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Role of C-Reactive Proteins as a Diagnostic & Prognostic Indicator In Neonatal Sepsis

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Abstract:

Aims and objectives *1) To assess role of CRP as a promising marker in diagnosis of neonatal sepsis.*
2) To determine the utility of CRP as a prognostic indicator in neonatal sepsis.

Study Design: *This was an observational study which was conducted in a tertiary care center in a metropolitan city over a period of 2 years*

Materials and methods: *Neonates admitted with clinical signs & symptoms suggestive of neonatal sepsis was studied. Detection of CRP in human serum was done by therapid slide latex agglutination qualitative method supplied commercially by Span Diagnostics Ltd. with cut off value of CRP being 6mg/dl.*

Results: *In this study of 200 neonates with signs and symptoms of neonatal sepsis 69.50% had positive CRP &30.50% have negative CRP on day 1 of admission. These cases were followed subsequently with starting of empirical antibiotics therapy and CRP repeated on day 5 and day 10 / or on discharge whichever is earlier. It showed that CRP positivity decreased over this periods to 9%.Negative predictive value of SERIAL CRP increases from 35% on day 1 to 94% on day 10 / or on discharge, which signifies that serial CRP value rules out sepsis with high accuracy and helpful in deciding duration of antibiotics in neonatal sepsis. Sensitivity of SERIAL CRP increases from 31% on day 1 to 53% on day10 / or on discharge which is significant. Mean duration of antibiotics on the basis of serial CRP values in neonates with signs and symptoms suggestive of sepsis is reduced from 14 days in non-study group to 9 days (approximately 40 % reduction in duration of antibiotics treatment) with p value<0.003,which is significant.*

Conclusion: *CRP is the rapid diagnostic test which has high sensitivity and negative predictive values in diagnosis of neonatal sepsis.CRP can be used as screening test for early diagnosis as well as deciding duration of antibiotics in neonatal sepsis.*

Keywords: *Sepsis, Serial CRP levels, Duration of antibiotic therapy.*

Introduction

In country like India and other developing countries, neonatal sepsis is the single most important cause of neonatal deaths in the community, accounting for over half of them. Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection with in the first 28 days of life. When pathogenic bacteria gain access into the blood stream, they may cause overwhelming infection without much localization (septicemia) or may get predominantly localized to the lung (Pneumonia) or the meninges (meningitis), joints (arthritis) or urinary tract infection with or without a positive blood culture[1].

Source of infection are usually hospital or community acquired and presents with septicemia or meningitis or pneumonia[2].Its clinical manifestations vary from being subtle to specific, testing the very skill of a pediatrician. Successful treatment depends on early initiation of appropriate antibiotic therapy, but early diagnosis of neonatal bacterial infections is difficult because clinical signs are non-specific and subtle. The inability to be certain of an infection coupled with nonspecific signs of life threatening illness in neonates resulted in widespread use of antibiotics aggravating the problem of antibiotic resistance. If diagnosed early and treated aggressively with antibiotics and good supportive care, it is possible to save most of mortalities & morbidities from neonatal sepsis[3].

The gold standard for diagnosis of neonatal septicemia is a positive blood culture, which even though demonstrates the infecting organism, has many drawbacks. It is costly, time consuming since it takes 48-72 hrs for result to come, demands a well-equipped laboratory, requires more blood and has success rate of about 40% only[4].These has prompted evaluation of surrogate marker of inflammation as possible tool for diagnosis of bacterial sepsis. There are many marker of inflammation of which C-Reactive Proteins are most extensively studied & widely used as early marker of sepsis.C-reactive protein (CRP), an acute phase reactant, it is so called because it is precipitated by C polysaccharide of streptococcus pneumonia, it is synthesized in the liver by hepatocytes in response to inflammation & tissue destruction, especially bacterial infection. Its concentration is less than 1mg/dl in healthy neonate & may rise more than 1000 times during an acute phase response within 4 to 6 hours of an inflammatory process. It falls quickly after efficient elimination of microbial stimulus, due to its short half-life of 19 hours[5]. Serial CRP levels are useful in diagnostic evaluation of neonates with suspected infection. CRP levels<6 mg/L, obtained 24 hours apart from the initial CRP after presentation, indicate that bacterial infection is unlikely. CRP levels can be expected to fall quickly after efficient elimination of the microbial stimulus. Thus CRP may sufficiently reflect the individual balance between the microbes and the immune system of the neonate for monitoring the effect of antibiotic treatment and for guiding the duration of antibiotic therapy. Unlike blood culture, CRP level is not affected by prior antibiotic therapy. Predictability of CRP improves with time, so serial measurements rather than a single measurement at presentation, are recommended[6-7].Serial serum CRP in deciding duration of antibiotics therapy in neonatal septicemia has Negative predictive value -98%, Sensitivity-92.3%, Specificity-85.7%[8-10].

