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Original Article

Use of Serial C-reactive Protein Measurements for Determination of the Length of Empiric Antibiotic Therapy in Suspected Neonatal Sepsis

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Abstract

Background: The management of neonatal sepsis especially in developing countries is problematic. There is no single reliable marker of infection available at the present. C-reactive protein (CRP) has long been used as a marker of infection. Serial measurements of CRP are recommended as a guide for duration of antibiotic therapy.

Objective: To evaluate the serial CRP measurement as a guideline for diagnosis and monitoring therapy and determining the length of antibiotic treatment in suspected neonatal sepsis.

Methods: The present descriptive study involves newborns suspected of having bacterial sepsis. CRP levels were measured initially and at least twice at 24-hr intervals until blood culture results were available. Antibiotic therapy started in neonates with clinical signs and symptoms of suspected sepsis. In neonates with negative blood culture, normal CRP (<6mg/L) was used as a criterion for the length of antibiotic treatment provided that the infants were in good clinical condition. These neonates were followed up for one month after discharge.

Results: Antibiotic therapy was discontinued in 91 patients who had negative blood cultures and two consecutive normal CRP levels. These neonates were followed for one month after discharge. Only one patient was re-admitted with pneumonia 21 days after discharge, giving negative predictive value of 98.9% ($CI_{95\%}$ 96.8%-100%). 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 ($p<0.000$).

Conclusion: 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.

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Keywords • C-reactive protein • Neonatal sepsis • Neonatal Infection • Antibiotic therapy

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Introduction

Neonatal sepsis is a fatal disease. Due to lack of a definitive diagnostic test and unacceptable low sensitivity of blood culture, accurate diagnosis is difficult. Therefore, the clinician ought to treat a number of neonates who do not have the disease. Between 4.4% and 10.5% of all newborns in the United States (about 180,000 to 429,000 neonates annually) receive systemic antibiotics.[1] It is estimated that between 11 and 23 non-infected newborns are taken antibiotics for each documented bacterial infection at intensive care nurseries.[2] The alteration in normal flora, medication errors, antibiotic resistance, intravenous infiltrates, antibiotic resistance, intravenous infiltrates, excessive financial and emotional costs to parents are the risks of unnecessary antibiotic therapy.[3]

Over the last decades, a variety of laboratory tests have been developed to enhance the early and accurate identification and treatment of infants with suspected sepsis. Good evidences exists to support the use of serial CRP measurements to establish or exclude the diagnosis of sepsis in full-term or near-tern infants.[4,5] Further, some authors advocate the use of serial measurement of C-reactive protein (CRP) to monitor therapy and determine the length of antibiotic treatment.[6,7,8]

CRP is a rapid responsive acute phase reactant that rises in response to infectious and non-infectious inflammatory processes. It is synthesized by the liver within 6-8 hours after exposure to an inflammatory stimulus.[9] As infection is the most likely cause of inflammation in the neonates, elevation of CRP has been shown to be a useful marker for sepsis in many studies. Because of its short half-life of 19 hours, CRP level can be expected to fall quickly after efficient elimination of microbial stimulus.[10,11] Thus CRP levels may sufficiently reflect the effects of antibiotics and is a useful marker determining the duration of antibiotic therapy.[12,13,14]

The objectives of this study were to evaluate the usefulness of CRP measurement for identification of bacterial sepsis and to assess its application for early discontinuation of antibiotic therapy in suspected cases of neonatal sepsis.

In this study, we used the results of normal serial CRP as a guide for stopping empiric antibiotic therapy in newborns with suspected bacterial infection provided that they were in good clinical condition.

Patients and Methods

This study was performed on newborns with suspected clinical sepsis admitted to the neonatal care unit of Emam hospital (Urmia, Iran) for antibiotic therapy during a period of sixteen months beginning in February 1999. Informed consent was obtained "in every case" from the parents and the neonates' physicians. Signs and symptoms suggestive of clinical sepsis were unexplained unstable temperature (hypo- and hyperthermia), lethargy, irritability, poor feeding or milk intolerance, vomiting, abdominal distension, bloody stool, respiratory dysfunction evidenced by apnea, tachypnea (>60 breaths/min); cardiovascular dysfunction such as persistent tachycardia (>160 beat/min) or bradicardia (<100 beat/min), poor peripheral circulation, prolonged capillary filling time (>3 s), seizure, sclerema, and biochemical and hematological parameters such as persistent acidosis, unexplained hypo- and hyperglycemia, thrombocytopenia ($<100\times10^9$/l) leukopenia ($<5\times10^9$/l) or leukocytosis (20×10^9/l).

