C-reactive protein: a useful marker for guiding duration of antibiotic therapy in suspected neonatal septicaemia?

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هل يُعَدُّ البروتين المتفاعل – C واسماً للدلالة على مدة المعالجة بالمضادات الحيوية في إنتان الدم المشتبه به لدى الولدان؟

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الخلاصة: هدف الباحث من دراسته إلى التعرُّف على مدى إمكانية استخدام مستويات البروتين المتفاعل – C CRP)) لتحديد متى يمكن إيقاف المضاد الحيوي بأمان في حالات الاشتباه بإنتان الدم لدى الولدان الذين يعالجون في مستشفى مدينة الرمادي في العراق. فأجريَ لهم عام 2005 اختبار البروتين المتفاعل – C وزرع للدم (وهو المعيار الذهبي للتشخيص) عند قبولهم وبعد مرور 48 ساعة ثم بعد مرور أربعة أيام ثم ستة أيام من البدء بالمعالجة. ومن بين الولدان الخمسة والخمسين الذين شملتهم الدراسة، كان مستوى البروتين المتفاعل – C يقل عن 6 مغ/ ل لدى 37 منهم (67.3٪) في الساعة الثامنة والأربعين، وأمكن إيقاف المضاد الحيوي لدى 32 منهم (82.5٪) عندما أصبح زرع الدم لديهم سلبياً. وتدل الحساسية المعتدلة (78٪) والقيمة التنبؤية السالبة (86٪) للبروتين المتفاعل – C في هذه الدراسة، على أن الاختبار لا يمكن أن يستخدم وحده دليلاً على مدة معالجة إنتان الولدان بالمضادات الحيوية.

ABSTRACT The study aimed to determine whether serum C-reactive protein (CRP) levels can be used to identify when antibiotics can safely be discontinued in cases of suspected neonatal septicaemia. Neonates with suspected neonatal septicaemia treated at a hospital in Al Ramadi city, Iraq, in 2005 had serum CRP and blood cultures (the gold standard) done at admission and at 48 hours, 4 days and 6 days after starting treatment. Of the 55 neonates, CRP was ≤ 6 mg/L at 48 hours in 37 (67.3%) and antibiotics could be stopped in 32 (82.5%), i.e. when blood culture was negative. The moderate sensitivity (78%) and negative predictive value (86%) of serum CRP in this study suggest that this test alone cannot be used for guiding duration of antibiotic treatment for neonatal sepsis.

La protéine C réactive est-elle un marqueur utile pour décider de la durée du traitement antibiotique administré aux cas suspects de septicémie néonatale ?

RÉSUMÉ Cette étude visait à déterminer si les niveaux de protéine C réactive (PCR) sérique peuvent être utilisés pour déterminer quand le traitement antibiotique peut être arrêté sans danger dans les cas suspects de septicémie néonatale. Les nouveau-nés présentant une suspicion de septicémie néonatale traités dans un hôpital de la ville d'Al Ramadi (Iraq) en 2005 ont fait l'objet d'un dosage de la PCR sérique et d'hémocultures (méthode de référence) lors de l'admission puis 48 heures, 4 jours et enfin 6 jours après le début du traitement. Sur les 55 nouveau-nés, 37 (67,3 %) avaient une PCR ≤ 6 mg/L à 48 heures et les antibiotiques ont pu être arrêtés chez 32 d'entre eux (82,5 %) lorsque l'hémoculture a été négative. La sensibilité limitée (78 %) et la valeur prédictive négative (86 %) de la PCR sérique dans cette étude semblent indiquer que ce test ne peut pas être utilisé seul pour déterminer la durée du traitement antibiotique des septicémies néonatales.

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Introduction

Infection is one of the major problems in neonates. It is estimated that infection contributes to approximately 30%–40% of the deaths of the 5 million neonates who die every year in low-income countries [*1,2*].

The diagnosis of neonatal septicaemia is difficult to establish based on the clinical criteria alone because of its subtle, variable and non-specific signs and symptoms. The use of safe and effective antimicrobial drugs has significantly contributed to the decrease in neonatal mortality [*3*]. However, the fear of missing a case of neonatal septicaemia, with its serious outcome, had led to overuse of antibiotics in this age group. Some studies reveal that empirical therapy results in treatment of as many as 30 uninfected infants for every 1 who is ultimately determined to have been infected [*4–6*]. For this reason, there have been many attempts to develop screening tests to identify infected neonates and guide the duration of treatment.

C-reactive protein (CRP), an acute-phase reactant, is synthesized in the liver in response to inflammatory cytokines and may rise more than 1000 times during an acute-phase response. It falls quickly after efficient elimination of the microbial stimulus due to its short half-life of 19 hours [*7,8*]. In addition to infections, CRP has been shown to be elevated in non-infectious conditions in neonates including meconium aspiration, respiratory distress syndrome, fetal hypoxia and intraventricular haemorrhage [*9*].

