorioamnionitis, 87% of mothers had a history of premature rupture of membranes. Of the early onset

babies (16), 56% of the babies required bag and mask ventilation, and 12.5% required intubation, making up a total of 68.5% of the babies requiring some form of external intervention at birth (Table 2).

Table 1: Characteristics of the patients in the study.

Variables	Group 1 (39)	Group 2 (21)	Group 3 (40)	Total (100)	p-value
Gender					
Male	30(76.9%)	15(71.4%)	28(70.0%)	73(73.0%)	0.77
Female	9(23.1%)	6(28.6%)	12(30.0%)	27(27.0%)	
Gestational age					
28-34 weeks	9(23.1%)	2(9.5%)	5(12.5%)	16(16.0%)	
34-37 weeks	17(43.6%)	4(19.0%)	11(27.5%)	32(32.0%)	<0.01
>37 weeks	13(33.3%)	15(71.4%)	24(60.0%)	52(52.0%)	
Gestational weight					
1000 to <1500 grams	9(23.1%)	4(19.0%)	3(7.5%)	16(16.0%)	
1500 to <2500 grams	24(61.5%)	9(42.9%)	20(50.0%)	53(53.0%)	0.065
>2500 grams	6(15.4%)	8(38.1%)	17(42.5%)	31(31.0%)	
Early onset neonatal sepsis	6(15.4%)	3(14.3%)	7(17.5%)	16(16.0%)	
Late onset neonatal sepsis	33(84.6%)	18(85.7%)	33(82.5%)	84(84.0%)	0.93
Mode of delivery					
Normal	15(38.5%)	9(42.9%)	4(10.0%)	47(47.0%)	0.34
LSCS	24(61.5%)	12(57.1%)	17(52.5%)	53(53.0%)	

Table 2: Baseline characteristics of PROM.

Characteristics of EONS	Frequency	Percentage
History of PROM (16)		
Yes	14	87.5%
No	02	12.5%
Chorioamnionitis (16)		
Yes	12	75.0%
No	04	25.0%
Resuscitation (16)		
Bag and mask	09	56.3%
Intubation	02	12.5%
None	05	31.3%

In this study, refusal of feeds was the most common complaint and was seen in 92% of the cases, followed by reduced movements and lethargy seen in 82% and 71% of the cases (Table 3).

There were nine cases of culture-positive sepsis accompanied by elevated levels of procalcitonin (>0.5 ng/dl) which tested negative for CRP (Table 4). The commonest organism which was isolated was *Acinetobacter* (14/39), followed by *Klebsiella pneumoniae* (10/39), *Staphylococcus aureus* (7/39),

CONS (5/30), *Pseudomonas aeruginosa* (1/39) and others (2/39).

Table 3: Distribution of symptoms and signs in all neonates presenting with sepsis.

Symptoms	N out of 100	Percentage
Convulsions	21	21.0%
Resp. rate >60/min	55	55.0%
Chest indrawing	42	42.0%
Nasal Flaring	35	35.0%
Grunting	18	18.0%
Bulging AF	7	7.0%
Temp >37.7/ <35.5	69	69.0%
Lethargy	71	71.0%
Reduced Movements	82	82.0%
Not able to feed	92	92.0%
Not attaching to breast	84	84.0%
Not Sucking at all	6	6.0%
Cyanosis/ Crepitations	36	36.0%
Reduced CRT	51	51.0%

CRP was statistically significant in detecting neonatal sepsis in all 3 groups of sepsis ($p<0.01$). The highest sensitivity in 1000-1500 gram neonatal sepsis with poor

specificity indicating even extremely premature infants was able to react with elevated CRP levels (Table 5).

PCT was statistically significant in detecting neonatal sepsis in all 3 groups of sepsis ($p<0.01$) with relatively better sensitivity and specificity in all 3 weight bands than CRP (Table 6).

