Original Research Article

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The evaluation of C-reactive protein as a screening tool for neonatal sepsis

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ABSTRACT

Background: Bacterial sepsis and meningitis continues to be major causes of neonatal mortality and morbidity in low birth weight infants. C - reactive protein (CRP) is a simple investigation which has diagnostic potential but the previous studies have yielded variable results. A combination of screening tests along with the clinical signs is useful to diagnose/rule out neonatal sepsis along with gold standard blood culture. The objective was to study CRP in relation to other haematological parameters in diagnosis of sepsis and to find out whether CRP estimation helps in early treatment interventions like stopping empirical antibiotic therapy in neonatal sepsis.

Methods: A prospective study of 62 neonates with suspected sepsis admitted in level 2 neonatal special care unit of TMH, Jamshedpur from 1st January 2010 to 30th September 2010 were evaluated after meeting inclusion criteria using clinical criteria, sepsis screen and blood culture, which was taken as gold standard for diagnosis of neonatal sepsis.

Results: Total blood culture positive cases were 26 (42%) and CRP was positive in total 24 cases (39%) of total 62 cases, of which, it is increased in 19 cases (79%) of total 26 culture proven cases and in 5 cases (21%) of culture negative cases. The CRP was increased in 14 cases (35%) out of total 40 cases in early onset sepsis (EOS) group as compared to 10 cases (45.5%) out of 22 in late onset group. The sensitivity of CRP is more in late onset sepsis (LOS) (45.5%) than in early onset sepsis (35%). CRP rise was highest with 73% in proven sepsis, where as it is 23% and 8% in probable and no sepsis groups respectively. The CRP in present study is having sensitivity of test: 73%, specificity of test: 86.1%. The PPV and NPV were 79.1 and 81.6% respectively. If CRP is added to septic screen, it has improved the specificity of the test. Whereas, sepsis screen has sensitivity of 88.5%, the specificity of 83.3%, PPV 79.3% and NPV 90.9%. So, totally empirical antibiotic therapy was stopped in 23 cases of "no sepsis" group including both early as well as late onset sepsis.

Conclusions: Based on the result of our study, the CRP is an effective parameter for the diagnosis of neonatal sepsis and when used in conjunction with the sepsis screen, which increases the sensitivity and specificity of the test, it can help identify septic neonates and help in appropriate management while also reducing the unnecessary use of antibiotics, thereby helping curb the growing menace of antibiotic resistance.

Keywords: CRP, EOS, LOS

INTRODUCTION

Bacterial sepsis and meningitis continues to be major causes of mortality and morbidity in the newborn particularly in low birth weight infants. World over 20

million newborn get infected each year. Of 4 million neonates dying each year, 36% are due to severe infections.² It is the commonest cause of neonatal mortality; it is responsible for about 30-50% of the total neonatal deaths in developing countries. It is estimated

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that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes.³

The incidence of early onset bacterial infection ranges from 1 to 8 per 1000 live births.4 The incidence of neonatal sepsis according to the data from national neonatal peri-natal database (NNPD, 2002-03) is 30 per 1000 live births.⁵ Laboratory diagnosis of neonatal sepsis continues to be a confusing issue-numerous tests but most of them lacking precise sensitivity and specificity. Simple blood counts are easy to do but are not specific while the band cell count and I:T ratio assessment needs an expert, making it difficult to be used routinely. CRP is a simple investigation but one should understand its pitfalls so that it is judiciously used. Indiscriminate use of antibiotic usage is leading to widespread development of antibiotic resistant organisms. Hence, this study was undertaken to evaluate the various diagnostic criteria in neonatal sepsis, especially with reference to the importance of CRP value in comparison to other hematological parameters and If CRP estimation along with other hematological parameters help in discontinuing empirical antibiotic therapy.

METHODS

A prospective study of 62 neonates with suspected sepsis admitted in level 2 neonatal special care unit of TMH, Jamshedpur from 1st January 2010 to 30th September 2010 were evaluated after meeting inclusion criteria using clinical proforma, sepsis screen and blood culture, which was taken as gold standard for diagnosis of neonatal sepsis. The study was approved by the ethical committee for post graduate studies, Tata Main Hospital, Jamshedpur, Jharkhand, India.

All inborn as well as out born babies admitted in special care nursery unit, suspected of having neonatal sepsis were included in study.

Exclusion criteria

All inborn as well as out born babies admitted with

- Intraventricular haemorrhage
- Meconium aspiration
- NEC
- Pneumothorax
- Those who underwent surgery
- Received immunization
- Birth asphyxia
- Antibiotic therapy prior to admission

During this study, a total of 130 patients were admitted in special care unit for suspected neonatal sepsis, among them, 68 cases had 1 or 2 exclusion criteria, 68 neonates were excluded from study. Hence, only 62 neonates from birth till 30 days of life were subjected into study group which includes both inborn as well out born babies.