Different cut-off values for raised CRP have been suggested by various studies using varying protocols [*10*]. Although several studies confirm that CRP level is useful in the early diagnosis of sepsis, there are reports to the contrary [*11–14*]. Some studies suggest serial rather than a single determination of CRP level may be more useful in the diagnosis of sepsis [*7*]. Furthermore, normalization of CRP levels has previously been proposed as a possible criterion for the discontinuation of antibiotic therapy [*15–19*].

The aim of the present study in Ramadi city, Iraq, was to determine whether C-reactive protein can be used as a guide in deciding the duration of treatment in neonates with suspected neonatal sepsis.

Methods

This prospective observational study was carried out over an 8-month period from 1 April 2005 to 1 December 2005 at the neonatal care unit of the maternity and children's hospital in Ramadi city, Iraq. A total of 55 neonates up to 4 weeks of age with birth weight > 1500 g and suspected septicaemia were enrolled in the study.

Septicaemia was assessed with a sepsis score which included the following signs and symptoms: refusal to feed, lethargy, poor cry, diarrhoea, vomiting, fever, excessive crying, jaundice, pyoderma, hypothermia, cyanosis, abdominal distention, seizures, conjunctivitis, vomiting, fever, apnoea, tachypnoea, and poor capillary refill. If the infant had 3 or more of the above signs or symptoms, septicaemia was suspected [*20*]. Neonates with a diagnosis of meningitis were excluded from the study because they require a longer duration of treatment. Also neonates who had congenital malformation, birth asphyxia, respiratory distress syndrome or meconium aspiration were excluded.

Serum CRP levels were determined and blood culture and antibiotic sensitivity tests were done in all cases, along with other investigations when indicated clinically, e.g. white blood cell count and differential, lumbar puncture and chest X-ray. The gold

standard for diagnosis of neonatal sepsis was the blood culture.

CRP values were estimated qualitatively by the latex agglutination method (kit manufactured by Atlas, UK). Blood samples of 1–2 mL for CRP were taken from the neonate from a peripheral vein under aseptic technique and collected in a disposable tube, and 1–2 mL for blood culture and sensitivity were taken and inoculated into blood culture medium and sent directly to the laboratory where they were processed under the supervision of an expert microbiologist.

The culture medium brain–heart infusion broth (Mast Diagnostics DM 106, UK) was used for primary isolation of the organisms by adding 1:10 (v/v) blood to the media according to the recommendation of the World Health Organization [*21*]. MacConkey agar, Salmonella–Shigella agar and blood agar (Mast Diagnostics DM 100, UK) were used for subcultures. The blood culture bottle and the inoculated plates were incubated at 37 ºC.

Serial analysis was done for CRP and values > 6 mg/L were taken as abnormal. Serum CRP was estimated at admission and again 48 hours, 4 days, and 6 days after starting treatment. If CRP at 48 hours was ≤ 6 mg/L (group 1) and the patient was clinically stable, the antibiotics were stopped and the patient was observed for 48 hours at the hospital and was discharged if blood culture was negative. Those neonates with CRP > 6 mg/L at 48 hours were labelled as group 2. Neonates in this group had their CRP estimates made at 4 and 6 days. Those with negative CRP at 4 days were labelled as group 2a and those who continued to have positive CRP at 6 days were labelled as group 2b. Antibiotics were stopped when CRP returned to normal. All neonates were observed for 48 hours in the hospital and followed for 4 weeks when possible, by appointment or by telephone. CRP estimation was not done after 6 days.

Sensitivity and negative predictive value of CRP estimation were calculated.

Results

Out of 55 neonates admitted to the neonatal care unit with suspicion of septicaemia, 14 weighed between 1500 and 2000 g, 7 were 2001–2499 g and 34 were > 2500 g. Table 1 shows the demographic data of the study sample.

Table 2 shows the presenting symptoms and signs. Refusal to feed (72.7%), lethargy (65.4%) and poor cry (50.9%) were the main presenting features, followed by tachypnoea (30.9%), fever (29.0%) and jaundice (29.0%).

Blood culture was positive in 21 (38.2%) neonates, out of which 11 (52.3%) were Gram-positive and 10 (47.6%) were Gram-negative. All 11 (100.0%) isolated Gram-positive cases were *Staphylococcus aureus*, while among the Gram-negative cases, *E. coli* was found in 5 (50%), *Klebsiella pneumoniae* in 4 (40%) and *Pseudomonas aeroginosa* in 1 (10%). CRP was positive in 27 patients (49.1%) at admission; 18 of whom remained positive at 48 hours.

Table 3 shows the duration of treatment and blood culture findings in relation to CRP values. Of the 55 neonates with suspected neonatal septicaemia, CRP was ≤ 6 mg/L at 48 hours in 37 cases (67.3%); 5 of these showed positive blood culture and therefore antibiotics could be stopped in 32 patients, giving a sensitivity rate of 78% and negative predictive value of 86%. In the remaining 18 neonates, CRP on the 4th day was ≤ 6 mg/L in 15 patients (group 2a); 13 of these had positive blood culture so antibiotics could be stopped in only 2 patients. On the 6th day 3 patients continued

Table 1 **Demographic data of neonates with suspected neonatal septicaemia (*n* = 55)**

Characteristic	No.	%
Sex		
Male	44	80.0
Female	11	20.0
Gestational age		
Preterm	11	20.0
Term	44	80.0
Residence		
Rural	38	69.1
Urban	17	30.9
Onset of sepsis		
Early onset	30	54.5
Late onset	25	45.5
Feeding		
Breast	21	38.2
Bottle	23	41.8
Mixed	11	20.0

to have elevated CRP; all of them had positive blood culture.