Overall, as the early marker of sepsis, procalcitonin (Sensitivity of 87.2%, specificity of 72.13%) is more sensitive as compared to other parameters predict sepsis in neonates (Table 7).

Table 4: Relation of blood culture with other blood parameters.

Parameter	No. of (+ve) cases / 100	Culture (+ve) / 39
TLC	09	05
IT ratio	42	17
ANC	05	03
Micro ESR	36	02
CRP	61	30
PCT>0.5 ng/dl (Day 1)	75	39
PCT >2 ng/dl (Day 1)	51	34
Blood culture	39	39

Table 5: CRP in different weight groups according to sepsis and gestational weight.

Sepsis CRP	Definite and probable sepsis		Clinical sepsis		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p-value
Birth weight (gms)	n	%	n	%					
1000-<1500	13	81.25	03	18.75	88.89	28.57	61.54	66.67	
1500-<2500	31	63.26	18	36.73	72.73	44.40	51.61	66.67	<0.01
>2500	16	45.71	19	54.28	75.00	38.77	14.21	65.32	

Table 6: Procalcitonin in different weight groups according to sepsis and gestational weight.

Sepsis PCT >2	Definite and probable sepsis		Clinical sepsis		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p-value
Birth weight (gms)	n	%	n	%					
1000-<1500	10	90.90	01	9.09	88.88	57.14	72.72	80.00	
1500-<2500	25	86.20	04	13.80	87.50	72.41	72.41	87.50	<0.01
>2500	09	81.81	02	18.19	83.33	76.00	45.45	95.00	

Table 7: Sensitivity, Specificity, PPV, NPV, and accuracy of sepsis parameter.

Study parameter	Cut-off range (positive)	Sensitivity	Specificity	PPV	NPV	Accuracy
Total leucocyte count	TLC <5000 or >20000	12.82%	93.44%	55.55%	62.64%	62.00%
Absolute neutrophil count	ANC <1750	7.69%	96.72%	60.00%	62.10%	62.00%
IT- ratio	IT >0.2	41.00%	57.37%	50.00%	60.34%	51.00%
C-reactive protein	CRP >10 mg/L	76.92%	49.18%	49.18%	76.92%	60.00%
Platelet count	PLT <1.5 Lac	58.97%	73.77%	58.97%	73.77%	68.00%
Procalcitonin (day 1)	PCT >2 ng/dl	87.20%	72.13%	66.67%	89.80%	78.00%

DISCUSSION

Sepsis is one of the three most common causes of neonatal deaths globally.¹⁰ It is considered a life-threatening clinical emergency that necessitates urgent diagnosis and treatment.¹¹ The blood culture not only takes time but it is also complicated with a low yield.⁶ The readily achievable hematological parameters TLC,

ANC, I/T ratio have a modest sensitivity and specificity for diagnosing sepsis.⁷ The need for accurate biomarkers to aid in the timely and accurate diagnosis of NS thus remains as important as ever. A high degree of sensitivity is essential to ensure that cases are not missed; however, specificity is also important to avoid exposing unaffected infants to unnecessary treatment.¹² Therefore, using fast diagnostic methods with a high degree of sensitivity and specificity including laboratory markers along with

clinical conditions could be beneficial to determine the optimum course of action.

