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Original Article

Comparative utility of C reactive protein and Blood culture for diagnosis of neonatal septicaemia

Shipra Galhotra*[1], Veenu Gupta[2], Deepinder Chhina[3], Harmesh Singh Bains[4], Ashish Chhabra[5]

Department of Microbiology, GGS Medical College, Faridkot, Punjab, India.
Department of Microbiology, Dayanand Medical College Hospital, Ludhiana, Punjab, India.
Department of Paediatric Surgery, GGS Medical College, Faridkot, Punjab, India.
Department of Pediatrics, Punjab Institute of Medical Sciences, India.

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Abstract:
Introduction: Neonatal septicaemia constitutes a significant cause of morbidity and mortality of neonates in India. The diagnosis of neonatal septicemia based on clinical manifestations is nonspecific which leads to initiation of unnecessary antibiotic treatment. Blood culture remains the gold standard for the diagnosis of neonatal sepsis. But many times, culture may be negative in symptomatic neonates, preterm neonates or very low birth weight babies. Further difficulty with blood culture is turnaround time of at least 18-24hrs and this facility is available only in well-equipped centers. C-reactive protein (CRP) production is a nonspecific response to a disease but along with clinical symptoms, it is helpful for the diagnosis of neonatal septicaemia. **Methods**: In this one year prospective study, 257 clinically suspected cases of neonatal septicaemia were enrolled. Screening for CRP was done by quantitative method and cut off value of CRP was taken as 6mg/l. Simultaneously, blood culture was done by automated BACTEC 9240 system. **Results**: Out of 257 cases, 67 showed positive CRP and 20 cases showed positive blood culture. The predominant organisms were *Staphylococcus* species followed by *Escherichia coli*. CRP test showed 50% sensitivity and 77%specificity, considering blood culture as gold standard method. **Conclusion**: CRP is a rapid tool for screening of neonatal septicaemia and a reliable marker in the absence of positive blood cultures. The use of both CRP and blood culture in combination would increase the yield of laboratory confirmed neonatal septicaemia cases.

⇑ Corresponding authors at:
Dr Shipra Galhotra, #240, New Flats, Medical Campus, Faridkot, Punjab.
E-mail address: shipragalhotra@gmail.com

Introduction

Sepsis occurs when active bacterial multiplication or bacterial products causes harm to the host and it is identified by one or more positive blood cultures in the presence of clinical signs of infection. [1]

Neonates are particularly vulnerable to infections because of weak immunological barrier and neonatal sepsis is a major cause of mortality and morbidity worldwide. [2] Diagnosis of neonatal sepsis based on clinical symptoms is not possible. Although isolating its causative microorganisms using blood culture has been the gold standard for its diagnosis, but its

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result is ready 24-72 hours after sampling and during this period, it is necessary to treat suspicious infants for sepsis with antibiotics according to clinical symptoms and risk factors. [3]

CRP is synthesized within six to eight hours of exposure to an infective process or tissue damage. It has a half-life of 19 hours and may increase more than 1000-fold during an acute phase response. [4] The ability to early diagnosis or rule out neonatal sepsis results in to limit inappropriate antibiotic exposure and lowering the cost of therapy. 1 Neonatal sepsis is responsible for about 30-50% of the neonatal deaths in developing countries. [5, 6]

Mortality rate in neonatal sepsis differs according to the type of organism involved. The highest mortality in neonatal sepsis is caused by Gram negative bacteria and *Enterococci*. [7] Early and appropriate antibiotics are the treatment options for neonatal septicaemia. The clinical and laboratory testing plays its role in the treatment of sepsis. [8]

Thus, present study was undertaken to evaluate the efficacy of CRP in the early diagnosis of neonatal septicaemia.

