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A CORRELATIVE STUDY OF C-REACTIVE PROTEIN WITH BLOOD CULTURE AND SENSITIVITY IN NEONATAL SEPSIS

Paediatrics

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ABSTRACT

Background :. Neonatal sepsis is clinical syndrome of bacteremia characterized by systemic signs and symptoms of infection in the first month of life. It continues to remain a leading cause of morbidity and mortality worldwide. It can be diagnosed by blood culture but it is time consuming. So, a reliable marker like CRP is needed for the early diagnosis of neonatal sepsis so that early treatment can be initiated.

Methods: This prospective study was conducted in the Department of Pediatrics, Alluri sitarama raju academy of medical sciences, Eluru from November 2017 to October 2018. The blood sample was collected from 68 clinically suspected cases of neonatal sepsis admitted in the NICU constituted material for the study.

Results: CRP is positive in 47 (69%) of cases with clinical sepsis. Blood culture is positive in 22(32.4%) of neonates with clinical sepsis. CRP s true positive in 21 out of 22 cases of culture positivity cases false positive in 26 out of 46 culture negative cases carrying sensitivity of 95.45%, specificity of 43.45% with PPV of 44.68% and NPV of 95.24% With analysis of levels of CRP values with prediction of culture positivity it is found that with increasing levels of CRP the positivity of blood culture increases and it carries P value 0.00 which issignificant.

Conclusion : CRP have high sensitive and good negative predictive value. So CRP can be used as early and predictable screening test for the early diagnosis of neonatalsepsis.

KEYWORDS

Blood culture, CRP (C- Reactive protein), Neonatal sepsis.

INTRODUCTION

Neonatal sepsis is clinical syndrome of bacteremia characterized by systemic signs and symptoms of infection in the first month of life. It continues to remain a leading cause of morbidity and mortality worldwide.[1,2]

The fulminant nature of neonatal septicemia and its high mortality rate has always posed a challenge to the skill of a pediatrician[3]. Due to non-specific clinical presentation; diagnosis of sepsis is a challenge to clinicians. It can be diagnosed by blood culture but it is time consuming. So, a reliable marker is needed for the diagnosis of neonatal sepsis so that early treatment can be initiated. Various cytokines, chemokines, acute phase reactants, cell surface markers and interferons have been evaluated to find out the effective marker for early diagnosis of neonatal sepsis[4].

C-reactive protein is an acute phase protein which may be useful in the early diagnosis of neonatal sepsis as it raises as much as a thousand fold within 4 to 6 hours of an inflammatory process. As infection is the most likely cause of inflammation in the neonate, CRP has been shown to be useful in the diagnosis of neonatal sepsis. Upon resolution of the inflammation, CRP levels rapidly decline with an elimination half-life of 19 hours. Thus CRP level is also a useful marker in determining the duration of antibiotictherapy.[5]

AIMS AND OBJECTIVES

- To determine Sensitivity and Specificity of CRP as an indicator of neonatal sepsis in comparison with bloodculture in neonates admitted to NICU of ASRAM hospital, Eluru.

METHOD OF COLLECTION OF DATA

SOURCE OF DATA:

This prospective study was conducted in the Department of Pediatrics, ASRAM Medical College, Eluru from November 2017 to October 2018. The blood sample was collected from 68 clinically suspected cases of neonatal sepsis admitted in the NICU constituted material for the study.

INCLUSION CRITERIA

Neonates present
ing with following:

1. Perinatal riskfactors:

- Low birthweight
- Prematurity
- Birthasphyxia
- Homedelivery
- PROM more than 24hours
- Maternal fever
- Instrumentation

2. Clinical riskfactors:

- Poor feeding, lethargy reducedactivity.
- Sclerema
- Hypothermia/fever
- Jaundice
- Apnea,tachypnea
- Abdominal distension and vomiting.
- Diarrhea
- Skinmottling
- Bleeding tendencies
- Seizures

EXCLUSION CRITERIA

- Neonates who received antibiotics beforeadmission
- Neonates with major congenitalmalformations.

METHODS

All neonates were categorized into 0-72 hours (early onset) or late onset (>3 days) sepsis based on day of presentation. Detailed history and clinical findings were recorded.

All neonates who are clinically symptomatic were screened using CRP and various hematological parameters with predetermined cut off value and at the same time blood culture was sent. Relevant to clinical situation CSF, Urine analysis and swabs of infective focus were taken. The cut off values of the positive rapid screening tests in this study are as follows:

1) C-Reactive protein (CRP) :>6 g/ml.
2) Total leucocyte count (Leukopenia) :< 5,000cells/cu.mm.
3) Absolute neutrophil count (Neutropenia) :< 1,750cells/cu.mm.

