Original Research Article

Role of serum procalcitonin as a marker for diagnosing neonatal sepsis

Haniya Jafar[1], Jyotsna Agarwal[1*], Raj Kumar Kalyan[1], Shruti Radera[1], Sheetal Verma[1], Mala Kumar[2], Shalini Tripathi[2]

[1]Department of Microbiology, [2]Department of Pediatrics, King George's Medical University, Lucknow, Uttar Pradesh, India

*Correspondence:
Dr. Jyotsna Agarwal,
E-mail: jyotsnaagarwal.micro@gmail.com

ABSTRACT

Background: Neonatal sepsis is a continuing problem causing significant burden on health care, especially in developing world. As blood culture has low sensitivity in diagnosis of neonatal sepsis, strong clinical suspicion along with combination of different laboratory tests is required. The data available for extensively studied acute phase reactant, procalcitonin (PCT) remains controversial. This study was done to assess role of PCT alone and in combination with different tests for diagnosing neonatal sepsis.
Methods: Blood samples of 275 neonates (>35 weeks of gestation) admitted to NICU, with suspicion of neonatal sepsis were collected for bacterial culture, serum procalcitonin level and sepsis screen (CRP, mESR, I/T ratio, Total Leucocyte Count, Absolute Neutrophil Count).
Results: Blood culture was positive in 30.5% of enrolled neonates. At a cut-off value of 0.5 ng/ml the sensitivity, specificity, PPV, NPV of serum PCT in neonatal sepsis cases was 73.8%, 47.1%, 48%, 80.4% respectively. Serum PCT was found raised in 60 (48.8%) clinically suspected cases of neonatal sepsis where sepsis screen and blood culture both were negative, also it was not raised in 17 (32.7%) of clinically suspected cases of septicemia where both blood culture and sepsis screen were positive. Amongst other individual tests, CRP was found to have best sensitivity (79.7%) and NPV (85%) followed by PCT (73.8% and 80.4%) while best specificity was found for I/T ratio (93.7%) followed by mESR (89%) for diagnosis of neonatal sepsis with positive blood culture. Best NPV was seen for combination of PCT+CRP+I/T ratio (95.6%) for the suspected cases of neonatal sepsis.
Conclusions: Thus, we conclude that serum PCT can play a useful role when combined with other test markers but may not find its way as a sole diagnostic marker for diagnosing neonatal sepsis in term/near term babies.

Keywords: Blood culture, C reactive protein, Neonatal sepsis, Procalcitonin

INTRODUCTION

Timely diagnosis and appropriate treatment of neonatal sepsis remains a challenge in present time. The incidence of neonatal sepsis in India is 30 per 1000 live births and sepsis contributes to 19% of all neonatal deaths according to National Neonatal Perinatal Database (NNPD, 2002-03).[1] In 2015, estimated global mortality rate due to neonatal sepsis was 2.875 per 1000 live births.[2]

Neonatal sepsis has subtle and nonspecific signs and symptoms. Though blood culture is considered as gold standard for the diagnosis, high chances of false negativity and delay in culture results often lead to inappropriate use of antibiotics with all its associated collateral damages. Various acute phase reactants have been studied by workers, and used as early diagnostic markers for neonatal sepsis, in the past. Amongst the newer ones, the serum procalcitonin (PCT) has been the

extensively studied and shows promising results.[3,4,5] Often sepsis screen (i.e. total leukocyte count, absolute neutrophil count, immature to total neutrophil ratio, micro-erythrocyte sedimentation rate and C reactive protein) is one of the first investigations to be done in clinically suspected neonatal sepsis; and results of both sepsis screen and serum PCT are available in a few hours, as compared to blood culture which may take 24-72 hours to show results. If we can evaluate the utility of serum PCT in clinically suspected cases of neonatal sepsis viz a viz sepsis screen status, it will be helpful for early diagnosis of neonatal sepsis.

Most of the studies on role of serum PCT as a diagnostic marker for neonatal septicemia have been carried out in relatively smaller sample sizes; therefore we planned the present study for evaluating the diagnostic efficacy of serum PCT alone and in combination with other diagnostic modalities for detection of neonatal sepsis in near term and term babies in a tertiary care hospital, with appropriate sample size calculation, so as to obtain statistically relevant results.

