Original Article

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Paediatrics Section

Serial Serum C-reactive Protein in the Diagnosis of Neonatal Sepsis: A Cross-sectional Study

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ABSTRACT

Introduction: C-reactive Protein (CRP) is an acute phase reactant secreted in increased amounts in the early hours of acute inflammation.

Aim: To evaluate serial CRP levels for the diagnosis of neonatal infection and to do comparative analysis of CRP levels with other parameters of sepsis screen.

Materials and Methods: Neonates with birth weight >1500 g and suspected to have sepsis were included. CRP was measured from the serum by quantitative turbidimetric immunoassay. The CRP 1 level was measured at the time of clinical presentation; CRP 2 and CRP 3 were measured at 24 and 48 hours respectively.

Results: A total of 100 neonates were included. CRP was positive in 72% cases (CRP 2 in 59% and CRP in 72% cases). On comparative analysis of CRP with symptomatology, culture of the body fluid, WBC count, proven sepsis; serial CRP levels showed increase in sensitivity, decrease in specificity, not much change in Positive Predictive Value (PPV), but increase in Negative Predictive Value (NPV). CRP 3 was significantly associated with culture positivity.

Conclusion: Serial CRP measurements are useful in the diagnosis of neonatal sepsis. CRP 3 level may virtually rule out or rule in the diagnosis of neonatal sepsis, and has very good correlation with blood culture.

Keywords: Acute phase reactant, Infection, Mortality, Newborn

INTRODUCTION

Neonatal sepsis is defined as invasive bacterial infection occurring in first 4 weeks of life [1]. The incidence of neonatal sepsis is lower in developed countries (2.7/1000 live birth) compared to developing countries (10-15/1000 live birth) [1]. The incidence of neonatal sepsis varies from 11-24.5/1000 live births in India [2].

Neonatal sepsis causes high morbidity and mortality during neonatal period, and is a thrust area for research in neonatal medicine. Many of the manifestations of the sepsis have their counterparts in non-infectious neonatal disorder [1]. The difficulty in early diagnosis of neonatal sepsis coupled with non-specific signs of life threatening illness during neonatal period has warranted widespread antibiotic use in many clinical settings leading to excess use of antibiotics and the resulting antibiotic resistance [3].

Though isolation of organism by culture of body fluids is the gold standard, there are problems associated with this method: result being influenced by prior antibiotic exposure, inadequate sample volume, and delay in getting the report (24 to 72 hours) [3]. Being exclusively produced in liver, CRP is an acute phase reactant whose level increases within six hours of acute inflammation, parallels the activity of inflammatory process, and then decreases faster than any other acute phase reactant. These characteristics make CRP very useful in monitoring response to antibiotics [4]. CRP value is reliable in the first 24-48 hours after the onset of infection [5]. After obtaining a normal CRP level, the probability of sepsis is 10 times less likely [5]. Similarly, for two successive normal CRP levels, the probability of sepsis becomes 30 times less likely [5].

So, monitoring serial CRP level may help in early diagnosis and management of neonatal sepsis, initiation and adjustment of antibiotic therapy, thereby reducing the length and cost of hospital stay as well as the parental anxiety.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Neonatal Unit, Department of Pediatrics at Sree Balaji Medical College and Hospital, Chennai, India from July 2013 to June 2014. A total of 100 neonatal sepsis cases having birth-weight >1,500 g constituted the study population. Neonatal sepsis

was diagnosed through clinical features along with the results of sepsis scoring (described later). Those with meconium aspiration syndrome, severe birth asphyxia, birth injuries, prior antibiotic administration, birth-weight <1,500 g, and any underlying surgical condition were excluded.

This study was approved by the Institute Ethical Committee. Neonates with suspected sepsis whose parents/guardians gave consent were enrolled in the study. Neonates with positive CRP and negative culture (considered as septic) were treated accordingly. Neonates were evaluated by thorough history from mother and detail clinical examinations. The findings were recorded in the predesigned proforma.

Neonatal sepsis was suspected in the following maternal conditions: Prolonged rupture of membrane (>18 hours), foul smelling liquor, vaginal examination >3 in labour, intrapartum fever, Urinary Tract Infection (UTI) in last trimester.

