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Original Article

The Role of Serial Serum C-Reactive Protein Level in the Diagnosis of Neonatal Infection

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ABSTRACT

Background: *Infection is one of the major problems in neonates. The diagnosis of neonatal septicemia is difficult to establish based on the clinical criteria alone. However, empirical therapy should not be delayed because of high mortality. Laboratory tests used to support the diagnosis have shown variable values. C-reactive protein (CRP), an acute phase protein, increases in inflammatory disorders and tissue injury. Serial CRP has been shown to be more useful than a single measured CRP in the diagnostic evaluation of neonates with suspected infection. This study was performed to determine prospectively whether, in the presence of proved or presumed bacterial infection, the sensitivity of serum C-reactive protein response could be enhanced by serial rather than single determinations.*

Materials and Methods: *All infants, aged<60 days treated for suspected bacterial infection were prospectively evaluated using a standardized clinical pathway, from march 2005 to march 2006. Infants were categorized as having proved sepsis (bacteria isolated from blood, cerebrospinal fluid, or urine culture) or probable sepsis (clinical and laboratory findings consistent with bacterial infection without a positive culture). CRP level was determined at initial evaluation and 24 hours later. Sensitivity, specificity, and predictive values were calculated for the first (CRP#1), second (CRP#2) and two serial serum CRP levels. CRP was measured qualitatively (a positive test result indicates a CRP level more than 6 mg/L). Infants who had received antibiotics prior to sepsis work-up were excluded. Positive blood culture was considered as the "Gold Standard" against which the performance of CRP was compared.*

Results: *One hundred infants underwent sepsis work-up during the study period of 1 to 6 days. Of 100 infants, 52 were females (52%) and 48 were males (48%). There were 9 cases (9%) of proven sepsis (positive blood culture) and 91 cases (91%) of probable sepsis as defined in method section. The most common causative organisms were Staphylococcus aureus (5), Coagulase negative staphylococcus (3) and Escherichia coli(1). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CRP#1 were 55.5%, 82.5%, 24% and 95% respectively. Sensitivity, specificity, PPV and NPV of serial CRP were 67%, 80%, 24% and 96% respectively.*

Conclusion: *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.*

Key words: *Bacterial infection, C-Reactive Protein, Blood culture, Newborn, Sensitivity, Specificity.*

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INTRODUCTION

Neonatal septicemia is a critical disease in neonatal period. Its incidence among live births is between 1 and 8 per 1000. Mortality of neonatal septicemia may be as high as 50% for infants who are not treated (1). The early diagnosis of neonatal sepsis presents a clinical dilemma. There is no reliable method to distinguish babies that are actually infected from those with suspected sepsis (2). A

common method is to be guided by blood culture results after 48 to 72 hours of incubation, by which time 98% of cultures ultimately yielding an organism will be positive (2). It is vital to identify as possible, but unreliable clinical signs and the absence of good diagnostic tests hinder an accurate early diagnosis (3). Initiation of antibiotic therapy before obtaining the diagnostic results is recommended for neonates with clinical signs or epidemiological factors associated with neonatal sepsis (4). These findings are diverse, often subtle, and nonspecific, so empiric therapy may result in treatment of as many as 30 uninfected infants for every 1 who has ultimately determined to have been many attempts to develop screening tests or scoring systems that can identify infected infants at the time of initial assessment, sparing others from invasive diagnostic procedures, intravenous antibiotic therapy, mother-infant separation, and heightened parental anxiety (4). Various laboratory studies have been conducted, but no single test or combination of findings permit withholding treatment from at-risk infants on the basis of negative results or are sufficiently specific to avoid unnecessary treatment of uninfected infants with abnormal results (4). The sensitivity of laboratory methods is limited at the time of presentation, but may substantially improve within 12 to 24 hours (4). Recent reports indicate that serial C- reactive protein levels during this interval may be useful for early identification of infants for whom antibiotic therapy can be safely discontinued (4,5).

C- reactive protein is a good discriminatory marker of bacterial sepsis in newborns (2). The predictive value of CRP improves with time and is most predictive between 24 and 48 hours after presentation with suspected infection (2). Serial measurements are therefore recommended rather than a single value (2, 4, 5).

The purpose of the present study was to determine prospectively whether, in the presence of proved or presumed bacterial infection, the sensitivity of serum CRP response could be enhanced by serial rather than single determinations.

MATERIALS AND METHODS

This prospective study was conducted in the neonatal unit of Ghods Hospital (affiliated with Ghazvin University of Medical Sciences) from March 2005 to March 2006. Subjects included were all babies evaluated and treated for suspected neonatal sepsis within the first 2 months of life. The standard unit protocol for management of infants with suspected sepsis was to obtain a complete blood count including differential white blood cell count and platelets, CRP and a blood culture at presentation, before antibiotic treatment. Other diagnostic studies, including by suprapubic aspirate, and decisions regarding initiation or duration of therapy were at the discretion of the attending neonatalogist. Serum CRP levels were obtained at the initial evaluation and at 24 hours later. The CRP was measured qualitatively (a positive test result indicates a CRP level more than 6 mg/L).

Infants who had received antibiotics prior to sepsis work-up were excluded. Positive blood culture was considered as the "Gold Standard" against which the performance of CRP was compared. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

RESULTS

A total of 100 infants were eligible for inclusion in the 1 to 6 days study. The demographic characteristics of the cases are described in table 1. Of 100 infants 52 were females (52%) and 48 were males (48%). There were 9 cases of proven sepsis and 9 cases of probable sepsis. Organisms were isolated from 9 blood cultures, 9 urine cultures and 2 CSF cultures (Table 2).