METHODS

This was a prospective observational study, done on neonates admitted to Neonatal Intensive Care unit (NICU) of a tertiary care hospital in north India from July 2016 to June 2017. The study protocol was approved by the Ethics Committee of the Medical University. Inclusion criteria consisted of all neonates (>35 weeks gestation age) admitted in NICU with clinical suspicion of neonatal sepsis whose parents/ guardians were willing to participate in the study.[6] Neonates with history of perinatal asphyxia and those with respiratory distress syndrome were excluded. With reported prevalence of neonatal sepsis in the range of 15-20%, a sample size of 246 was calculated with 95% confidence limit and 5% confidence level.

Information about demographic data, date of birth/ time of birth, date of admission, mode of delivery, inborn/ outborn, birth weight, weight at admission, gestational age, APGAR score at 1 min and 5 min, antenatal, perinatal, postnatal events, signs and symptoms of sepsis, febrile illness in mother within 2 weeks prior to delivery, foul smelling liquor, rupture of membrane (>24 hrs), any invasive procedures were extracted from the records. Blood culture, serum PCT levels and sepsis screen [Total Leukocyte Count (TLC), Absolute Neutrophil Count (ANC), immature to total neutrophil (I/T) ratio, micro Erythrocyte Sedimentation Rate (microESR), C Reactive Protein (CRP)] were performed on all samples (Figure 1). Sepsis screen was considered positive if ≥2 sepsis screen tests were positive.[6]

For the purpose of analysis, the suspected cases of neonatal sepsis were divided into 2 groups: cases with positive blood culture and cases with negative blood culture (Figure 2).
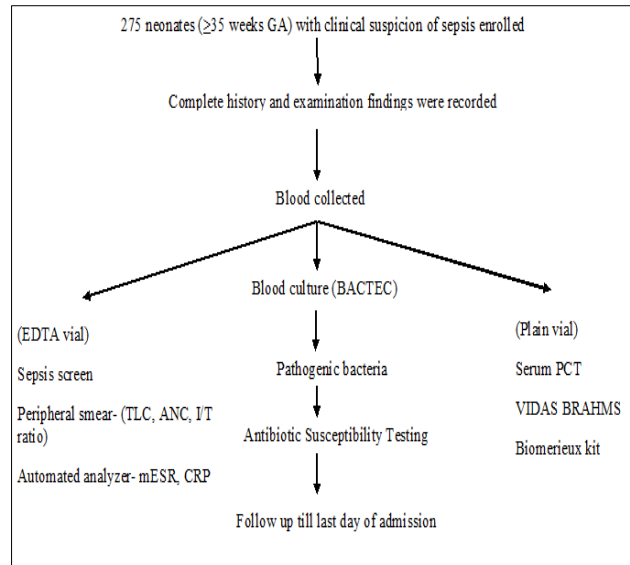
Figure 1: Work up plan.
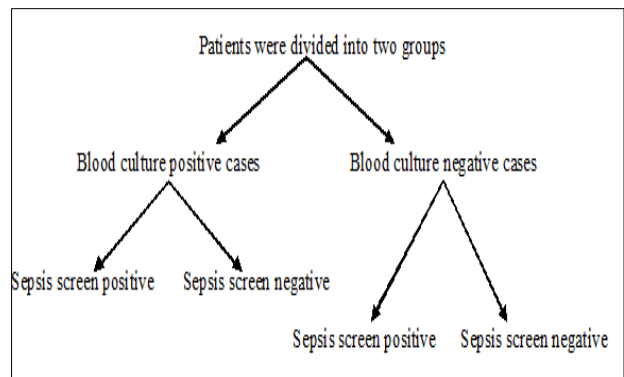
Figure 2: Work up plan for statistical analysis.

Blood culture showing no growth of microorganism after 5 days of aerobic incubation or growth of skin contaminants (*Bacillus species, Corynebacterium species, Micrococcus*) was considered as negative blood culture.

Serum PCT cut off for sepsis was taken as 0.5 ng/ml as per previous reports and as per the manufacturer of kits (VIDAS BRAHMS PCT). Blood for PCT was collected only once from each neonate at the time of blood culture collection.[3]

RESULTS

A total of 275 neonates were prospectively enrolled in the study; of which 150 (54.5%) neonates were cases of early onset sepsis and 125 (45.4%) were of late onset sepsis. Maternal risk factors were positive in 19.5% of enrolled neonates, with premature rupture of membrane (PROM)>24 hours being most common (14.9%). Neonatal risk factors were present in 71.3% neonates, with low and very low birth weight being most common associated findings (50.5%) (Table 1).