CRP is easily available and the most commonly used biomarker at an affordable rate through an automated method.¹³ However, the elevation of CRP due to physiological rise after birth or non-infection associated conditions such as fetal distress, stress delivery, and maternal fever, meconium aspiration, and prolonged transition in the absence of systemic infection limits its use for accurate diagnostic modality for neonatal sepsis. Due to variable sensitivity and high specificity, CRP is better a useful negative predictor of neonatal sepsis.⁶ There were continuing search for a new marker aiming to differentiate between bacterial sepsis and non-infectious conditions. PCT rises markedly within 6 hours of bacterial infection, peaking at 18–24 hours, remain elevated for up to 48 hours. CRP starts to increase 4–6 hours later than PCT after the beginning of inflammation, reaching its peak about 36 hours later, remain high for at least 24–48 hours and then decline 5 days later than PCT despite treatment with antibiotics. A physiological increase of procalcitonin has been reported up to 48 hrs. postpartum in healthy and preterm neonates and is normalized after 3 days.¹³ This most likely represents endogenous synthesis attributed to direct stress on the baby during the perinatal period or to the adaptation to an extrauterine environment. Even with physiological peak, PCT is useful in the diagnosis and monitoring of neonates at risk of infection. In contrast to CRP, local bacterial infections, severe viral infections, intracellular organism (such as Mycoplasma) and inflammatory reactions of non-infectious origin are either not associated with increased PCT or are only associated with a slight increase in PCT.¹⁴

In this study, sepsis was more common in males (73%) than females (27%) and more in term(52%) neonates collectively than preterm(48%) in all three sepsis group, which is consistent with the findings of the study by Hakeem A et al.¹⁴ It was seen that infection was more common in low birth weight baby (69%) compared to babies of normal birth weight (31%) in studies reported from India and Bangladesh as similar in this study.^{14,15} In this study 84% of babies had late-onset sepsis and 16% had early-onset sepsis similar to the studies by Lim WH et al with late-onset sepsis compromising majority (93.7%) (Table 1).¹⁶ Refusal to feed was the most common complaint (92%), followed by reduced movement (82%) and lethargy (71%) inconsistent with the study by Guha et al and Jaswal RS (Table 3).¹⁷

In our study total white blood cells, counts have poor sensitivity with better specificity (93.44%), positive predictive value (55.55%), and negative predictive value (62.64%) and accuracy (62%) with a p-value of 0.19 which is not significant. The poor predictive value is in collaboration with the study by Laurent R et al.¹⁸ In our study absolute neutrophil count has poor sensitivity (7.69%), good specificity (96.72%) and accuracy 62%, is following the study by Gerdés JS.¹⁹ In this study I: T ratio have poor sensitivity (41%) but comparatively good specificity (57.4%) with positive predictive value (50%), negative predictive value (60.3%) and accuracy only 51% (Table 7). This is following the study by Walliullah SM et al which shows sensitivity and specificity 70% and 56% respectively.²⁰ Thus, above hematological parameters can help in estimating the probability of sepsis.

Table 8: Different studies showing the sensitivity and specificity of CRP vs. procalcitonin.

Author	Parameters	N	Sensitivity	Specificity	PPV	NPV
Boo NY et al ²¹	PCT \geq 2 ng/ml	87	88.9%	65.2%	40.0%	95.7%
	CRP age-specific		55.6%	89.9%	58.8%	88.6%
Sakha et al ²³	PCT > 2 ng/ml	117	66.7%	50.0%	28.6%	83.3%
	CRP > 3.5 mg/l		70.4%	72.2%	43.2%	89%
Chiesa et al ²⁴	PCT \geq 1 (birth)	134	79.0%	95.0%	—	—
	CRP > 4 (birth)		74.0%	83.0%	—	—
Sucilathangam G et al ²¹	PCT > 0.5 ng/ml	50	92.8%	75.0%	59.0%	96.0%
	CRP > 6 mg/l		50.0%	69.4%	38.8%	78.1%
Mamdouh M. Esmat et al ²⁵	PCT > 19 ng/ml	61	70%	54.9%	27.4%	88.2%
	CRP ≤ 48 mg/l		90%	37.3%	25.9%	93.9%
Present study	PCT > 2 ng/ml	100	87.2%	72.13%	66.7%	89.8%
	CRP > 10 mg/l		76.92%	49.18%	76.9%	60.0%

The incidence of blood culture positivity was 39% in the present study, which is less than the study by Jaswal RS (42%) and more than the study by Sucilathangam G