All the data was analysed statistically by using with software "Graph Pad InStat" downloaded from site www.graphpad.com. The hematological parameters with CRP are studied and compared with gold standard blood culture by applying the sensitivity, specificity, positive predictive value, negative predictive values for each and every septic screen parameter. The chi-square test was applied to estimate p-value for detecting statistical significance of every parameter. Similar method was applied to detect test of significance for CRP and its role as a single test for diagnosis of neonatal septicemia was obtained. Subsequently, the statistical significance of combination of CRP and septic screen was analyzed by similar methods.

Parameters evaluated are

- Complete blood count
- Immature/total neutrophils ratio (I/T RATIO)
- Band cells
- Platelets count
- Single CRP done at 24 hours of life for suspected EOS and or, after 24 hours of onset of clinical features s/o neonatal sepsis
- Single blood culture before starting of antibiotics.

1cc blood was collected in a plain vial. Immunoturbidimetric test was used for quantitative determination of CRP.

CRP reagent composition is as follows

- Tris buffer
- Sodium chloride
- Polythylene glycol 6000
- Goat's anti-CRP antiserum
- Preservative.

If aggregation was found then it is further diluted to find titres of 1:12, 1:24 and so on. Normal value is up to 0.5 mg/dl.

Diagnosis

Proven (definitive) sepsis

Blood culture positive cases with either positive clinical signs or positive septic screen. Following parameters were considered significant in septic screen:

- Total WBC: $\leq 5000 \text{ cells/c.mm}$.
- I/T Ratio : ≥ 0.2
- CRP : \geq 6mg/l
- Band cells : $\geq 20\%$.
- Platelet count ≤ 1 , 50,000 cells/mm.³

Considered as a positive septic screen if any two or more of above criteria are met.

Probable sepsis

If septic screen was positive or clinically symptomatic but blood culture negative.

No sepsis

Sepsis screen as well as blood culture are negative and baby is asymptomatic.

Positive CRP

≥ 6mg/l is taken as positive screening tool

RESULTS

Blood culture was positive in 26 cases (42%) and negative in 36 cases (58%). Blood culture is taken as gold standard test, so based on culture. 42% (26) cases are labelled as definitive sepsis cases.

Table1: Distribution of cases according to culture positivity.

Culture	Bacteriologically positive	Bacteriologically negative	Total
No. of cases	26	36	62
Percentage	42%	58%	100%

Sensitivity of test: 73%, specificity of test: 86.1%, positive predictive value of test: 79.1%, negative predictive value of test: 81.6%, odds ratio: 16.5, The p-value using chi-square test: The two-sided P-value is < 0.0001, considered extremely significant and degrees of freedom = 1. Odds ratio= 16.829. Thus, increase in CRP is significantly associated with occurrence of sepsis (Table 2).

Table 2: CRP values in sepsis.

CRP value	Culture positive	Culture negative	Total
Abnormal	19 (79%)	5 (21%)	24 (39%)
Normal	7 (18.4%)	31 (81.6%)	38 (61%)
Total	26 (42%)	36 (58%)	62 (100%)

CRP in sepsis (p value < 0.0001) extremely significant.

Table 3: Test of significance for 'septic screen'.

Sepsis screen	Culture positive	Culture negative	Total
≥ 2 tests	23	6	29
< 2 tests	3	30	33
Total	26	36	62

The sensitivity of sepsis screen test is 88.5% with specificity of 83.3% and PPV of 79.5%, NPV of 90.0%. Odds ratio: 38.33, chi-square test, so two-sided P-value is < 0.0001, considered extremely significant. Any 2 or more septic screen tests positive are significantly associated with sepsis (Table 3).

If CRP is added to septic screen

Sensitivity of test: 73.1%, specificity of test: 86.1%, positive predictive value of test: 79.2%, negative predictive value of test: 82%. Chi-square test: Two-sided P value is < 0.0001, considered extremely significant, degrees of freedom = 1 and odds ratio= 16.829 (Table 4).

Table 4: Test of significance for sepsis screen with CRP.

Sepsis screen with CRP	Culture positive	Culture negative	Total
Positive with CRP	19	5	24
Negative with CRP	7	31	38
Total	26	36	62

When, positive CRP value is added to sepsis screen, is definitively associated with sepsis.

Table 5: Distribution of CRP positivity in early and late onset sepsis cases.