**Table 1: Demographic and clinical profile of neonates enrolled in study.**

SN	Characteristic	N (%)
General Profile and Perinatal Events		
1.	Gender	
	Male	175 (63.6%)
	Female	100 (36.3%)
2.	Gestational age at birth	
	Near term (35-37 weeks)	120 (43.6%)
	Term (>37 weeks)	155 (56.4%)
3.	Mode of delivery	
	Normal vaginal delivery	129 (46.9%)
	Lower Section Cesarean Section (LSCS)	146 (53.1%)
4.	Place of delivery	
	Inborn	115 (41.9%)
	Outborn	160 (58.2%)
5.	Apgar <7 at 1 min	57 (20.7%)
6.	Mean birth weight (kg)	2.39±0.53
7.	Maternal risk factors	56 (20.3%)
	Premature rupture of membrane (PROM)>24 hrs	41 (14.9%)
	Fever >2 wks	13 (4.7%)
	Foul smelling liquor	2 (0.7%)
8.	Neonatal risk factors	196 (71.3%)
	Prematurity	120 (43.6%)
	Low birth weight	134 (48.7%)
	Very low birth weight	5 (1.8%)
	Mechanical ventilation	27 (9.8%)
At Admission		
9.	H/o antibiotic exposure in neonates before admission	53 (19.3%)
10.	Mean weight at admission (kg)	2.40±0.54
11.	Mean Age at time of admission	5.69±6.17
	≤72 hrs	150 (54.5%)
	>72 hrs	125 (45.5%)
12.	Mean Total Leucocyte Count (/mm3)	12805±6608
13.	Mean Absolute Neutrophil Count (/mm3)	7156±3413
14.	Mean Micro ESR (mm in 1st hr)	6.65±3.98
15.	Mean CRP (mg/L)	15.65±19.84
16.	Mean Serum PCT (ng/ml)	6.59±14.32
17.	Serum PCT (>0.5 ng/ml)	163 (59.3%)
18.	CSF Findings (n=46)	
	Mean CSF protein (mg/dl)	195.02±46.13
	Mean CSF sugar (mg/dl)	24.96±11.80
Outcome		
19.	Blood culture positive	84 (30.5%)
	Blood culture negative (sterile or contaminated)	191 (69.4%)
20.	Mortality	40 (14.5%)
	Improved on treatment and discharged	180 (65.5%)
	Left Against Medical Advice	55 (20%)

There were 163 (59.3%) neonates with serum PCT levels above the cut-off (>0.5 ng/ml). Blood culture was positive in 90 (32.7%) cases, of which 6 blood cultures showed growth of either skin contaminants or mixed microbiota which were unlikely to cause infection. Thus, total blood culture positive was 84 (30.5%). Blood culture results were compared to serum PCT levels, results are shown in (Table 2). Serum PCT was found raised in 73.8% of positive blood culture cases and 52.9% of blood culture negative cases.

We compared serum PCT with other sepsis markers individually as well as in various combinations in blood culture positive and negative cases (Table 3). For a single test, CRP was found to have best sensitivity (79.7%) and negative predictive value (NPV) (85%) followed by PCT. Serum PCT was found raised in 60 (48.8%) clinically suspected cases of neonatal sepsis, where sepsis screen and blood culture both were negative, also it was not raised in 17 (32.7%) of clinically suspected cases of septicemia where both blood culture sepsis screen were positive.

Table 2: Serum PCT level and blood culture result of enrolled neonates.