(28%).^{17,21} Maternal intrapartum antibiotic prophylaxis, low level of bacteremia (60%–70%), and small blood volume collections from infants have been considered as reasons for the lack of confidence in negative culture

results.¹¹ In most of the culture-positive cases, the other sepsis screening tests were negative, but the level of PCT was elevated. This is similar to a study by Ali AM et al and Boo et al findings.²¹

In neonates, an elevated PCT level help in predicting severity, and low PCT levels help in ruling out septicemia as a diagnosis. Mean PCT levels were significantly high according to infection severity: 5.9 ± 4.2 ng/dl in proven sepsis group; 2.0 ± 1.7 ng/dl in probable sepsis group and 1.22 ± 1.21 ng/dl in clinical sepsis group ($P < 0.01$). This finding was comparable with that of the study which was conducted by Koksal N et al.²² Thus, the PCT assessment could help the physicians in limiting the number of prescriptions for the antibiotics.¹⁴ If the value of procalcitonin >0.5 ng/dl was taken as a cut off for diagnosis of sepsis then PCT was positive in 100% cases of proven sepsis, 71.4% in probable sepsis and 52.5% in clinical sepsis and in combined groups, PCT was positive 90% cases of proven plus probable and 59% of probable plus clinical sepsis group with a p -value <0.01 in all groups. In the present study, the sensitivity of PCT for detecting sepsis (>0.5 vs. >2 ng/ml) was 100% vs. 87.2%, its specificity 59.01% vs. 76.2%, its positive predictive value was 60.935 vs. 66.7% and its negative predictive value was 100 vs. 89.80 % and the sensitivity of CRP for predicting sepsis (more than 10 mg/ L) was 76.92%, its specificity was 49.18%, its positive predictive value was 49.18% and its negative predictive value was 76.92% (Table 8).

Table 9: Optimum diagnostic cut-off values.

Optimum Cut off value CRP: 17.65 mg/l		Optimum Cut off value PCT: 1.8 ng/dl	
Sensitivity	74.40%	Sensitivity	94.90%
Specificity	72.10%	Specificity	68.90%

An elevated level of PCT has been shown to have a sensitivity and specificity of in the range of (87-100%).²⁶ Similar to our findings Resh et al have found Procalcitonin to have a sensitivity of 83% with a PCT level cut off value of >2 ng/dl.²⁷ Contrary to our study Guibourdenche J et al found Procalcitonin to be 87% sensitive and 90% specific in excluding bacterial infection with negative predictive value 93% in Preterm and full-term infected babies.²⁸ Thus many studies in neonates report a higher sensitivity and a lower specificity for PCT than for CRP. The considerable heterogeneity of the results among the studies evaluating different markers for detection of neonatal sepsis can be explained by the lack of a universally acceptable definition of neonatal sepsis, different cut-off values incorporated in the studies and physiologic alterations of some markers such as PCT that occur in healthy neonates.²⁵

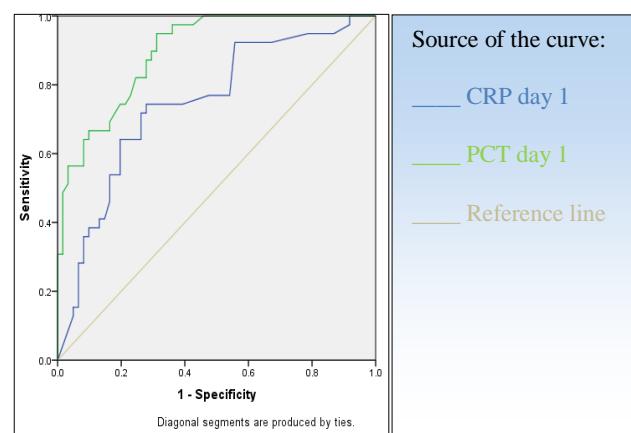
Elevated PCT has prognostic implications, as the course of PCT predicts the risk for mortality in critically ill patients with infections. The result from this study

suggests PCT as a good predictor of mortality as almost all neonates who died (75%) had elevated PCT >10 ng/dl. This is in agreement with Adib et al.²⁹ Overall mortality was 4/123=3.25% of which 2.5% is proven sepsis and 0.75% in probable sepsis group.