Materials and Methods

A total of 257 neonates up to the age of 28 days, who were admitted in NSCU, DMCH Ludhiana from Jan 2010 to Dec 2010, with clinical diagnosis of neonatal sepsis, were included in the study. Patients with neonatal sepsis were enrolled based on signs and symptoms as lethargy, poor cry, refusal to feed, changes in body temperature (fever and hypothermia), jaundice, apnoea, respiratory distress, tachycardia, tachypnoea, cyanosis, vomiting, distension of abdomen, sclerema, seizures, bulging fontanelle, irritability, grunting etc. Blood was collected for CRP test and blood culture. CRP test was carried out from the serum by using quantitative method. Serum levels greater than 6 mg/l of CRP was considered as criteria for sepsis. 1-3 ml of blood was inoculated aseptically into commercially prepared BD BACTEC Peds Aerobic /F vials at the bedside. In cases where no growth was obtained after 7 days of incubation, then it was considered as a negative blood culture. In culture, positive cases, smears were prepared and examined after Gram's staining. Simultaneously, sub-cultures were done on blood Agar and MacConkey's agar and the plates were then incubated at 37°C for 18-24 hours. Growth was identified by standard microbiological techniques.

Results

Out of 257 clinically suspected cases of neonatal sepsis, 20 had positive blood cultures, which indicate prevalence of 7.7%. Remaining 237 (92.3%) blood cultures were negative. CRP was reactive in 67 (26%) cases out of which 57 (22.1%) were false positive and CRP was non-reactive in 190 (74%) cases out of which 10 were false negative (3.9%)

Table 1: Correlation of CRP test and blood culture (n=257)

CRP	Blood culture		Total (%)
	Positive (%)	Negative (%)	
Positive	10 (3.9%)	57(22.1%)	67 (26%)
Negative	10 (3.9%)	180 (70%)	190 (74%)
Total	20 (7.8%)	237 (92.2%)	257 (100%)

Table 2: Negative blood cultures with high CRPs had antibiotics given prior to obtaining blood culture (n=69)

CRP Positive	History of antibiotics	No history of antibiotics
69	21 (30.4%)	48 (69.6%)

Table 3: Statistical analysis of CRP test

Validity of CRP values	In present study (%)
Sensitivity	50%
Specificity	77%
Positive predictive value	14.9%
Negative predictive value	95%

Table 4: Correlation of blood culture isolates with CRP

Organisms	Blood culture positive (%)	CRP test positive (%)
Gram positive organisms (13)		
S. aureus	6 (30%)	3
S. epidermidis	5 (25%)	3
E. faecalis	2 (10%)	1
Gram negative organisms (7)		
E. coli	3 (15%)	0
B. cepacia	2 (10%)	2
P. aeruginosa	1 (5%)	0
A. baumannii	1 (5%)	1
Total	20 (100%)	10

The main isolates in blood culture were Gram positive organisms like *S .aureus* (30%), *S. epidermidis* (25%) and *E. faecalis* (10%) and Gram negative organisms include *E. coli* (15%) *B. cepacia* (10%) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. (Table-4)

Discussion

The varying microbiological pattern of neonatal septicaemia warrants need for an ongoing review of causative organisms. [9] Total blood culture positivity rate among neonates with sepsis in our study was 7.7% comparable to Martin *et al.* who reported bacteriologically proven sepsis in 9.5% of cases [10] whereas lower rate of 4.1% was reported by Aletayeb *et al.* [11]

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A low blood culture isolation rate could be due to administration of antibiotic before blood collection, blood culture technique [12] or sepsis due to anaerobic, viral or fungal pathogens. [13] A higher isolation rate of 52.63% reported by Murty *et al*. probably due to a low sample size (n=22) [14] and a much higher rate of 64% found by Tallur *et al*. [15] This higher isolation as compared to our study could be because of the organisms which were isolated in this study are nosocomial pathogens and many of the neonates might have acquired them nosocomially. This indicates that nosocomial infections are less in our hospital and better patient care is given. This higher isolation as compared to our study could be because of the organisms which were isolated in this study are nosocomial pathogens and many of the neonates might have acquired them nosocomially. This indicates that nosocomial infections are less in our hospital and better patient care is given.