Neonatal sepsis may present with following signs and symptoms: Refusal to feed, vomiting, lethargy, abdominal distension, fever, hypothermia, icterus, cyanosis, apnea, pallor, umbilical discharge, tachypnea, and others (seizure, diarrhoea, skin pustule or petechiae). Neonates with ≥3 of these signs and symptoms were suspected to have neonatal sepsis.

The laboratory and radiological evaluation done for the diagnosis and confirmation of infection were following: serial measurements of CRP, WBC count, IT ratio, toxic granules; blood culture and sensitivity, CSF analysis and culture, and chest X-ray.

Measurement of CRP

A-15 CRP kit bio-system (Costa Brava, Barcelona, Spain) was used for quantitative measurement of CRP from the serum by turbidimetric immunoassay. The CRP 1 level was measured at the time of presentation, CRP 2 and CRP 3 were measured at 24 and 48 hours respectively. A CRP value of >1 mg/dl was taken as positive.

Total WBC Count

(a) A total count of < 5,000/cumm or > 20,000/cumm was taken as abnormal and considered suspicious of sepsis.

(b) IT Ratio (Immature:Total neutrophil ratio) >0.2 was considered abnormal.

(c) Presence of to xic granules in peripheral smear study was considered abnormal.

Blood Culture and Sensitivity

One ml of blood was collected in a bottle containing 10 ml of brain heart infusion (in the dilution of 1:10). This was then incubated at 37°C under aerobic condition and subcultures were made on Mac Conkey agar and Mannitol salt agar after 24 hours of incubation. Cultures were taken as sterile if no growth occurred at 96 hours.

CSF Culture and Sensitivity

CSF analysis was done in all cases of suspected sepsis.

Chest X-ray

Chest X-ray was done in neonates with suspected sepsis

Categorization of Neonatal Sepsis

(a) Proven Sepsis: If pathogenic bacteria were isolated from blood, CSF or urine.

(b) Probable Sepsis: If clinical along with laboratory findings were consistent with bacterial infection without positive culture.

(c) Clinical Sepsis: Neonates in whom only clinical features were consistent with sepsis, without laboratory abnormalities or growth of organism in body fluid cultures.

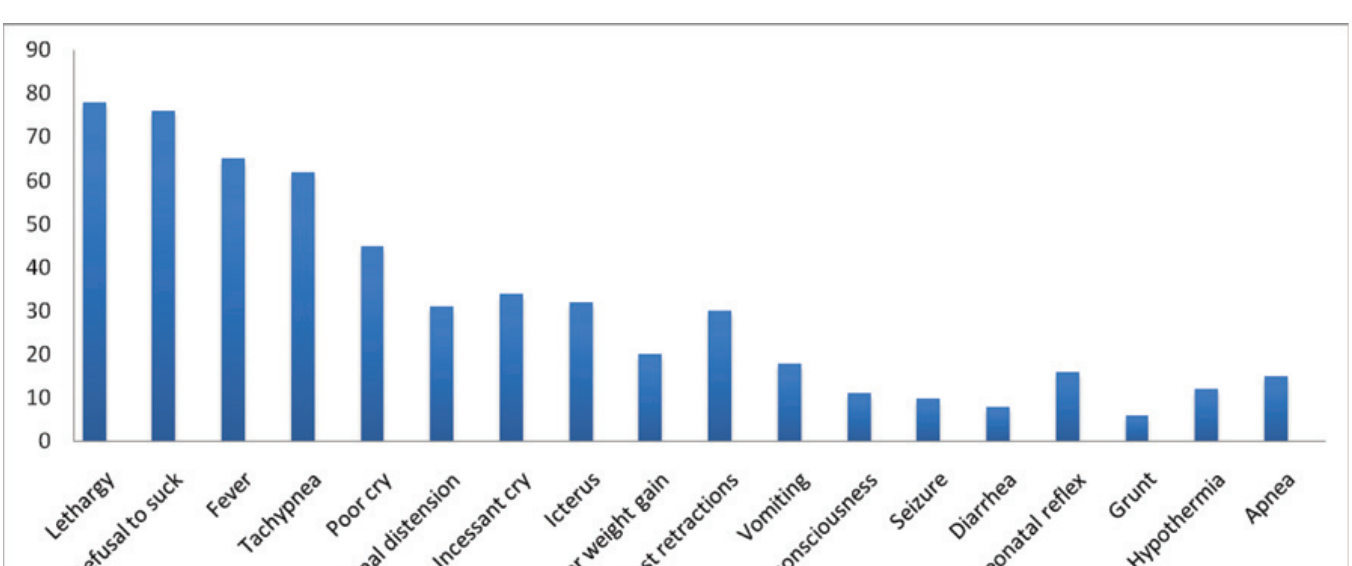
When neonatal sepsis was suspected, antibiotics [septicemia and pneumonia: ampicillin (100 mg/kg/day) and gentamicin (5mg/kg/day)/amikacin (15/kg/day); meningitis: cefotaxime (100mg/kg/day) and amikacin] were started empirically considering the obstetric factors, sepsis score, and laboratory findings. The antibiotics were used for 7-14 days depending upon the clinical condition and culture findings. Daily follow-up of the cases was done till discharge.

