Prognostic value of C-reactive protein in neonatal sepsis

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(Ann Coll Med Mosul 2013; 39 (2): 136-142).
Received: 18th Feb. 2013; Accepted: 29th Sept. 2013.

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. Empirical treatment should not be delayed because of the high mortality. Blood cultures are considered the gold standard for diagnosis of neonatal sepsis. C-reactive protein (CRP) is an acute phase protein found in the blood, the levels of which rise in response to inflammation. During the acute phase response, levels of CRP rapidly increase within 2 hours of acute insult, reaching a peak at 48 hours.

Objective: To investigate the diagnostic value of CRP. To show the benefit of doing serial measurement of CRP in neonatal sepsis in providing additional support for the observation and follow up of patient with sepsis. To show the prognostic meaningful of CRP in neonatal sepsis.

Methods: A hospital-based cross sectional study design was conducted in Mosul over one year period from the 1st of Nov. 2010 to the 30th of Oct. 2011. A total of 198 neonates aged 1-28 days who were admitted to pediatrics wards in Al-Khansaa Teaching Hospital in Mosul during the study period under provisional diagnosis of sepsis and had a positive C-reactive protein level >6 mg/l were included in the study. All patients were sent for blood culture, and the final diagnosis of sepsis depended on the result of blood culture.

Results: Male gender constituted 63.5% of patients with sepsis compared to 51% patients without sepsis. Refusal to feed and tachypnea were the most frequent complaints in both groups (sepsis and no sepsis). All patients at admission had high CRP while only 52% had culture-proven sepsis. After 72 hrs of admission, CRP was still high in approximately half of the patients after receiving treatment but only 62% of them had positive blood culture. Higher initial CRP titer constituted 40.4% of the sepsis group compared to only 23.4% of no sepsis group, the difference was significant (p=0.009). CRP levels between 6 mg/L and 12 mg/L were more frequently observed among no sepsis than in sepsis groups (14.4% and 37.2% respectively). In patients with CRP ≥40 mg/L, CRP was significantly higher in patients with blood culture positive than in patients with suspected sepsis but negative blood culture, and after 72 hours of treatment high levels of CRP still constituted 60.6% of cases with proven sepsis compared to 46% among the suspected sepsis group but with negative blood culture. Death rate was 5% and E. coli was the predominant micro-organism isolated.

Conclusion: Gram-negative micro-organisms are a predominant cause of neonatal sepsis in our community. Predictive value of CRP could be enhanced by serial rather than a single measurement. A high cut off value of CRP may be needed to diagnose neonatal sepsis.

Keywords: Neonatal sepsis, CRP, blood culture.

أهمية بروتين سي التفاعلي في دراسة عقابيل الخمج لدى الأطفال الحديثي الولادة

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الخلاصة

يعتبر خمج الدم من أهم المشاكل التي قد يعاني منها الطفل حديث الولادة والتي تستوجب تشخيصا مبكرا وعلاجا سريعا حتى قبل ظهور نتائج الفحوصات، والتي تعتمد غالبا على زراعة الدم. ومن المعروف أن نتيجة فحص الدم تحتاج الى عدة أيام للحصول

عليها، لذلك أصبح من الضروري إيجاد بدائل مخبرية مساعدة سريعة تمكن الأطباء من تشخيص خمج الدم وعلاجه بسرعة. أجريت عدة دراسات لبحث جدوى الإستعانة ببروتين سي التفاعلي للمساعدة في تشخيص خمج الدم، حيث أن نسبته في الدم ترتفع بسرعة خلال ساعتين من الإلتهاب وتصل ذروتها خلال ٤٨ ساعة.

أهداف البحث: يهدف البحث للتحقق من القيمة التشخيصية لبروتين سي التفاعلي، ولمعرفة فائدة القياس التسلسلي له في تشخيص خمج الدم ولتقييم فائدته في متابعة تطور خمج الدم عند حديثي الولادة.

طريقة البحث: دراسة مقطعية أجريت في مستشفى الخنساء التعليمي للأطفال في الموصل، لمدة عام كامل إبتداء من تشرين الثاني ٢٠١٠. تم إختيار ١٩٨ طفلا من كلا الجنسين تراوحت أعمارهم بين ١-٢٨ يوما، أدخلوا المستشفى للإشتباه بإصابتهم بأعراض خمج الدم والذين كانت نسبة بروتين سي التفاعلي لديهم > ٦ ملغم/لتر. وتم سحب عينات الدم من جميع المرضى وإرسالها للمختبر لغرض زراعة الدم، وتم الإعتماد على نتيجة الزراعة لغرض التشخيص النهائي للإصابة بخمج الدم.