ROC Curve: diagnostic efficacy

Unlike sensitivity and specificity, which can be greatly affected by the threshold chosen, the AUC is a global parameter that estimates the diagnostic accuracy of an index test.

In the ROC analysis to determine the diagnostic usefulness of PCT compared with CRP, the area under the curve was higher for PCT (0.896 with 95% confidence interval [CI], 0.838-0.954) than for CRP (0.746 with 95% CI, 0.637-0.840), showing that PCT is highly effective early diagnostic marker of neonatal infection; however, CRP levels also showed a high result ($p < 0.01$) (Figure 2). This is similar to study by Rajeev D et al with PCT vs. CRP (AUC 0.92 vs. 0.74) and contrary to study by Park et al in which CRP has higher AUC than PCT.^{30,13} The cutoff levels with optimum diagnostic efficiency derived from the curve for CRP was >17.65 mg/l and PCT was >1.8 ng/ml (Table 9). These findings support the usefulness of the PCT to establish an early diagnosis and follow up of neonatal sepsis.



Area under curve for Procalcitonin and CRP for the diagnosis of neonatal sepsis were 0.896(95% CI: 0.838-0.954) and 0.746(95% CI: 0.637-0.840) respectively; $p < 0.01$

Figure 2: ROC curve procalcitonin and CRP for the diagnosis of neonatal sepsis.

Table 10: PCT guided duration of antibiotic therapy (in days).

Diagnosis	n	Days of antibiotics		p-value
		Mean \pm SD		
Definite sepsis	39	12.46 \pm 4.62		
Probable sepsis	21	4.53 \pm 1.78		<0.0001
Clinical sepsis	40	3.75 \pm 1.33		

PCT level decreases 24-48 hours after antibiotics are initiated. Serial measurements of Procalcitonin offer promise in the decision to initiate and/or control the duration of antibiotic therapy. The duration of antibiotics can be determined by observing the time to normalization of PCT following clinical resolution of sepsis. In our study time to normalization of PCT levels were 12.46 ± 4.62 days in neonates with culture-positive sepsis, 4.53 ± 1.78 days in neonates with probable sepsis 3.75 ± 1.33 days in neonates with clinical sepsis group (Table 10). There was no morbidity and mortality in any neonate in the 4-week follow-up. This is in agreement with Athhan et al and (NeOPInS) trial study.^{31,32} Serum procalcitonin levels seem to be significantly increased in proven sepsis and decrease dramatically in all types of sepsis after appropriate antibiotic therapy. If after appropriate treatment PCT levels start to rise, the adequacy of treatment must be questioned, leading perhaps to a change of antibiotics or reviewing supportive care or diagnosis of sepsis.

This study has several limitations. Nonhomogeneous population, small sample size, and the difficulties of serial sampling in premature and unstable neonates represent a major obstacle to get adequate blood volume in our study. PCT-LIA Immuno-luminometry (Quantitative) is a research tool and is available only in tertiary centers. Semi-quantitative PCT test kits increase the risk of false negativity.

CONCLUSION

PCT is a more reliable marker of inflammation than CRP in the early diagnosis of neonatal sepsis both in terms and pre-terms, in determining the severity of sepsis, and in decreasing the use of unnecessary antibiotics allowing decreased microbial resistance and earlier discharge with the related cost savings. The combination of PCT and CRP along with validated clinical algorithm improves the accuracy of diagnosis of neonatal sepsis limiting the ongoing treatment of culture-negative sepsis.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Bharti AK, Verma MK, Gupta A, Mishra DK. Role of procalcitonin in diagnosis of neonatal sepsis and procalcitonin guided duration of antibiotic therapy. *Int J Contemp Pediatr* 2020;7:1692-700.