Materials and Methods

The present prospective study was conducted on neonates admitted in neonatal intensive care unit with signs and symptoms suggestive of neonatal sepsis over a study period of 2 years to determine whether C-reactive protein (CRP) can be used for diagnosis (to determine sensitivity, specificity, positive and negative predictive value) and prognosis as a parameter to identify the time point when antibiotic therapy can safely be discontinued in suspected of neonatal sepsis.

This was an prospective observational study which was conducted on 200 neonates (< 28 days of life) admitted in neonatal intensive care unit of tertiary care center in metropolitan city during Nov 2012 to Oct. 2014 with suspected sepsis as per the signs and symptoms mentioned below were included in this study. Approval of ethical committee was obtained.

Case Selection

Signs and symptoms on the basis of which cases were selected were devided in between general symptoms (Fever, hypothermia, poor feeding, edema, not doing well), respiratory system (Apnea, tachypnea, intercostals or subcostal retractions, grunting), Central nervous system (Irritability, lethargy, seizures, bulging anterior fontanels, high pitched cry, neck retraction), Cardiovascular system (Tachycardia, bradycardia, poor perfusion, hypotension, shock) Gastrointestinal system (Vomiting, diarrhea, abdominal distension, hepatomegaly), renal system (Oliguria, acute renal failure) and hematological (Jaundice, splenomegaly, pallor, patechiae, purpura, bleeding).

CRP Estimation

1) Sample collection: 1-2 cc of venous blood was drawn with sterile needle and kept in the test tube till complete clotting and separated serum is visible for testing. The laboratory requires 0.10-0.15 ml of SERUM, therefore 0.3-0.5ml (depending on hematocrit) of whole blood will be required, in a lithium heparin (green top) tube (plain bulb).

2) C- Reactive Protein Assay: CRP was done serially on day1, day 5 & day10 of admission / discharge whichever is earlier. This test was done by using diagnostic kit for in-vitro detection of CRP in human serum by the *rapid slide latex agglutination qualitative* method supplied commercially by Span Diagnostics Ltd. In our study CRP estimation done by microbiologist using same method with cut off value of CRP being 6mg/dl.

Statistical Analysis

Contingency table analysis and chi square(x2), Pearson Chi-Square, Onaway ANOVA test and McNemar-Bowker Test were applied wherever statistical analysis was necessary. All the statistical calculations were done through SPSS (Statistical Presentation System Software) for Windows, Version 20.0 (SPSS, 2012. SPSS Inc. New York).

Results

This observational study included 200 neonates admitted in neonatal intensive care unit in metropolitan city over the period of two year with signs and symptoms suggestive of sepsis of which 117 (58%) neonates were male and 83 (42%) neonates were female. Of this 200 neonates 143 (72%) neonates are vaginally delivered &57 (28%) neonates delivered by LSCS.

Maternal risk factors were present in 33 (17%) cases of which PROM is most common in 20 (60%) neonates with signs and symptoms suggestive of neonatal sepsis.

Neonatal risk factor were present in 174 (87%) neonates; of which most common being low birth weight in 87 (43.5%) neonates followed by prematurity in 55 (28%) neonates.