النتائج: كانت نسبة الأطفال الذكور المصابين بخمج الدم ٦٣,٥% مقارنة ب ٥١% من الإناث. قلة الرضاعة وزيادة سرعة التنفس كانتا أكثر الأعراض شيوعا عند الأطفال مدار البحث. وكانت نسبة بروتين سي التفاعلي مرتفعة عند جميع المرضى عند دخول المستشفى، لكن ٥٢% منهم فقط كانت لديهم زراعة دم موجبة. لوحظ أن نسبة بروتين سي التفاعلي بقيت مرتفعة عند نصف المرضى تقريبا بعد ٧٢ ساعة من بدء العلاج، كما أن نسبة إيجابية زراعة الدم لديهم إرتفعت الى ٦٢% . لوحظ أن نسبة بروتين سي التفاعلي في المجموعة بين (٦-١٢ ملغم/لتر) كانت أكثر عند المرضى الذين لديهم زراعة دم سالبة. كما لوحظ وجود علاقة معنوية عالية بين المرضى الذين تتجاوز قيمة بروتين سي التفاعلي لديهم ٤٨ ملغم /لتر وبين إيجابية فحص زراعة الدم قبل بدء العلاج، وإستمرت هذه النسبة عالية حتى بعد ٧٢ ساعة من بدء العلاج. لم تتجاوز نسبة الوفاة للمرضى المشاركين في البحث ٥%، وكانت جرثومة اى كولاي هي السائدة كمسبب لخمج الدم.

الإستنتاجات: إن الإصابة بخمج الدم المسببة بالجراثيم (ذات صبغة غرام السالبة) مازالت تشكل مشكلة كبيرة للأطفال حديثي الولادة. وإن القيمة التنبؤية لبروتين سي التفاعلي ترتفع عند إجراء قياسات متتابعة له. نحتاج الى قيم عالية لبروتين سي التفاعلي لغرض تشخيص الإصابة بخمج الدم.

INTRODUCTION

C-reactive protein (CRP) is an acute phase protein found in the blood, the levels of which rise in response to inflammation. Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the C1q complex.[1] It is discovered by Tillett and Francis in 1930.[2] It was initially thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer.[3] However, discovery of hepatic synthesis demonstrated that it is a native protein.[4-6] It was so named because it was first discovered as a substance in the serum of patients with acute inflammation that reacted with the C- (capsular) polysaccharide of pneumococcus.[6] It is synthesized by the liver in response to factors released by macrophages and fat cells.[4–6] It is released in response to a wide range of acute and chronic inflammatory conditions like bacterial, viral, or fungal infections[7] which cause release of interleukin-6 and other cytokines that trigger the synthesis of CRP and fibrinogen by the liver. CRP is a more sensitive and accurate reflection of the acute phase response than the ESR. In the first 24 hrs, ESR may be normal but CRP is elevated. Also CRP returns to normal more quickly than ESR in response to therapy.[7-9]

Normal serum CRP concentration in healthy human is usually lower than 6 mg/L, slightly increasing with aging.[9,10]

Sepsis remains one of the most common diseases of the neonatal period and is still a significant cause of mortality and morbidity.[11] Neonatal sepsis generally exhibits an insidious onset, with signs and symptoms in the majority of patients are highly nonspecific such as grunting, poor feeding, pallor, apnea, lethargy, irritability, hypothermia, and abnormal cry. There may be nonspecific clinical signs; tachypnea >60/min, nasal flaring, retraction, cyanosis, respiratory distress, bradycardia (<100/min), tachycardia (>180/min), hypotonia, seizures, poor skin color, and capillary refilling time longer than two seconds.[11,12]

Blood culture is considered the gold standard for diagnosis of neonatal sepsis. Nevertheless, its positivity varies widely (50% to 87%) and the

results are not available rapidly for use in defining therapeutic management. For this reason, neonatologist tries to find an alternative, faster laboratory tests for diagnosis of neonatal sepsis.[13] The tests used include the white blood cell count (WBC) and assays for markers of inflammatory reaction in serum, such as, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and procalcitonin.[13,14] Unfortunately, despite the availability of effective antibiotics, early diagnosis represents a major challenge because of the non-specific nature of signs and symptoms[15-18] and non-availability of standard microbial culture results in the first 48 hrs.[19]

Aim of the study

1) To investigate the diagnostic value of CRP.
2) To show the benefit of doing serial measurements of CRP in neonatal sepsis in providing additional support for the observation and follow up of patient with sepsis.
3) To show the prognostic meaningful of CRP in neonatal sepsis.