The pattern of bacterial isolates was different in different studies due to geographical variations and use of different antibiotics at different centers. Also, spectrum of pathogens in India and south-east Asian countries is different from Western data where group B *streptococci* and coagulase negative *staphylococci* (CONS) are the predominant pathogens. Gram-negative *bacilli* are predominant pathogens in developing countries with *K. pneumoniae* being the most common. [16] But in our study, Gram positive bacteria (65%) were more common than the Gram-negative bacteria (35%). In recent years, S. aureus was predominant gram positive organism isolated in neonatal sepsis in our local region similar to our study whereas previous studies have reported predominance of *K. pneumoniae*. [16, 17, 18, 19]

This change in pattern of organisms causing sepsis from total Gram negative to predominantly Gram positive may be due to prolonged and improved intensive care facilities, invasive procedures, long lines/central catheters and parenteral nutrition. There were 25% cases of coagulase negative *staphylococci* (CONS) like studies in Kuala Lumpur and Taiwan. [7, 20] The increase in number of premature patient population with longer duration of NICU hospitalization and increase in the placement of central vascular catheters might be responsible for the rise of infections from commensal organisms. [21]

Gram negative organisms were isolated in 35% cases with *E. coli* as the commonest isolate whereas Mustafa and Ahmed (64.5%) and Aletayeb *et al.* (92.8%) found higher incidence of Gram negative organisms. [11, 22] The non-fermenters in this study were 20% while study done in South India showed prevalence of 12.2% for these bacteria. [23] The present study was undertaken to assess the utility of CRP test as marker for diagnosis of neonatal septicaemia. Serum concentration of CRP increase several hundred-fold in response to bacterial infection, making it an attractive diagnostic test for neonatal sepsis.

The relatively low cost of the readily available CRP test makes it an attractive single test to screen for neonatal sepsis. But in our study, it was raised only in 26% cases while a study from Surat and Iraq showed rise of CRP in58.7% and 75.4% cases. [2, 3] CRP was raised in (50%) cases of culture proven sepsis while in a study from Iraq, (36.8%) cases showed raised CRP. [3] Low positivity of CRP in blood culture positive sample might be due to early sample collection as CRP rises after 6-8 hours of birth. In this study 30.4% patient with high CRP has received antibiotics before taking blood culture. (Table 2) Blood culture negativity could be because of sensitive bacteria which responded to antibiotics and high CRP could be because of certain amount of inflammation is still present.

In our study, we found sensitivity of CRP 50%, specificity 77%, positive predictive value (PPV) 14.9 % & negative predictive value (NPV) 95% considering blood culture as gold standard method. (Table 3) CRP was not having a good correlation with neonatal sepsis in a study done at Pakistan with 23% sensitivity and 84% specificity. [24] Our study has good co-relation with study of Ayazi *et al*. which has sensitivity of 76% and specificity of 60%. [25] Whereas Anuradha *et al*. found CRP sensitivity 100%, specificity 87.3%, PPV 88.3% and NPV 100% and B K Jha found sensitivity 100%, specificity 65.67%, PPV 87.3% and NPV 100%. There are conflicting results on CRP in literature. [26, 27] There are some limitations in this study. Although a set of strict criteria was used to define true BSI, the lack of 2 positive blood cultures for CoNS as documentation of BSI is a weakness of this study. This was a prospective, single-center cohort study, which inevitably restricts its generalizability compared to that of a, multicenter study. The timing of blood sampling for culture and CRP also was not uniform because some septic work-up may be delayed because the initial septic symptoms were nonspecific and subtle. Furthermore, some CRP levels may have been falsely low because they were obtained too early before they started to rise around 4–6 h after sepsis onset. Lastly, a group with elevated CRP but without infection was not enrolled as controls. Thus, a multicentric prospective study as well as control group is warranted to scientifically delineate the sensitivity and specificity of CRP as a predictive marker of neonatal sepsis. But still, CRP can be used as a septic marker in resource limiting setting

Conclusion

Estimation of serum CRP is simple for diagnosis of neonatal septicaemia. CRP is a very good inflammatory marker and highly sensitive in case of neonatal septicaemia. Instead of waiting for 48-72 hrs for a blood culture report, result of CRP test is available within an hour. Empiric antibiotic therapy can be started immediately as soon as CRP report is available, so as it can reduce the morbidity and mortality in those neonates. CRP highly correlates with infection positivity, and can be used as a diagnostic as well as prognostic marker.

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