Most common clinical signs & symptom of neonatal sepsis is of respiratory system (retraction, grunting and nasal flaring) in 52 (15%) neonates, skin changes like mottling & clammy skin being second most common in 23 (12%) neonates.

In this study of 200 neonates with signs and symptoms of neonatal sepsis 69.50% had positive CRP &30.50% have negative CRP on day 1 with cut off value of CRP being 6 mg/dl, values of CRP below which considered as negative. These cases are followed subsequently with staring of empirical antibiotics therapy (IV cefotaxim and amikacin in 88% cases; IV ampicillin and gentamycin in 12% cases) and CRP repeated on day 5 and day 10 / or on discharge whichever is

earlier, showed that CRP positivity decreased over this periods to 9% with mean duration of antibiotics is 9 days.

The incidence of blood culture positive cases in neonatal sepsis is 27% (culture positivity rate).

Of this 200 neonates with signs & symptoms suggestive of sepsis 18 (9%) died &182 (91%) discharged after successful treatment. There is significant correlation between CRP values & outcome (p value <0.05) of neonates with signs and symptoms of neonatal sepsis as well as between CRP values & blood culture at any time of hospital stay for diagnosing sepsis shown by Pearson chi 69 square test with p value consistently less than 0.05 in this study (p value-0.000 on day 1 of admission, 0.000 on day 5 of admission, 0.01 on day10 of admission / or on discharge).With regard to these there was a significant correlation between serial CRP estimations and neonatal sepsis which in turn can be used as promising marker for diagnosis & prognosis in neonatal sepsis.

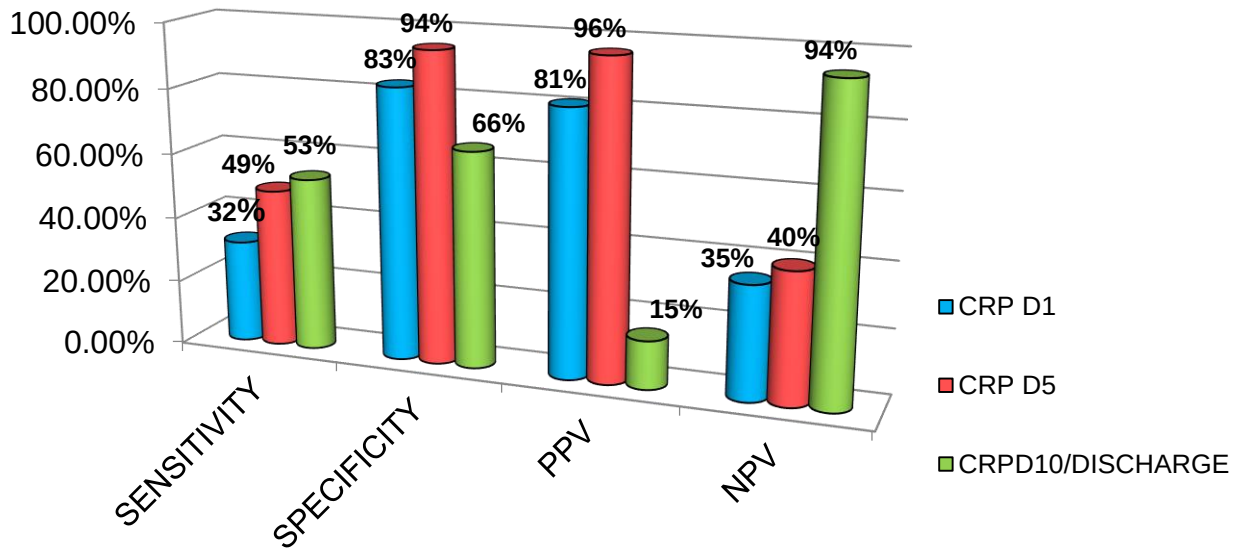
Negative predictive value of SERIAL CRP increases from 35% on day 1 to 94% on day 10 / or on discharge, which signifies that serial CRP value rules out sepsis with high accuracy and helpful in deciding duration of antibiotics in neonatal sepsis.