PATIENTS AND METHODS

The present study was conducted in Mosul over one year period from the 1st of Nov. 2010 to the 30th of Oct. 2011. A hospital-based cross sectional study design was adopted in order to achieve the objectives of the study.

It was decided to include all neonates who were admitted to pediatrics wards in Al-Khansaa teaching Hospital in Mosul during the study period under provisional diagnosis of sepsis and have a positive C-reactive protein level (CRP).

A positive CRP is a level equal or more than 6 mg/L.[9] A total of 198 neonates aged 1-28 days were included in the study, the mothers were interviewed and a questionnaire form was filled for each patient which contained information regarding age, sex, and presenting symptoms. The neonates were examined by one of the authors; the elicited sings were also recorded in the questionnaire form. An initial CRP level was recorded and followed by recording of another level after 72 hours. Any neonate with initial CRP level below 6 mg/L was excluded. All patients were sent for blood culture, and the final diagnosis of sepsis depended on the result of blood culture.

Analysis of the data was conducted by using SPSS, Minitab, and excel computer systems, X2 test and Z test of two proportions were used to conduct the statistical analysis.

RESULTS

Table 1 shows the demographic characteristics of study population, it was clear from the table that more than one third of the study population were in the first week of life in both sepsis and no sepsis groups (53.9% and 42.6% respectively), on the other hand only 3.8% of patients who have sepsis were in their fourth week of life compared to 11.7% of patient who have no sepsis.

Male gender constituted 63.5% of patients with sepsis compared to 51% in no sepsis group. Weight of equal to 2.5 Kg or more constituted about one third of the study population in both groups.

Table 2 shows the main presenting symptoms among the study population. It is clear from the table that refusal to feed was a complaint in more than 90% of both groups (sepsis and no sepsis). Lethargy was less frequent among cases with sepsis (82.7%) compared to 95.5% of cases without sepsis, the difference was statistically significant. Seizure was reported in 12.5% of cases with sepsis compared to only 4.3% of no sepsis group, the difference was significant (p=0.039). No significant difference between the two groups was observed regarding other symptoms.

Table1. Demographic characteristics of study population, Mosul 2012.

Characteristic	Final diagnosis according to blood culture			
Age (Days)	Neonatal Sepsis		No Neonatal Sepsis	
	No.	%	No.	%
1-7	56	53.9	40	42.6
8-14	26	25.0	18	19.1
15-21	18	17.3	25	26.6
22-28	04	03.8	11	11.7
Total	104	100	94	100
Gender				
Male	66	63.5	48	51.0
Female	38	36.5	46	49.0
Total	104	100	94	100
Weight				
≥ 2.5 Kg	35	33.7	31	33.0
< 2.5 Kg	69	66.3	63	67.0
Total	104	100	94	100

Table 2. Presenting symptoms among study population, Mosul 2012.

Presenting symptom	Final diagnosis according to blood culture				P value
	Neonatal Sepsis		No Neonatal Sepsis		
	No.	%	No.	%	
Refusal to feed	95	91.3	85	90.4	0.822 (NS)
Lethargy	86	82.7	90	95.5	0.004 (S)
Yellow discoloration of skin and sclera	15	14.4	23	24.5	0.07 (NS)
Vomiting	15	14.4	19	20.2	0.281 (NS)
Poor crying	37	35.6	43	45.7	0.145 (NS)
Seizure	13	12.5	4	4.3	0.039 (S)
Abdominal distention	2	1.9	7	7.4	0.062 (NS)
Apnea	13	12.5	10	10.6	0.638 (NS)
Diarrhea	2	1.9	5	5.3	0.196 (NS)

Chi squared test was used.

Table 3 shows the presenting signs among the study population. Tachypnea was the most frequent sign in both groups (37.5% and 44.6% respectively). Fever was observed in about 10% of both groups. No statistical differences have been observed between the two groups regarding any sign.