STATISTICAL ANALYSIS

All the data were entered into the Microsoft excel sheet. The data were analysed using SPSS software (version 20.0 Chicago, IL, USA). Statistical tests used for comparison included Chi-square test. The p-value <0.05 was taken as significant. Besides these, sensitivity, specificity, PPV, and NPV for serial CRP values were calculated.

RESULTS

A total of 100 neonatal sepsis cases were evaluated. Of 100 cases, 54(54%) were male, birth weight of 32(32%) was between 1500 to 2500 g, 47(47%) were delivered by caesarean section (emergency-29; elective-18). According to the age of onset of sepsis, 38(38%) were early onset sepsis (onset at ≤ 72 hours of life) and 62(62%) were late onset sepsis (onset >72 hours of life). Proven sepsis were seen in 18(18%), probable sepsis in 49(49%), and clinical sepsis in 33(33%) neonates. Early onset sepsis was seen in 20(52.6%) males and 18(47.4%) females. Late onset sepsis was seen in 34(54.8%) males and 28(45.2%) females. Proven sepsis was equally divided in early and late onset group. Probable sepsis was less in the early onset group (n=15, 30.6%) than in the late onset group (n=34, 69.4%). Clinical sepsis was less in the early onset group (n=14, 42.4%) than in the late onset group (n=19, 57.6%). Proven



[Table/Fig-1]: Clinical presentations of neonates with sepsis (digits inside the bars represent the percentage).

sepsis was more in early onset group (n=12, 66.7%) than in the late onset group (n=6, 33.3%). Probable sepsis was more in the early onset group (n=26, 53%) than in the late onset group (n=23, 47%). Clinical sepsis was less in the early onset group (n=16, 48.5%) than in the late onset group (n=17, 51.5%).

Clinical Presentation

The clinical presentations were as follows: Lethargy (78%), refusal to suck (76%), fever (65%), tachypnea (62%), poor cry (45%), excessive cry (34%), icterus (32%), abdominal distention (31%), chest indrawing (30%), poor weight gain (20%), vomiting (18%), poor reflexes (16%), apnea (15%), hypothermia (12%), altered sensorium (11%), seizure (10%), diarrhoea (8%), and grunt (6%) [Table/Fig-1].

Laboratory and Radiological Evaluation

WBC count <5,000/cumm was seen in 20(20%) cases, and >20,000/cumm in 40(40%) cases. IT ratio > 0.2 was seen in 34 (34%) cases. Toxic granules were found in 25(25%) cases. Chest X-ray was abnormal in 15(15%) cases. CSF was abnormal in 3(3%) cases, but culture was negative in all of those cases. Similarly, blood culture was positive in 18(18%) cases; 9(50%) in early onset sepsis and 9(50%) in late onset sepsis. *S. aureus* (38.9%), *E. coli* (33.3%) and *K. pneumoniae* (27.8%) were the most common organisms isolated. Sepsis caused by gram negative organisms was more common in early and late onset sepsis [Table/Fig-2].