Of the 55 patients, we were able to follow up 34 for 4 weeks. Relapse occurred in only 1 patient in group 2a.

Discussion

The present study was designed to evaluate the usefulness of serum CRP levels as a screening test in guiding the duration of treatment in suspected neonatal septicaemia. A screening test should ideally detect all infected cases (high sensitivity) with a high negative predictive value so that disease can be easily excluded [*22*].

The incidence of positive blood culture in the present study was 38.2% which is similar to the results of other studies [*7,23,24*]. The pattern of bacterial isolates is similar to that observed in Ramadi city a few years ago by Al-Zwaini [*25*]. Furthermore, it is similar to that observed in other developing countries, such as Saudi Arabia [*26,27*] and Nigeria [*28*]. The failure of detection of group B streptococci in this study is in line with the low incidence reported by the author and with reports from many developing countries [*25,29–33*]. Differences in vaginal colonization between women in industrialized and developing countries are probably the reason for this difference. This suggestion needs to be confirmed by future studies.

The most common symptoms presented were refusal to feed in 72.7% of neonates, followed by lethargy and poor cry, which is similar to the observation of Jaswal et al. [*7*] and Guha et al. [*34*]. Hypothermia was not a prominent feature in the present study (noted in 12.7% of neonates), and fever was more common (in 29.0%), perhaps related

Table 2 **Distribution of clinical signs and symptoms in neonates with suspected neonatal septicaemia (*n* = 55)**

Symptoms and signs	No. of neonates	%
Symptoms		
Refusal to feed	40	72.7
Lethargy	36	65.4
Poor cry	28	50.9
Fever	16	29.0
Vomiting	13	23.6
Diarrhoea	7	12.7
Excessive cry	6	10.9
Signs		
Tachypnoea	17	30.9
Jaundice	16	29.0
Cyanosis	15	27.2
Vomiting	12	21.8
Seizures	10	18.0
Poor capillary refill	6	10.9
Hypothermia	7	12.7
Abdominal distention	5	9.0
Pyoderma	1	1.8
Conjunctivitis	1	1.8

Table 3 **Duration of treatment and blood culture findings of 55 neonates with suspected neonatal septicaemia in relation to C-reactive protein (CRP) values to guide antibiotic treatment [*14*]**

Group	No. of neonates	CRP value at 48 hours (mg/L)	Duration of treatment (days)	No. with positive blood culture
Group 1 (*n* = 37)	32	≤ 6	2	0
	5	> 6	> 2	5
Group 2a (*n* = 15)	2	> 6	4	0
	13	> 6	> 4	13
Group 2b (*n* = 3)	3	> 6	> 6	3

n = total number of neonates.

to the hot climate of this region at time of the study.

Several previous studies have suggested the normalization of CRP as a possible guide for discontinuation of antibiotic therapy [*15–19*]. A study by Jaswal et al. revealed a 100% negative predictive value with no relapse following discontinuation of treatment after normalization of CRP levels [*7*]. Furthermore, Squire et al. were able to stop antibiotics in 65.5% of cases within 72 hours and could reduce the duration of treatment by 20% in suspected neonatal septicaemia [*17*].

Contrary to these results, our study reveals CRP to be a poor guide for the duration of treatment in neonatal septicaemia, with modest sensitivity and negative predictive value (78% and 86% respectively) at 48 hours following initiation of antibiotics. Additionally, the relapse seen in 1 case in this study makes it hard to accept that CRP alone is a safe guide for deciding how long to treat neonates with suspected neonatal sepsis. A similar conclusion was drawn by Ehl et al., despite a high negative predictive value [*3*].

CRP in this study was measured qualitatively by the latex agglutination test, which is simple to perform and easy to interpret but is non-specific and must be correlated with other laboratory data and clinical findings. Quantitative techniques are comparatively less non-specific but time-consuming [*35*]. Furthermore, a variety of non-infective disorders can give positive results. These factors probably explain the current results. From the results of this study it can be concluded that serum CRP values had modest sensitivity and negative predictive value in neonatal sepsis and hence serial serum CRP values alone cannot be used as a parameter for guiding the duration of antibiotic treatment in a group of newborns with suspected neonatal septicaemia. This highlights the importance of correlating the clinical and laboratory data, using tests that are easy to perform, have a high predictive value and that identify all infected infants (high sensitivity). Blood culture remains the gold standard for diagnosing and treating neonatal septicaemia.

The main limitation of this study was the small number of patients and the lack of a control group. Therefore, further study using a quantitative method for measuring CRP and a larger multicentre sample would be of value.

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