It was evident that the high initial level of CRP constituted 40.4% of the sepsis group compared to only 23.4% of no sepsis group, the difference was significant (p=0.009). On the other hand CRP levels between 6 mg/L and 12 mg/L was more frequently observed among no sepsis group (37.2%) compared to sepsis group (14.4%) (P=0.000), (**Table 4**).

Table 5 shows the CRP levels after 72 hours of admission, again the high levels of CRP (group 4) constituted 60.6% of cases with sepsis compared to 46% among the no sepsis group, the difference was not significant.

Figure 1 shows the main microorganisms that are discovered by culture among cases with sepsis. E. coli was the most common microorganism isolated (33.7%) followed by Klebsiella (26.9%). Proteus was isolated in one case only.

Table 6 shows that ten patients died (seven cases from sepsis group and three among no sepsis group). Forty percent mortality was among the group with initial CRP≥48 mg/L compared to 30% among groups with initial CRP≥ 24 mg/L<48 mg/L and ≥ 12 mg/L<24 mg/L respectively.

Table 3. Elicited signs among study population, Mosul 2012.

Elicited sign	Final diagnosis according to blood culture				P value
	Neonatal Sepsis		No Neonatal Sepsis		
	No.	%	No.	%	
Tachypnea	39	37.5	42	44.6	0.305 (NS)
Hypothermia	11	10.6	14	14.9	1.34 (NS)
Fever	10	9.6	10	10.6	0.811 (NS)
Umbilical discharge	2	1.9	3	3.2	0.570 (NS)
Tachycardia	5	4.8	2	2.1	0.308 (NS)
Bradycardia	2	1.9	0	0	***
Poor capillary refilling	5	4.8	2	2.1	0.302 (NS)

Chi squared test was used.

Table 4. Distribution of study population according to initial CRP titer, Mosul 2012.

C -reactive protein level	Neonatal Sepsis		No Neonatal Sepsis		P value
	No.	%	No.	%	
Group1 CRP≥6mg/L<12mg/L	15	14.4	35	37.2	0.000 (S)
Group2 CRP≥12mg/L<24mg/L	25	24	28	29.8	0.362 (NS)
Group3 CRP≥24mg/L<48mg/L	22	21.2	9	9.6	0.020 (S)
Group4 CRP≥ 48mg/L	42	40.4	22	23.4	0.009 (S)
Total	104	100	94	100	

Z two proportions test was used.

Table 5. Distribution of study population according to 72 hours CRP titer, Mosul 2012.

Positive C reactive protein level after 72 hours	Neonatal Sepsis		No Neonatal Sepsis		P value
	No.	%	No.	%	
Group1 CRP≥ 6mg/L<12mg/L	0	0	3	8.1	****
Group2 CRP≥12mg/L<24mg/L	9	14.8	11	29.7	0.088 (NS)
Group3 CRP≥24mg/L<48mg/L	15	24.6	6	16.2	0.367 (NS)
Group4 CRP≥ 48mg/L	37	60.6	17	46.0	0.154 (NS)
Total	61	100	37	100	

Z two proportions test was used.

Table 6. Distribution of mortality among study population according to initial CRP titer, Mosul 2012.

C- reactive protein level	Mortality among study population					
	Neonatal Sepsis		No Neonatal Sepsis		Total	
	No.	%	No.	%	No.	%
Group 1 CRP≥6mg/L<12mg/L	0	0	0	0	0	0
Group 2 CRP≥12mg/L<24mg/L	2	28.6	1	33.33	3	30
Group 3 CRP≥24mg/L<48mg/L	2	28.6	1	33.33	3	30
Group 4 CRP≥ 48mg/L	3	42.8	1	33.33	4	40
Total	7	100	3	100	10	100

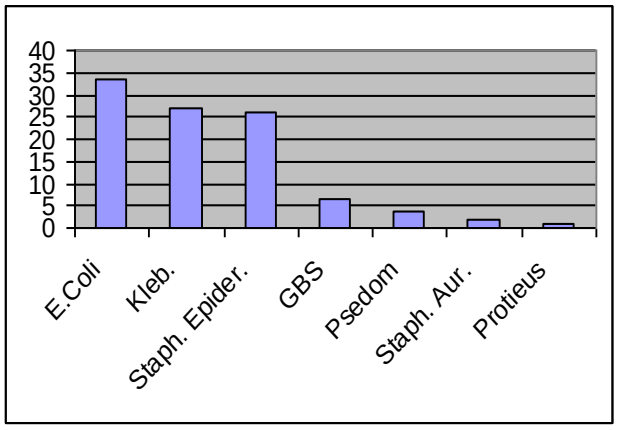

Figure 1. Distribution of sepsis cases according to culture results, Mosul 2012.