Sensitivity of SERIAL CRP increases from 31% on day 1 to 53% on day10 / or on discharge which is significant.

Mean duration of antibiotics on the basis of serial CRP values in neonates with signs and symptoms suggestive of sepsis is reduced from 14 days in non study group to 9 days (approximately 40 % reduction in duration of empirical antibiotics treatment) with p value<0.003,which is significant.

Table 1-Sensitivity, specificity, positive & negative predictive values of CRP

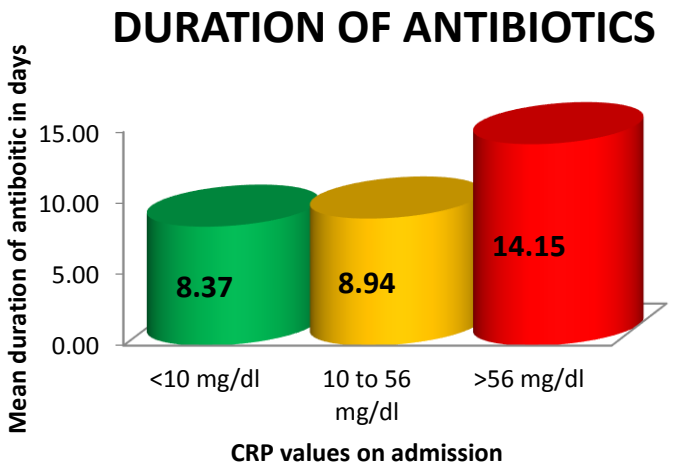
CRP VALUES	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
DAY 1	31.62%	83.33%	81.13%	34.97%
DAY 5	48.75%	94.83%	96.30%	40.15%
DAY10/OR ON DISCHARGE	53.33%	66.10%	14.89%	93.98%



Graph 1-Sensitivity, specificity, positive & negative predictive values of CRP

Table 2-Correlation between mean duration of antibiotics and CRP values on admission

CRP values on admission	No. of patients	Mean duration of antibiotics	Std. Deviation	One-way ANOVA test	
<10 mg/dl	62	8.37	4.11	F Value	P Value
10 to 56 mg/dl	97	8.94	4.46	26.265	0.000
>56 mg/dl	41	14.15	4.14	Difference is significant	
Total	200	9.85	4.82		

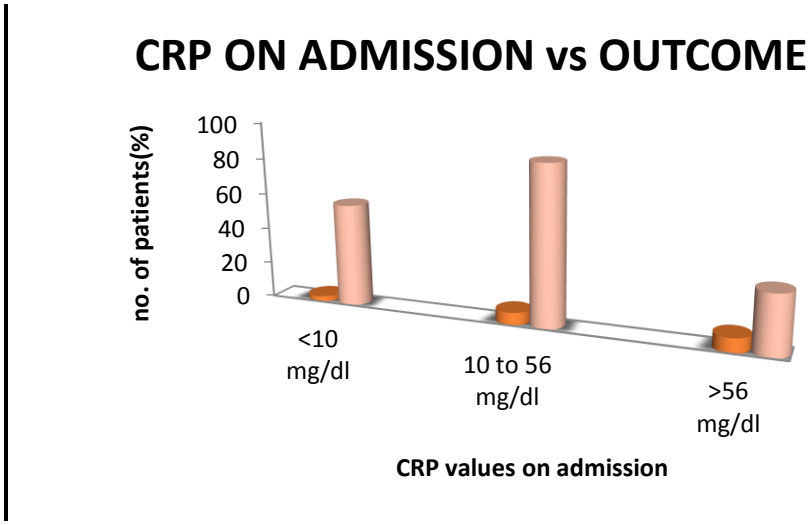


Graph 2-Correlation between mean duration of antibiotics and CRP values on admission.

Table 3- Correlation between CRP on admission& outcome of patients.