Serum procalcitonin	Blood culture		Total
	Positive	Negative	
Positive (>0.5 ng/ml)	62	101	163
Negative	22	90	112
Total	84	191	275
Sensitivity	Specificity	Positive predictive value	Accuracy
73.8%	47.1%	38.0%	55.3
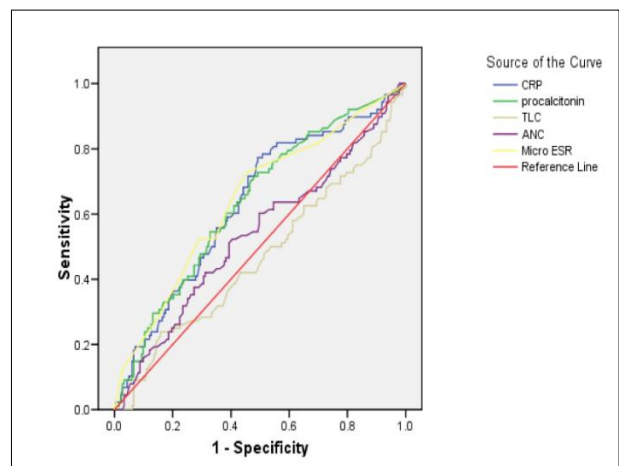
Figure 3: Comparison of Receiver operating characteristics curve of PCT, CRP, TLC, ANC, mESR for diagnosis of neonatal sepsis.

Best specificity was found in I/T ratio (93.7%) followed by mESR. As for the various permutations and

combinations of tests of sepsis screen; CRP+PCT combination had high sensitivity and NPV; 90% and 90.7% respectively; best specificity was found for PCT + mESR (96.7%). Although best NPV was seen in combination of PCT+CRP+I/T ratio (95.6%). Those cases where PCT was positive in blood culture positive were taken as true positive (TP) while those cases where PCT was positive in blood culture negative were taken as false positive (FP) for statistical analysis. Raised serum PCT levels (>0.5 ng/ml) were significantly associated with increased mean mESR (P=0.002) and blood culture positivity (OR=2.51; P=0.002).

We also compared serum PCT with 'sepsis screen' results in both blood culture positive and blood culture negative cases (Table 4 and 5).

Serum PCT was found raised in 60 (48.8%) clinically suspected cases of neonatal sepsis, where sepsis screen and blood culture both were negative, also it was not raised in 17 (32.7%) of clinically suspected cases of septicemia where both blood culture sepsis screen were positive.

Receiver operator characteristic curve analysis showed that only CRP, serum PCT and mESR showed statistically significant area under curve (AUC) value, however, for these parameters too, the AUC values were only between 0.633 to 0.645 (95% CI), Therefore, no further cut-off value was traced as the minimum acceptability criteria for AUC>0.7 could not be met (Figure 3).

Table 3: Performance of various laboratory tests in diagnosis of neonatal sepsis.

Laboratory test	Culture Positive (n=84)	Culture Negative (n=191)	Sensitivity	Specificity	PPV	NPV
Serum PCT >0.5ng/ml	62	101	73.8	47.1	38.0	80.4
Serum CRP >6 mg/L	67	94	79.7	50.7	41.6	85
I/T Ratio > 0.2	12	12	14.2	93.7	30.0	76.1
mESR >15mm in 1st hr	5	21	5.9	89	12.5	72.3
In combination						
PCT + CRP	50	55	90	47	47.6	90.7
PCT+ CRP+ IT ratio	10	11	83.3	80	47.6	95.6
PCT+CRP+mESR	4	2	44.4	96.1	66.6	90
PCT+mESR	4	3	16	96.7	57.1	81
PCT+I/T Ratio	13	14	44.4	85.5	48.1	83.8

Table 4: Serum PCT level and sepsis screen result among blood culture positive cases.

Blood culture +ve cases (n= 84)		Sepsis screen	
		Positive	Negative
Serum PCT	Positive	35	27
	Negative	17	5
Sensitivity	Specificity	PPV	Diagnostic accuracy	p-value
67.3	15.6	56.5	47.6	0.084

Table 5: Serum PCT level and sepsis screen result among blood culture negative cases.

Blood culture -ve cases (n=191)		Sepsis screen	
		Positive	Negative
Serum PCT	Positive	41	60
	Negative	27	63
Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy	p-value
60.3	51.2	40.6	70	54.5	0.127

DISCUSSION

Neonatal sepsis is a major cause of mortality and morbidity all over the world, especially in preterm and low birth weight newborns.[7-9] With serum diagnostic markers, there is scope of early and accurately identifying sepsis to reduce mortality. During the 12-month study period, blood samples from 275 neonates who were admitted in the neonatal intensive care unit with clinical

suspicion of sepsis were tested for sepsis screen, serum PCT level, blood culture and analyzed. Neonates ≥ 35 weeks of gestation were included to remove confounding factors for serum PCT as seen in the past.[10-12] In present study neonatal sepsis was found in babies with significantly lower birth weight (mean birth weight 2.39 ± 0.39); and PROM was associated with increased risk of neonatal sepsis (Table 1), similar findings have been found in previous studies.[13,14]

Blood culture positivity was 30.5% in our study. Blood culture positivity rate ranging from 16- 65% have been described in various studies done in low- and middle-income countries.[15,16,17] Blood culture has disadvantage of poor positivity rate besides being a time taking process.