Analysis of Serial CRP Values

The CRP 1 level measured at the time of presentation, CRP 2 and CRP 3 were measured at 24 and 48 hours respectively. Of 100 cases, CRP 1 was positive in 30(30%) cases, CRP 2 in 59(59%) cases, and CRP 3 in 72(72%) cases. The distribution of CRP positive cases were as follows: 20 in early onset sepsis, 52 in late onset sepsis, 18 in proven sepsis, 40 in probable sepsis, and 14 in clinical sepsis group [Table/Fig-3].

Organisms Isolated	Early Onset Sepsis		Late Onset Sepsis		Total
	Blood	CSF	Blood	CSF	
E. coli	2	-	4	-	6(33.3%)
K. pneumoniae	4	-	1	-	5(27.8%)
S. aureus	3	-	4	-	7(38.9%)
Total	9	-	9	-	18(100%)

[Table/Fig-2]: Types of organisms isolated in culture.

Comparative Analysis

Relationship between the CRP levels with clinical presentations, laboratory investigations and also with the type and onset of sepsis were analyzed. The usefulness of CRP level to predict or to exclude different types of sepsis was assessed by examining the relationship of CRP level with the positivity of blood or CSF culture. Similarly, CRP positivity in relation to abnormalities of WBC count and different symptoms was also assessed.

CRP and Clinical Symptoms

The two most common symptoms seen among the neonates presenting with neonatal sepsis were lethargy and refusal to feed. On comparative analysis, serial measurement of CRP

Type of Sepsis (Based on Diagnosis)						
	Positive			Negative		
	CRP 1	CRP 2	CRP 3	CRP 1	CRP 2	CRP 3
Proven Sepsis	8(8%)	17(17%)	18(18%)	10(10%)	1(1%)	0
Probable Sepsis	20(20%)	33(33%)	40(40%)	29(29%)	6(6%)	9(9%)
Clinical Sepsis	2(2%)	9(9%)	14(14%)	31(31%)	24(24%)	19(19%)
Total	30(30%)	59(59%)	72(72%)	70(70%)	41(41%)	28(28%)
Type of Sepsis (Based on Time of Onset)						
Early Onset	8(8%)	16(16%)	20(20%)	30(30%)	22(22%)	18(18%)
Late Onset	22(22%)	43(43%)	52(52%)	40(40%)	19(19%)	10(10%)
Total	30(30%)	59(59%)	72(72%)	70(70%)	41(41%)	28(28%)

[Table/Fig-3]: CRP positivity and negativity in three sepsis categories.
The statistical analysis between positive CRP measurements and type of sepsis (based on diagnosis) showed following relationships: CRP 1 (χ^2 for trend = 13.5; p=0.001), CRP 2 (χ^2 for trend = 24.5; p=0.0001), and CRP 3(χ^2 for trend = 23.6; p=0.00001).
The statistical analysis between positive CRP measurements and type of sepsis (based on time of onset) showed following relationships: CRP 1 (χ^2 for trend = 2.34; p>0.05). CRP 2 (χ^2 for trend = 7.23; p=0.007), and CRP 3 (χ^2 for trend = 11.4; p=0.001).

showed increase in sensitivity (CRP 1=38%, CRP 2=69%, CRP 3=87%), decrease in specificity (CRP 1=100%, CRP 2=77%, CRP 3=81%), not much change in PPV (CRP 1=100%, CRP 2=92%, CRP 3=94%), but increase in NPV (CRP 1=31%, CRP 2=41%, CRP 3=64%) for lethargy. For refusal to feed, there was increase in sensitivity (CRP 1=37%, CRP 2=61%, CRP 3=74%), decrease in specificity (CRP 1=92%, CRP 2=46%, CRP 3=33%), not much change in PPV (CRP 1=93%, CRP 2=78%, CRP 3=78%) and NPV (CRP 1=31%, CRP 2=27%, CRP 3=26%).