The following patients were excluded: newborns who had undergone mechanical ventilation, had surgical operation, had exchange transfusion, diagnosed with bacterial meningitis, urinary tract infection, pneumonia, those with metabolic aberrations, chromosomal abnormalities and the neonates who had received parenteral antibiotic therapy before admission, patients who had been resuscitated before admission and newborns with birth weight less than 2000 gm.

Clinical and laboratory investigations

At the time of admission, clinical findings were documented. CRP levels were measured initially and at least twice again at 24-h intervals until the results of blood culture (BC) were available. Blood sugar, complete blood count, chest radiograph, culture of spinal fluid and arterial blood gas (ABG) were also assessed when indicated. Antibiotic therapy (ampicillin 100 mg/kg every 6-8 h and gentamicin 2.5 mg/kg every 8 h) was started in neonates with clinical signs and symptoms of suspected sepsis.

CRP measured semi-quantitatively by ENISON lab kits (Tehran). A positive CRP (>6 mg/L) was selected for inclusion of the patients in the study. This cut off value was chosen because it has been shown that CRP of 7 mg/l was more efficient than CRP of 10 mg/l for screening of neonatal sepsis[15] and that the commercial lab kits were more capable of measuring CRP levels of 6, 12, and 24 up to 192mg/l. CRP determination and clinical evaluation were repeated daily until BC results

were obtained.

According to the results of BC, the neonates with positive BC (either with normal or positive CRP) were treated with routine antibacterial agents.[16] Antibiotic therapy was discontinued as soon as the two consecutive CRP levels returned to normal.

In neonates with negative blood culture, serial negative CRP values (<6mg/l) were used as the decision-making criterion for the length of antibiotic treatment provided that the infants were in good clinical condition.

Follow-up

Upon discharge from hospital, the parents of all neonates with negative blood culture were given an information sheet containing important clinical signs and symptoms of neonatal bacterial infection and also warned not to bring the infant to the hospital in the case of disease recurrence.

Information about recurrent bacterial infections and the need for further antibiotic treatment were obtained by weekly visits of patients or through telephone, for one month after discharge from the hospital, if necessary.

Statistical Analysis

For comparison of the result of this study with respect to reducing the length of antibiotic therapy, we calculated the mean duration of antibiotic treatment of 100 neonates admitted and treated for suspected bacterial sepsis with negative BC before conducting this study. The patients were selected randomly with the same inclusion and exclusion criteria based on their medical records.

Results

During 16 months of the study, the entry criteria were met by 110 patients (42 males and 68 females). Thirteen patients had positive and 97 negative BC. Of newborns suspected of neonatal sepsis with negative BC, 6 had positive CRP. The CRP results were negative in 91 patients with negative BC. The mean age of the patients was 4.9±7.8 days.

Gram-negative rods were isolated from blood of 13 neonates with positive CRP. In neonates with negative blood culture, CRP levels were positive in 6 (6.2%), and negative in 91 (93.8%) patients. The mean duration of antibiotic therapy was 3.3±1.0 days in the study group, but that for the neonates with suspected bacterial sepsis treated prior to conducting this study was 5.9±1.7 days ($p<0.000$). Only one patient with negative BC and normal CRP was re-admitted with pneumonia after 21 days of discharge. The history of this patient along with clinical examination revealed that his recent problem was, most probably, not related to the first admission, but even by inclusion of this case, the negative predictive value of CRP for stopping antibiotic therapy was 98.9% ($CI_{95\%}$: 96.8%- 100.0%).