DISCUSSION

Based on clinical picture alone the diagnosis of neonatal infection is difficult to establish, yet it is imperative that treatment is instituted early because of the high mortality associated with neonatal infection.

In the present study 63.5% of the infected babies were boys and this was similar to other studies.[20,21] This possibly may be due to impaired defense mechanisms and low immunoglobulin G levels in boys .[3,6,7,21]

All our patients (198) at admission had high serum CRP level while only 104 (52%) of them had culture-proven sepsis and this was in agreement with study done in England, in which culture-proven sepsis were 55.4%.[22] The low positivity of blood culture underscores the need for other tests in diagnosing neonatal sepsis.

After 72 hrs of admission, CRP was still high in approximately half (98 patients) of our patients after receiving treatment for neonatal sepsis but only 61 (62%) of them had positive blood culture. Serial CRP measurements can be helpful in monitoring the response to treatment and to determine the duration of antibiotic therapy.[23,24] In a cohort of 60 neonates with early-onset sepsis, Ehl *et al*[25] demonstrated that after initiation of a successful antibiotic therapy, CRP values further increased, peaking and consecutively decreasing after 16 hrs. A CRP level that returned to the normal range may indicate that antibiotic was effective, allowing its discontinuation,[26] provided that the clinical condition of the neonate has improved and culture results were negative.

On the other hand, in group 1 patients (CRP ≥ 6< 12 mg/L) 37.2% of patients with suspected sepsis but negative blood culture, had high CRP compared with only 14.4% of them with positive blood culture. This is because a raised CRP is not necessarily diagnostic for sepsis, as elevations may also occur as a physiologic phenomenon after birth or non-infection-associated conditions (PROM, prolong labor meconium aspiration, IVH, perinatal asphyxia and fetal distress).[27-29] In 1982, Ainbender *et al*[30] described CRP values > 20 mg/L in 11 of 100 uninfected infants consecutively admitted to the special care nursery. The authors described that 8 of the 11 infants had, either singly or in combination, shock, meconium aspiration pneumonitis, fetal distress, maternal fever and PROM, and none was found to be infected. Forest *et al*[31] reported elevated CRP values between 11 and 70 mg/L in 16/49 uninfected neonates admitted to the NICU with diagnoses of intraventricular hemorrhage (IVH), meconium aspiration pneumonia, anoxic encephalopathy, PROM, respiratory distress syndrome, chorioamnionitis, aspiration pneumonia, and transitory tachypnea. Therefore, concerns were raised about the reliability of CRP during the early stage of the disease being neither able to diagnose nor to rule out an infection with certainty.

Moreover, in group 4 patients (CRP ≥48 mg/l) CRP was significantly higher with blood culture positive than in patients with suspected sepsis but negative blood culture (p value = 0.009), and after 72 hours of treatment a high levels of CRP still constituted 60.6% of cases with proven sepsis compared to 46% among the suspected sepsis group but with negative blood culture. An elevated CRP measured at the time of the first clinical suspicion probably reflects a more advanced infectious process.[25]

In this study the death rate was 5 % and this is lower than that in India which was 13.3%.[21]

Refusal to feed and lethargy were the most common presenting symptoms in both sepsis and no sepsis groups. There was no statistical difference between symptoms and signs of both groups apart from seizure which was more common in sepsis group and lethargy which was more common in non- sepsis group and this may be due to other causes like hypoglycemia or electrolytes disturbances or IVH.

E.coli was the predominant organism isolated in this study with 34%, while in India, [21] Serbia [32] and Bangladesh[33] klebsialla was the most common isolated micro-organism. Staphylococcus epidermidis was the most common micro-organism isolated in studies done in Nottingham, England [22] and China. [3]

CONCLUSION

Sepsis with Gram-negative micro-organisms is a predominant cause of neonatal sepsis in our community.

The routine ordering of serum CRP for neonate with sepsis is based on weak evidence. Predictive value of CRP could be enhanced by serial rather than a single measurement. A high cut off value of CRP may be needed to diagnose neonatal sepsis. Further, future studies with large number of patients are needed to definitively determine the diagnostic accuracy of CRP levels in neonates with infections.

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