CRP and Body Fluid Culture

On comparative analysis of CRP and culture of body fluid, serial measurement of CRP showed increase in sensitivity (CRP 1=44%, CRP 2=94%, CRP 3=100%), decrease in specificity (CRP 1=73%, CRP 2=49%, CRP 3=34%), not much change in PPV (CRP 1=27%, CRP 2=29%, CRP 3=25%), but increase in NPV (CRP 1=85%, CRP 2=97%, CRP 3=100%). CRP 2 and 3 were significantly associated with culture positivity, CRP 3 being more significant than CRP 2. The statistical analysis showed significant relationship (p=0.003).

CRP and WBC Count

On comparative analysis of CRP and WBC count, serial measurement of CRP showed increase in sensitivity (CRP 1=23%, CRP 2=42%, CRP 3=57%), decrease in specificity (CRP 1=60%, CRP 2=15%, CRP 3=5%), not much change in PPV (CRP 1=47%, CRP 2=42%, CRP 3=48%), but decrease in NPV (CRP 1=34%, CRP 2=15%, CRP 3=7%). CRP 2 and 3 were significantly associated with low WBC count, CRP 3 being more significant than CRP 2.

CRP and Onset / Type of Sepsis

Performance of serial CRP estimation in the diagnosis of neonatal sepsis has been detailed [Table/Fig-4].There was increase in sensitivity and NPV with decrease in specificity and PPV in serial CRP measurements, both in early and late onset proven sepsis.

	CRP 1	CRP 2	CRP 3
Early Onset Sepsis			
Proven Sepsis			
Sensitivity	22%	89%	100%
Specificity	79%	72%	62%
PPV	25%	50%	45%
NPV	77%	95%	100%
Probable Sepsis			
Sensitivity	40%	60%	77%
Specificity	91%	70%	60%
PPV	75%	56%	50%
NPV	70%	73%	83%
Late Onset Sepsis			
Proven Sepsis			
Sensitivity	67%	100%	100%
Specificity	70%	36%	19%
PPV	27%	21%	17%
NPV	92%	100%	100%
Probable Sepsis			
Sensitivity	41%	67%	88%
Specificity	71%	25%	21%
PPV	64%	53%	58%
NPV	50%	37%	60%

[Table/Fig-4]: Performance of serial CRP in different sepsis categories.

WBC Abnormality and Culture

In proven culture positive sepsis, WBC abnormality had

sensitivity of 44%, specificity of 37%, PPV of 13% and NPV of 75%. The statistical analysis did not show significant relationship (p=0.13)

Toxic Granules and Culture

In proven culture positive sepsis, toxic granules had sensitivity of 56%, specificity of 81%, PPV of 40% and NPV of 89%. The statistical analysis showed significant relationship (p=0.001)

I:T Ratio >0.2 and Culture

In proven culture positive sepsis, I:T ratio >0.2 has sensitivity of 83%, specificity of 77%, PPV of 44% and NPV of 95%. The statistical analysis showed significant relationship (p=0.0001).

Comparison of Validity of Individual Lab Tests against Blood Culture as Gold Standard Test

Among the individual lab tests, CRP 3 had the highest sensitivity (100%) and NPV (100%) whereas, toxic granules had highest specificity (81%) and I:T ratio has the highest PPV (44%).This has been detailed in [Table/Fig-5].

Laboratory test	Sensitivity	Specificity	PPV	NPV
WBC Abnormality	44%	37%	13%	75%
Toxic Granules	56%	81%	40%	89%
IT Ratio>0.2	83%	77%	44%	95%
CRP 1	44.44%	73.17%	27%	85%
CRP2	94.44%	48.78%	29%	97%
CRP 3	100%	34.15%	25%	100%

[Table/Fig-5]: Comparison of validity of individual lab tests against blood culture as gold standard test.