Discussion

Neonatal sepsis with its high mortality rate still remains a diagnostic and treatment challenge for neonatal health care providers. Developing countries have both the highest incidence and mortality rates.[17]

Rapid and correct diagnosis and treatment of neonatal bacterial infection is an important priority. Isolation of microorganism(s) in one or more blood cultures is the gold standard of diagnosis for neonatal sepsis, although it has some limitations. It may take 1 to 2 days to obtain culture results.[18,19] Intrapartum antibiotic exposure of mothers may interfere with blood culture sensitivity.[10] The most important criteria of a reliable test, are its high sensitivity combined with a high negative predictive value. No single test is 100% reliable, but compared to other tests, serum CRP measurement proved most useful. CRP is a highly sensitive acute phase protein, with levels rising as much as 1000-fold during acute inflammatory processes. Inflammation caused by infection or tissue damage stimulates the circulating inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF)-α. These cytokines stimulate hepatocytes to increase the synthesis and release of positive acute phase proteins, including CRP. IL-6 is the major cytokine which stimulates CRP production. CRP levels begin to rise within 4 to 6 hrs after the onset of signs of infection or tissue injury and peak 24 to 48 hrs thereafter. They rapidly disappear as the infection or inflammatory process resolves.[20-22] Key functions of CRP within the innate immune system include the ability to 1) recognize and bind to phosphocholine exposed in damaged cell walls which is found in many bacteria, fungi, and parasitic infections; 2) act as an opsonin, marking bacteria, damaged cell walls, and nuclear debris for phagocytosis; 3) bind to C1, the first component of the classical pathway of the complement that triggers phagocytic activity; and 4) bind to polymorphonuclear leukocytes and monocytes , stimulating the production of inflammatory cytokines.[23]

In this study, CRP was used for diagnosis of neonatal sepsis with high negative predictive value of 98.9%. These findings, establishes that the serial measurements of CRP is a key decision parameter for guiding the duration of

antibiotic therapy.

Ehl et al., in a prospective study, evaluated the role of CRP measurement as a means of guiding the duration of antibiotic therapy.[6] Negative CRP correctly identified 120 of 121 infants without further need for antibiotic therapy. This corresponds to a negative predictive value for CRP of 99%. The mean duration of treatment was 3.3±1 days in the CRP guided group and 5.9±1.7 days in the study group.

In another study, 101 episodes of suspected clinical sepsis were investigated in 68 very low birth weight infants. The concomitant use of CRP and IL-6 allowed anti-microbial treatment to be discontinued at 48 h without waiting for microbiological results, provided that the infants were in good clinical condition.[24]

Franz et al. described that combination of positive IL-8 and/or CRP >10 mg/l in neonates with suspected bacterial infection is feasible (with 96% sensitivity) and cost effective in reducing antibiotic therapy.[7] Philip and Mills used CRP determination for minimizing the length of antibiotic exposure in neonatal sepsis and the mean duration of treatment in their study was 3.1 days.[25] Pourcyrous et al. suggested that it would be appropriate to discontinue antibiotic therapy if three serial CRP measurements were normal.[9]

In a study conducted at Johannesburg hospital, 100 infants with negative serial CRP values (≤10 mg/l) were evaluated for suspected sepsis in the first 24 h of life. Repeated CRP measurements were performed between 24 and 48 h after birth and it was found that 99% of neonates did not need further antibiotic therapy with negative predictive value of 99%.[8]

Some authors carried further and used normal serial CRP to discriminate between false positive and true positive blood cultures. They discontinued antibiotic therapy in asymptomatic infants with normal serial CRP, even in those with positive blood cultures.[26] Other studies showed that serial measurements of CRP were useful for diagnosis and monitoring the effectiveness of treatment of neonatal sepsis.[27,28,29]

Our study had the following limitations that needed consideration: 1) the laboratory method used to measure CRP levels was semi-quantitative. This method of testing CRP levels was less expensive than quantitative method and is therefore, suitable for developing countries although it is not as sensitive as quantitative methods. 2) the CRP level of 6 mg/l was the cutoff point for discontinuing antibiotic treatment. This level was lower than the traditional levels of 10 mg/l which was the criterion for selection of patients in most studies, but in our study it proved to be more sensitive. 3) we excluded infants with birth weights of < 2000 gm, because according to some reports regarding preterm population, CRP levels did not always rise in overwhelming sepsis.[8,30]

The analysis of our study showed that serial determination of CRP in suspected neonatal sepsis had a good predictive value for BC results and provided a reliable guideline for stopping unnecessary antibacterial therapy.

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