In our study serum PCT was found raised in 73.8% of positive blood culture cases and 52.9% of blood culture negative cases. Raised PCT in blood culture negative cases may be due to physiological rise of PCT within 96 hours of birth or due to non-infective cause. Moreover, 26.2% neonates with positive blood culture had low PCT. This may be because of antibiotics administration during antepartum and intrapartum period, which may affect PCT concentration in umbilical cord; even postnatal administration of antibiotics is known to decrease PCT concentration.[18]

Sensitivity, specificity, PPV of TLC for clinical suspected cases of neonatal sepsis with positive blood culture, in our study was strikingly poor. TLC has been reported to vary widely in response to sepsis.[4,19-21] due to many factors like neonatal age, method of sample collection, mode of delivery, maternal hypertension etc.[19,22,23] In our study best specificity for clinical suspected cases of neonatal sepsis was found for I/T ratio followed by mESR. I/T ratio >0.2 had 14.2% sensitivity, 93.7% specificity, 30.0% PPV; similar to results in other studies when used alone.[19,21,24] Micro ESR >15 mm in 1st hr. had sensitivity of 5.9%, specificity of 89%, PPV of 12.5%, NPV of 72.3%; similar to previous published studies.[25-27] For CRP, at cut off 6 mg/L; sensitivity, specificity, PPV and NPV were 79.7%, 50.7%, 41.6%, 85% respectively. Previously, Sharma et al, observed that CRP had 80% sensitivity and 93% specificity, whereas Nargis W et al, reported 85% sensitivity and 33% specificity for CRP.[28,29] This variation could be because of the different methodologies used to measure CRP and the different cut offs used.[27] Sharma et al, also observed that specificity of two test combination was higher than that of individual tests.[28] In present study too we noticed that used alone, none of the tests were good enough to diagnose sepsis but increasing diagnostic value was seen in combination of PCT with other markers. Previous reports show comparable results.[19,30-34]

We also compared the results of PCT with sepsis screen in both blood culture positive and negative cases (Table 4 and 5). At a cut-off value of 0.5 ng/ml, 48.8% of neonates, who were sepsis screen and blood culture negative, showed elevated PCT; which may be due to other non-infective states as also reported in past.[35] PCT level of many neonates was assessed within 48 hours of birth and this may have influenced results due to physiological peak of serum PCT concentration as elevated PCT has been observed even in healthy neonates within first four days of life.[35]

Among the culture negative, but clinically suspected neonatal sepsis cases, 35.6% in our study had two or more sepsis screen tests positive, as has been found by other workers too.[23] Clearly, culture negativity cannot exclude sepsis totally, even though it is the gold standard.[36] In this study, we found 27 cases among blood culture positive group, where sepsis screen was negative but PCT was positive; thus serum PCT was able to help in diagnosing neonatal sepsis earlier. But at the same time serum PCT was high in 60 cases where blood culture and sepsis screen both were negative. That leaves us to decipher that used alone, serum PCT may not be of much help in diagnosing neonatal sepsis in term/near term babies.

In receiver operator curve analysis, the AUC values for CRP, serum PCT, mESR was less than 0.7 thus indicating that these parameters had a limited discriminating role in independent assessment. With a large sample size in our study, the value of serum PCT can better reflect the certainty of results. A limitation of our study, however, is that, we did not determine PCT level serially or after treatment due to cost factor.

CONCLUSION

Early and accurate diagnosis of neonatal sepsis remains challenging due to non-specific signs and variable turnaround time/ cut offs values/ sensitivities of different diagnostic modalities. The findings of our study indicate that serum PCT, at a cut off value of 0.5 ng/ml, for definite sepsis had moderate diagnostic value when used alone. In combination with other parameters of sepsis screen, it had higher sensitivity & specificity. Most worthy combination was PCT with CRP and I/T ratio with sensitivity (83.3%), specificity (80%), PPV (47.6%), NPV (95.6%).

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