DISCUSSION

Of the 100 neonates included in the present study, 20(52.6%) cases were male and 18(47.4%) were female in early onset sepsis whereas, in late onset sepsis 34(54.8%) were male and 28(45.2%) were female with almost similar percentage. This preponderance of males over females have been shown in various other studies [6,7]. This may suggest the possibility of a sex linked factor in host susceptibility. The common clinical symptoms and signs in this study were lethargy, refusal to feed, fever, tachypnea, poor cry, abdominal distension, and icterus. Similar, are the findings in other studies too [4,6]. Though, fever is a less common manifestation of neonatal sepsis, 65% of the cases in the present study had fever [8]. The serial CRP level correlated with the common symptoms with increased sensitivity, but with less specificity and not much change in the predictive value. Thus, clinical presentation/symptomatology should be given importance even in the face of a negative CRP level.

In the present study, blood culture was positive in 18% of cases, and CSF culture was negative in all the cases. This is low in comparison to various other studies, in which the rates have been up to or more than 50% [9,10]. This lower rate of isolation may be due to prior administration of antibiotics before blood collection or infection by unusual organisms (e.g., anerobes). *S. aureus* (38.9%) was the most common organism to be isolated followed by gram negative organisms like *E. coli* (33.3%), and *K. pneumoniae* (27.8%). These findings are consistent with other study findings [9,10]. Recently, a trend has been observed in the type of organism causing neonatal sepsis, worldwide, with the gram positive organisms taking the edge over the gram negative organisms. Though, the exact reason might not be known, the possible explanations could be: carriage of the organisms in health personals working in neonatal area, over crowding, and improper hand washing. In the present study, CRP 2 and 3 were significantly associated with culture positivity (CRP 3 being more significant than CRP 2). The NPV of CRP 3 was almost 100%. This means, serial determination of CRP with the CRP 3 being negative can guide safe discontinuation of antibiotics provided other features of sepsis are not there. Similar has been the conclusion in different studies [11,12]. In one study, CRP was abnormal in 33% in the culture-negative (possible sepsis) group compared to only in 9% in the culture-negative (no sepsis) group [11].

The present study showed positive CRP 1 in 11% cases of proven sepsis and 27.7% cases of probable sepsis with no significant correlation (p>0.05), positive CRP 2 in 23.6% cases of proven sepsis and 45.8% cases of probable sepsis with significant correlation (p<0.05), and positive CRP 3 in 25% cases of proven sepsis and 55.5% cases of probable sepsis with highly significant correlation (p<0.05). Serial measurement of CRP has highly significant correlation (p<0.05) in cases of probable sepsis and proven sepsis, which is consistent with other study indicating that serial CRP monitoring had clinical utility in diagnosis of neonatal sepsis [12].

In the present study, CRP 1 was positive in 21% cases of early onset and 35.4% of late onset sepsis. The CRP 2 was positive in 42.1% cases of early onset and 69.3% of late onset sepsis. The CRP 3 was positive in 63.1% cases of early onset and 83.8% of late onset sepsis. The sensitivity, specificity, PPV and NPV in the present study is similar to other study, which found that the sensitivity of CRP 2 was substantially higher, but maximum sensitivities were achieved by combination of CRP 2 and CRP 3 [12]. The statistical analysis showed that serial measurement of CRP 2 and CRP 3 had significantly high correlation compared to single measurement of CRP 2 only in cases of proven and probable sepsis of early as well as late onset (p<0.05). These findings are consistent with the findings of others. One study found the sensitivity between 78.9% - 98%, specificity between 84% - 97% and NPV of 99% in detecting sepsis [13]. Another study reported the sensitivity of 91%, specificity of 93% [14].

Similarly, another study reported sensitivity of 100%, specificity of 94%, PPV of 91.6% and NPV of 100%, and concluded that predictive value of CRP could be enhanced by serial rather than a single measurement [15].

When comparison of validity of individual lab tests against blood culture as gold standard test was done, following were the observations in the present study: CRP 3 had the highest sensitivity (100%) and NPV (100%), whereas toxic granules had highest specificity (81%) and I:T ratio has the highest PPV (44%).

LIMITATIONS

The present study has following limitations: small sample size, CRP measurement was not compared with other parameters like procalcitonin, and hospital based data.

CONCLUSION

Serial measurement of CRP should be used for the diagnostic evaluation of the neonates with suspected sepsis as it is a very good screening test for the early detection of sepsis. Serial CRP negativity almost excludes neonatal sepsis and help guide the duration of antibiotic therapy.

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