CRP DAY1		Outcome		Total
		Died	Discharge	
<10 mg/dl	Count	3	57	60
	%	5.0%	95.0%	100.0%
10 to 56 mg/dl	Count	7	88	95
	%	7.4%	92.6%	100.0%
>56 mg/dl	Count	8	33	41
	%	19.5%	80.5%	100.0%
Total	Count	18	179	197
	%	9.1%	90.9%	100.0%

Chi-Square test	Value	df	P Value	Association is
Pearson Chi-Square	7.011(a)	3	0.072	Significant



Graph 3- Correlation between CRP on admission& outcome of patients.

Discussion

In India Incidence of neonatal sepsis is 30 per 1000 live birth. Sepsis is commonest cause of neonatal mortality & is responsible for 30-50% of total neonatal deaths in developing countries sepsis related mortality is largely preventable with prompt diagnosis, rational antibiotic therapy & aggressive supportive care[2].CRP is one of the most widely available, most studied, and most used laboratory tests for neonatal bacterial infection and despite the continuing emergence of new infection markers it still plays a central role in the diagnosis of early onset sepsis of the neonate.

Serial measurements of serum CRP levels are useful in monitoring the course of neonatal septicemia. It provides an early indication of response of treatment. It can help in decision of initiating or discontinuing antibiotic therapy. The persistence or insignificant decline of serum CRP with treatment signifies about inadequate treatment or development of complications. In present study CRP is done serially on day 1, day 5 & day 10/ or on discharge. Sensitivity of single CRP for diagnosing neonatal sepsis is low but this can be increased by serial CRP measurement as evident in present study that is on day1 sensitivity is 31.62%,on day 2 increased to 48.75% & on day 10 / or on discharge sensitivity reaching up to 60% (Table-1). Results of this study is comparable with studies conducted by Himayun et al (2009), the sensitivity of CRP at 0 hours were 40%, the corresponding values at 24 hours were 70% which implies a single CRP value done at the time of admission lacks sensitivity.

A negative CRP value is more important than a positive CRP value in that it excludes infection with a high certainty. In our study negative predictive values of serial CRP is as high as 93.98%(Table-1).This observations comparable with other studies as Nuntnarumit Pet al (2002) shown that the negative predictive value of CRP for proven neonatal sepsis is 100 per cent which concludes Predictive value of CRP could be enhanced by serial rather than a single measurement[11].Parviz Ayazi et al (2007)found out that NPV of serial CRP was 96%[12].R.S. Jaswal et al (2003),showed that Negative predictive value of serial CRP was 100% in deciding duration of antibiotic therapy in suspected neonatal septicemia[13].Sidra Younis et al (2014) revealed negative predictive of raised CRP was found to be 95.2%[14].Bomela HNet al (2000) showed that repeat CRP estimation correctly identified 99 of 100 infants in the study as not requiring further antibiotic therapy (negative predictive value, 99%; 95% confidence intervals, 95.6 to 99.97%)[15].

Serial CRP measurement is a good practical guide for discontinuing antibiotic therapy in neonates with suspected sepsis. These neonates can be

discharged from the hospital earlier, with significantly reduced cost, complications of treatment and family anxiety. In present study on the basis of serial CRP measurement mean duration of antibiotics is reduced from 14 days in non-study group to 9 days(approximately 40 % reduction in duration of empirical antibiotics treatment)with p value<0.003.This results are comparable with J. Khashabi et al (2004), the mean±SD duration of treatment was 3.3±1.0 days in the study group and 5.9±1.7 days in neonates prior to conducting the study (p<0.000) i.e. 50% reduction in duration of empirical antibiotics treatment[16].Jason Pryor et al (2013) showed that of the 120 patients in the CRP study group, average length of antibiotic therapy was 9 days compared to 16 days in the historical control group i.e.44% reduction in duration of empirical antibiotics treatment[17].

Conclusion

Our study concludes that CRP is the rapid diagnostic test which has high sensitivity and negative predictive values in diagnosis of neonatal sepsis.CRP can be used as screening test for early diagnosis as well as deciding duration of antibiotics in neonatal sepsis. Rational use of CRP levels not only can reduce the mortality and morbidity in neonatal sepsis but also it can prevent irrational use of antibiotics which may go a long way in preventing antibiotics resistance.

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