4) Band cell count to total neutrophil count ratio (I/T) :>0.2.
5) Platelet count (thrombocytopenia) :< 1.5lakhs/cu.mm

The empirical antibiotic therapy was started according to antibiotic guidelines in the NICU, if CRP was positive, awaiting the culture reports.The duration of treatment and duration of hospital stay was noted in all neonates.

STATISTICALANALYSIS

The data were recorded in the form of mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Chi square or Fisher s exact tests were used on those categorical variables. CRP positivity in qualitative test is taken into consideration and semi quantitative is not taken.

CRP levels and Sensitivity, Specificity, Positive and Negative predictive values were calculated by taking culture positivity as gold standard. The statistically significant difference level was set at p<.05. All statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Chicago,IL).

RESULTS

In the present study, 65% (44 of 68) had early onset while remaining 35% (24 of 68) had late onset neonatal sepsis. Thus early onset sepsis was more common than late onset sepsis.

Data regarding distribution of early onset and late onset sepsis:

	Frequency	Percent
LONS EONS Total	24	35.3
	44	64.7
	68	100.0

1) A CRP (qualitative) positive case was found in 47 of 68 (69.1%) neonates with clinical sepsis. Its mean value was 25.84 mg/L with a SD of 29.19. CRP semi- quantitative value was more than1mg/L in all 68 neonates with a mean of 3.112 mg/L and SD of 1.8.

Data regarding CRP levels in neonates

CRP Level		Frequency	Percent
	<6 or =6	21	30.9
	6.1 - 15	17	25.0
	15.1 - 30	9	13.2
	30.1- 45	8	11.8
	>45	13	19.1
	Total	68	100.0

Neonates were classified according to CRP levels and 21 neonates had 6 or below 6 CRP levels. 17 of 68 had CRP value between 6 and 15, while 9 had CRP value between 15 and 30. 13 neonates had CRP level above 45.

In the study, culture was positive in 22 of 68 (i.e. 32%) neonates with clinical course compatible with sepsis.

Data regarding culture positivity of neonates:

Culture		Frequency	Percent
	Negative	46	67.6
	Positive	22	32.4
	Total	68	100.0

Klebsiella was the most common offending organism in this study constituting next in order was E. coli, Enterobacter species and followed by Acinetobacter, Staph aureus, Pseudomonas, and Coagulase negative streptococci.

Comparison of CRP and culture positivity:

CRP * Culture		Culture		Total	P value
		Negative	Positive		
CRP	negative	20	1	21	0.001
	positive	26	21	47	
Total	46	22	68		

A CRP positive case was found in 21 of 22 (95.45%) neonates with culture positive sepsis and was statistically significant. CRP negative but culture positive cases were found in 1 of 22 (4.55%) neonates. Thus in detecting neonatal sepsis, the CRP had **Sensitivity of 95.45%, Specificity of 43.48, PPV of 44.68 and NPV of 95.24.**

Comparison of CRP against early and late onset neonatal sepsis:

CRP * EONS/LONS					
		EONS	LONS		P value
CRP	negative	12	9	21	0.383
	positive	32	15	47	
Total	44	24	68		

DISCUSSION

A CRP (qualitative) positive case is found in 47 of 68 (69.1%) neonates with clinical sepsis in the present study. Similar result is seen in study by Mehrotra[10].The mean value is 25.84 mg/L with a SD of 29.19. In the study by Ganeshan, the serum CRP value in clinically suspected cases of neonatal sepsisis33.33±26.35mg/l while in Khalak sstudy, it is 37.5mg/L[9] andinboth studies the values are significantly higher than controls. CRP semi- quantitative value was more than1mg/L in all 68 neonates with a mean of 3.112 mg/L and SD of 1.8[5].

In the present study, neonates were classified according to CRP levels and 21 neonates had 6 or below 6 CRP levels. 17 of 68 had CRP value between 6 and 15, while 9 had CRP value between 15 and 30. 13 neonates had CRP level above 45. In Mehrotra study, total 50 cases of suspected neonatal sepsis CRP is done out of which, less than 37 weeks gestation were 21were studied and out which 14 cases were found to positive in the range of 12 µg to 24 µg/ml and remaining 7 cases were found negative. In more than 37 weeks of gestation 29 cases of suspected Neonatal Sepsis study for CRP, out of which 20 were found to be positive in the range of 6 to 12 µgram / ml. and remaining 9 cases were found to benegative[10].

In the study, culture is proven positive in 22 of 68 (i.e. 32%) neonates with clinical course compatible with sepsis. Several studies report an incidence of culture positivity ranging between 25 to 70% of neonates with suspected clinical sepsis. In a community survey done in rural India, 10% of the sample has positive culture[11].