The most common causative organisms were *staphylococcus aureus* (5), Coagulase negative Staphylococcus (3) and *Escherichia coli* (1).

Sensitivity, specificity, PPV and NPV of CRP#1 were 55.5%, 82.5%, 24% and 95% respectively. Sensitivity, specificity, PPV and NPV of serial CRP were 67%, 80%, 24% and 96% respectively.

Table 1. Demographic characteristics of study population

	No. (%)
Male	48 (48%)
Female	52 (52%)
Proven sepsis	9 (9%)
Probable sepsis	91 (91%)
Total patients	100 (100%)

Table 2. Bacteriology of positive blood cultures

Organism	No.
Staphylococcus aureus	5
Staphylococcus Epidermidis	3
Escherichia Coli	1
Total Positive Blood Culture	9
Total No. Of Blood Cultures Performed	100

Table 3. Studies evaluating the sensitivity and specificity of CRP in infants

Author(s) and sample	Testing method	Cutoff value	Samples collected	Test and timing	Sensitivity	Specificity	Comments
Russel et al. n= 56 premature and term infants	Quantitative rate nephelometry	>8 mg/L	Serial: daily	CRP	71%	72%	
				I:T Ratio	34%	73%	
Pourcyrous et al. n=187 premature and term infants	Quantitative immuno-nephelometry	>/=9 mg/L	Serial: at least 2 initial and 12 to 24 hours later			91%	
Kawamura et al. n=108 term and n=240 preterm infants with suspected sepsis	Quantitative laser nephelometry	>10 mg/L	Serial: at least 3 levels		Preterm: 61.5%	Preterm: 95%	Infected infants' levels peaked at 48 hours
					Term: 75%	Term: 97.8%	
Franz et al. n=223 preterm infants	Quantitative nephelometry	>/=10 mg/L	Serial: 2 levels initial and 12-60 hours later	CRP and IL-8	93%	100%	
				CRP alone	41%	41%	
Benitz et al. n=1,002 EOS and n=184 LOS preterm and term infants	Qualitative rate nephelometry	>10 mg/L	Serial: 3 levels first level on admission, and the next2 mornings (at least 8 hours apart between level 1 and level 2)	Initial CRP 1 for EOS	35%	90%	
				Initial CRP 1 for LOS	61.5%	92.5%	
				CRP 2 and 3 for EOS	88.9%	97.6%	
				CRP 2 and 3 for LOS	96.4%	71.8%	
Berger et al. n=195 term and preterm infants	Qualitative immunoassay	>20 mg/L	Serial: 3 levels initial level and then every 12-24 hours	CRP	75%	86%	Infected infants' levels peaked 24 positive culture
				I:T Ratio	78%	73%	
Ayazi, Parviz et al. n=100 infants	Qualitative latex agglutination	>6 mg/L	Serial: first level on admission and then 24 hours later		67%	80%	

DISCUSSION

Serum concentrations of CRP increase several hundred-fold in response to bacterial infection, making it an attractive diagnostic test for neonatal sepsis. Since the clinical signs of neonatal sepsis are vague and nonspecific, and there is no single reliable marker of infection available at presentation, all babies with suspected sepsis have to be treated with antibiotics pending blood culture results.

CRP has been used as a marker of infection and predictability of CRP improves with time, so serial measurements rather than a single measurement at presentation, are recommended (2, 5).

Our data indicate that sensitivity is enhanced by serial determination of CRP. Single determination of CRP is inadequate. These results are in accord with those of Pourcyrous (5). Blood culture data indicate increased sensitivity with serial determinations within 24 hours of initiating a work up. From 9 patients with proven sepsis, only one patient had negative CRP and positive blood culture (*staphylococcus epidermidis*). Several explanations have been postulated for the relatively negative response of CRP to this organism. One of the explanations is the low virulence of some etiologic bacteria (5,6).

We believe that in this study most of the positive blood cultures with normal CRP are the result of contamination during collection (5,7).

Of 91 cases of probable sepsis (negative blood culture), CRP was positive in 19 cases.

Therefore, CRP was abnormal in about 21% of cases in this heterogeneous group. However, the relatively high incidence of abnormalities in infants with meconium aspiration is noteworthy. The abnormal CRP response is also attributable to a coexisting pneumonia or to chemical pneumonitis caused by meconium (5). The other reasons for abnormal CRP and negative blood culture are tissue injury (bruising, cephalhematoma) or surgery (5).

Persistently normal CRP in most uninfected cases suggests high specificity (80%). This specificity rate is comparable with that of (91%) the research done by Pourcyrous et al (5). Our data indicate that CRP#1 and serial CRP had sensitivity of 55.5% and 67% respectively, which are a little different from those found by Benitez et al. (CRP#61.5, Serial CRP#96.4) (4).

Han et al. described that sensitivity, specificity, PPV and NPV of serial CRP were 82%, 78%, 15% and 98.9% respectively. But the sensitivity, specificity, PPV and NPV of serial CRP of our research were 55%, 80%, 24% and 90% respectively (8).

Table 3 indicates studies evaluating the sensitivity and specificity of CRP in infants (9). Therefore utilizing serial CRP determination could be a good criterion for detection of most bacterial infections.

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