Types	Early onset sepsis No of cases +CRP cases	Late onset sepsis No of cases +CRP cases	Total cases No of cases total CRP + cases
Proven sepsis	18 12(66.7%)	8 7(87.5%)	26 19(73%)
Probable sepsis	8 1(12.5%)	5 2(40%)	13 3(23%)
No sepsis	14 1(7%)	9 1(11%)	23 2(8%)
Total	40 14(35%)	22 10(45.5%)	62 24

CRP was increased in 14 cases (35%) out of total 40 cases in early onset sepsis group as compared to 10 cases (45.5%) out of 22 in late onset group. The sensitivity of

CRP is more in late onset sepsis (45.5%) than in early onset sepsis (35%).CRP rise was highest with 73% in proven sepsis, where as it is 23% and 8% in probable and

no sepsis groups respectively (Table 5). So, all babies in no sepsis group are observed for minimum period of 72 hours. to 120 hours. In the nursery, No baby developed clinical signs of sepsis, after which they are discharged and reviewed in OPD after 3 days, all of them were doing well. All others (both proven and probable sepsis group) received treatment according to our nursery

protocols. The mortality in proven sepsis group is 12% as compared to 7.7% in probable sepsis group. No baby died in the" no sepsis" group. The overall mortality in the sepsis group (both proven and probable sepsis) is 10.25%. All those babies who died had raised CRP levels (Table 6).

Table 6:	Outcome of	' patients.
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Type of sepsis	Total no	CRP positive	Survived	Expired	Mortality
Proven sepsis	26	19	23	3 (all were CRP positive)	12%
Probable sepsis	13	3	12	1 (CRP positive)	7.7%
No sepsis	23	2	23	-	0%

DISCUSSION

This observational study was conducted in paediatric department of Tata Main Hospital, Jamshedpur, Jharkhand, India during the study period of 9 months after approval from ethical committee. This study included 62 neonates with suspected sepsis admitted in Level 2 neonatal special care unit of TMH, Jamshedpur from 1st January 2010 to 30th September 2010 were subjected into study after meeting inclusion criteria using clinical criteria, sepsis screen and blood culture, which was taken as gold standard for diagnosis of neonatal sepsis.

In present study, blood culture was positive in 26 cases (42%) and negative in 36 cases (58%). Blood culture is taken as gold standard test, so based on culture, 42% (26) cases are labelled as definitive sepsis. This is consistent with 40% by Namdeo et al, 40% by Mustafa et al. ^{5,6}

'C' reactive protein which is an acute phase reactant was considered positive if levels were \geq 6mg/l. This was higher than those seen by other studies. Paul et al considered CRP levels \geq 4mg/l as abnormal; Sharma et al considered CRP levels \geq 6mg/l as positive value.^{7,8} Present study is consistent with other studies. CRP in this study is having sensitivity of 73% which is less than Singh et al with 80% sensitivity and Paul et al with 87.5%. In present study sensitivity is higher than Philip et al which were 47% compared to other study.^{7,9,10} In present study, sensitivity (73%) is low compared to Nuntnarumit P et al who observed the sensitivity of 100% probably because of timing of CRP estimation and lower cut off value for CRP (Table 2, 5).¹¹

But in this study, sensitivity and specificity are comparable to Ehl S et al, Hajiehe B et al and Zwaini A et al, who noticed 78%, 79%, 78% and 84%, 85%, 84% respectively. 12-14 The specificity of present study is 86.1% which is comparable to Singh et al noted 86% and Paul et al noted 83.3% but lower than Sharma et al noted specificity of 93.8%. 7-9

Septic screen was positive in 29 neonates out of whom 23 were culture positive and 6 were culture negative. Sensitivity of septic screen was 88.5% which is nearly similar with those shown by Singh et al 86% and higher than that noted by Bhandari et al 72%. The specificity of septic screen in present study is 83.3% which is higher than those shown by Desai et al (44.1%). Singh et al observed a higher specificity of 90%. The specificity by Bhandari et al was 100% 15 (Table 3).

So based on blood culture and septic screen reports, total cases were divided into sepsis (both proven and probable = 39) and no sepsis (culture as well as septic screen negative = 23). They were observed for 72 hours to 120 hours in nursery and discharged home and on subsequent follow up in paediatric OPD, found to be doing well.

CRP is added to septic screen, the specificity has increased from 83.33% to 86.1%. The positive predictive value also remains unchanged. This result is consistent with the study by Sharma et al.⁸ But the sensitivity has decreased from 88.5% to 73.1% which is comparable to Rod well's HSS showing CRP as a single test has a sensitivity of 76% and negative predictive value of 96%. A combination of CRP with haematological parameters reduced the sensitivity of negative value of the HSS 17 (Table 4).

The mortality in proven sepsis group is 12% on the contrary to 7.7% in probable sepsis group. No baby died in the" no sepsis" group. The overall mortality in the sepsis group (both proven and probable sepsis) is 10.25% which is comparable to most of the neonatal care units' statistics. All those babies who died had raised CRP levels.

CONCLUSION

CRP is an effective parameter for the diagnosis of neonatal sepsis and when used in conjunction with the sepsis screen, which increases the sensitivity and specificity of the test, it can help identify septic neonates and help in appropriate management while also reducing the unnecessary use of antibiotics, thereby helping curb the growing menace of antibiotic resistance.

This simple, inexpensive, readily available test whose results are available almost immediately can be an extremely important part of our armoury in the prompt and accurate diagnosis of neonatal sepsis.

Limitations of the study were small study group; serial CRP estimations could have improved the diagnostic ability of the CRP for neonatal sepsis.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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