The qualitative method of CRP estimation, which is a rapid, inexpensive and simple test to perform, was found to have better sensitivity, specificity and NPV of 95.45%, 43.48% and 95.24%, respectively. This implies that CRP would correctly identify close to 95% of neonates with sepsis and would have 95% probability in excluding sepsis. The C-reactive protein may therefore, help in the early detection of neonatal sepsis while awaiting blood culture results. CRP may also be invaluable in the management of neonatal sepsis in resource poor centres where facilities for blood culture may not be readily available.

Several studies report a sensitivity and specificity of 48–78 % and 71–88 %, respectively, for a single determination of CRP at 4–12 h after symptom onset.[16-20] In Ganeshan s study, based on the cut-off value of CRP>13.495 mg/l showed sensitivity of 80% and specificity of 65.7%[4]. Also in the same study, the culture positive cases among the clinically suspected septic neonate group demonstrated slightly higher levels of serum biomarkers (IL-6, CRP and hs-CRP) as when compared to culture negative suspected septic neonates. (5.27mg/Liter to 91.8mg/liter in culture+vevs5.0mg/liter to 66.75 mg/liter in culture –ve). A meta-analysis was done including 31 studies, involving 1695 cases and 4003 controls. The overall results suggested that CRP had a moderate specificity (77%) and high diagnostic value (AUC 84.6%) and diagnostic accuracy (with high DOR 12.65) for neonatal sepsis, while the sensitivity (69%), PLR (3.83), and NLR (0.38) were moderate. It should be noted that although no threshold effect was detected, significant heterogeneity was observed across the included studies when used the estimation of diagnostic accuracy variables[14]. Meta regression analysis showed that there is variable study heterogeneity irrespective of test time, cutoff value, assay method of CRP, neonatal sepsis. However, subgroup analysis of studies with cutoff 10 mg/L and test time 0 h still showed significant heterogeneity. Thus, cutoff value (10 mg/L) and test time (0 h) may be potential for diagnosis of neonatal sepsis. Importantly, the specificity reached to 92% in the subgroup analysis.[14]Of 986 episodes of neonatal culture-proven bloodstream infections of late onset in a study by Lai et.al, 247 (25.1 %) had CRP ≤10 mg/L at the onset of clinical sepsis. Among these, 247 (25.1 %) had a plasma CRP level ≤ 10 mg/L, 563 (57.1 %) had a plasma CRP level of 11–100 mg/L, and 176 (17.8 %) had a plasma CRP level > 100 mg/L[21].

In our study, increase in the CRP value increased the specificity and positive predictive value, which is low when only CRP positive or negative is taken based on cut off value of 6mg/L. In the study by khalak, increasing the cutoff values for CRP increased the sensitivity and the positive predictive value and proved if concentrations of CRP remain low, infection is unlikely and discontinuing antibiotic therapy is reasonable[9]. Also the data showed that there was a progressive improvement in sensitivity of a single CRP value as the cutoff is increased. The study conclude that a single CRP level obtained during neonatal sepsis evaluation of even preterm infants can be helpful in assisting with the decision to discontinue antibiotics in the presence of a low CRP value. This is consistent with what has been published in the literature using two successive CRP values. Also it concluded that CRP could be used to predict early onset neonatal sepsis. It has been recently proposed that using biomarkers in conjunction, particularly PCT and CRP (early and late- phase biomarkers) could assist in decision-making of a sepsis diagnosis. Use of these markers to discontinue antibiotic therapy would aid in promoting antibiotic stewardship in both preterm and term neonates. When some of these signs, particularly, heart rate or respiratory changes are considered in concert with CRP levels; strong association with sepsis has been reported.[22]

SUMMARY

1. CRP is positive in 47 (69%) of cases with clinical sepsis.
2. Blood culture is positive in 22(32.4%) of neonates with clinical sepsis.
3. CRP s true positive in 21 out of 22 cases of culture positivity cases false positive in 26 out of 46 culture negative cases carrying sensitivity of 95.45%, specificity of 43.45% with PPV of 44.68% and NPV of95.24%
4. With analysis of levels of CRP values with prediction of culture positivity it is found that with increasing levels of CRP the positivity of blood culture increases and it carries P value 0.00 which significant.
5. In culture positive sepsis cases (either EONS or LONS) CRP positivity is found to be significant.

CONCLUSION

In babies who were affected by neonatal sepsis, CRP has high sensitive and good negative predictive value. CRP levels had statically significant association with culture proven sepsis.CRP had more sensitivity and high negative predictive value. So CRP can be used as early and predictable screening test for diagnosis of neonatal sepsis.

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