Significance of C-reactive protein in Neonatal Sepsis in Diyala Province, Iraq, Hospital Based Study

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Abstract

Background: C-reactive protein is a well-recognized acute phase reactant that is greatly involved to support the diagnosis of neonatal septicemia.

Objectives: To high light the correlation between C- reactive protein and neonatal septicemia.

Patients and Method: A cross sectional study on hundred neonates infant demonstrated to have sepsis were studied during the period from 1st October 2014 to 28th February 2015. One group study was evaluated; age ranged from 29 week gestational age to 29 days post-natal. The data of patients in the group study collected from Al- Batool Teaching Hospital for Maternity and Children - neonatal intensive care unit.

Result: There were 100 patients included in this study; that 61 patients (61%) were pre term (29 to 36 weeks gestational age), 39 patients (39%) were full term 37 weeks' gestational weeks - 29 days post-natal).

Males were 56 (56%), and females were 44 (44%). Fifty-seven (57%) were delivered by vaginal delivery; were as 43 (43%) delivered by caesarian section. The C- reactive protein level correlate well with the diagnosis of the neonatal sepsis as 86 (86%) patients had a positive result versus 14 (14%) who had negative results.

Conclusions: C-reactive protein is very useful, cheep, and available test to confirm the diagnosis of neonatal sepsis and to follow the response of the patients to the antibiotic treatment.

Key Words: C-reactive protein, neonate, sepsis, preterm.

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Introduction

Despite the advances in neonatal care, neonatal sepsis remains a serious and potentially life-threatening disease with a mortality rate ranging from (1.5%) in term to almost (40%) in very-low-birth weight infants [1, 2].

The signs and symptoms of neonatal sepsis may be subtle and nonspecific being clinically indistinguishable from various noninfectious conditions such as respiratory distress syndrome or maladaptation. The current practice of starting empirical antibiotic therapy in all neonates showing infection-like symptoms results in their exposure to adverse drug effects, Nosocomial complications, and in the emergence of resistant strains [3].

There is great interest in rapid diagnostic tests that are able to distinguish infected from uninfected newborns, especially in the early phase of the disease [4].

Despite the promising results for some diagnostic markers, current evidence suggests that none of them can consistently diagnose 100% of infected cases. C-reactive protein (CRP) is the most extensively studied acute-phase reactant so far, and despite the ongoing rise (and fall) of new infection markers, its wide availability and its simple, fast, and cost-effective determination make it one of the preferred indices in many neonatal intensive care units (NICUs) [5].

C-reactive protein was first described in 1930 by Tillet and Francis at Rockefeller University [6].

During the acute-phase-response, CRP's hepatic synthesis rate increases within hours and can reach 1,000-fold levels [7].

The production of CRP in the hepatocytes [8, 9]. Is part of the acute-phase response, physiological and metabolic reaction to an acute tissue injury of different etiologies (trauma, surgery, infection, acute inflammation, etc.) which aims to neutralize the inflammatory agent and to promote the healing of the injured tissue [10, 11].

Levels remain high as long as the inflammation or tissue damage persists and then decrease rapidly. The half-life time has been reported to be 19 h in any of the diseases studied, being the fractional catabolic rate independent of the plasma CRP concentration [12,13].

Any elevation of serum CRP in the neonate always represents endogenous synthesis, since it passes the placenta in exceedingly low quantities [14].

De novo hepatic synthesis starts very rapidly after a single stimulus with serum concentrations rising above 5 mg/l by about 6 h and peaking at around 48 h [15].

For the diagnosis of early-onset sepsis in clinical practice, the sensitivity is more important compared to the specificity, as the consequences of unnecessarily treating an uninfected infant bear fewer complications than not treating an infected child.

In diagnosis of early-onset sepsis, previous studies reported on widely differing sensitivities and specificities of CRP ranging from 29 to 100% and from 6 to 100% respectively [16,17].

Serial CRP measurements can be helpful in monitoring the response to treatment in infected neonates, to determine the duration of antibiotic therapy, and to recognize possible complications [18,19].

This may be related to the arbitrary choice of optimal cutoff points as well as the insensitive analytic methods with various limits of quantification used in the past to detect the CRP pattern in the earliest course of infection, in particular in the very early neonatal period. [20]

This study aim to high light the role and the significance of the CRP as a laboratory aid in diagnosing neonatal sepsis in our area.

Patient and Method

A cross sectional study on 100 new born infant admitted with sepsis according to the clinical evaluation was studied during the period from 1st of October 2014 to 28th of February 2015. One group study were evaluated; The data of patients were collected from the Al-Batool Teaching Hospital for Maternity and Children at neonatal intensive care unit, blood samples aspirated on admission to the casualty unit and then in the word and analyzed in the main central laboratory of the hospital .

Sixty seven patients were delivered by vaginal delivery, were the other thirty three patients delivered by cesareans section. Nineteen patients were died before the end of our study. We send the entire patient for CRP level before and after initiation of antibiotics chemotherapy. This is true for WBC count as well.

Also correlate the CRP value with the clinical picture of the patients, depending on the clinical bases for the diagnosis of neonatal sepsis and CRP value.

The antibiotic items and the duration of the treatment varied according to the clinical response and laboratory follow up. The patient's age in the group study ranged from day one of life neonates with 29 week gestational age to 29days postnatal. The conditions that may increase the CRP value like perinatal asphyxia, pneumothorax, fetal distress, prolonged labor, birth injury evaluated in the study.

Maternal conditions that are augment suspicion about neonatal sepsis like maternal pyrexia, urinary tract infection, and flu like illness, lower abdominal pain, and premature rupture of amniotic membrane were considered. In the study categorized neonatal sepsis as early neonatal sepsis occurs in the first seven days of age and late neonatal sepsis occur after the 1st week of age.

Statistical analysis: The data was performed using the Statistical Package for the Social Sciences (SPSS), version 22, IBM, US, 2013. Descriptive statistics were presented as frequencies (No.) and proportions (%).

Results

As it shown in table (1) the age of the 100 patients in this group study was ranged between (29 weeks gestational age - 29 days post- natal), furthermore , age group distribution revealed that 61 patients (61%) were pre term (29 to 36 weeks gestational age),39 patients (39%)were full term (37 weeks gestational weeks – 29 days post-natal) .

Table (1): Age distribution of neonates in the studied group.

Pre term baby		
Gestational age (GA)	**No.**	**%**
29 week GA	1	1
30week GA	3	3
31week GA	2	2
32 week GA	8	8
33week GA	12	12
34 week GA	15	15
35 week GA	13	13
36 week GA	7	7
Total	61	61%
Full term baby		
37 week GA	9	9
38 week GA	7	7
39 week GA	4	4
1-28 day post- natal	18	18
Total	39	39%

Table (2) Out of the 100 patients, males were56 (56%), and females were 44 (44%), with a male to female ratio of 1.2:1.

Table (2): Gender distribution of neonates in the studied group.

Gender	**No.**	**%**
Male	56	56
Female	44	44
Total	100	100%

Table (3) the patients in this group study also distributed according the type of delivery as 57 patients (57%) were delivered by vaginal delivery and the remaining 43 patients (43%) were delivered by caesarian section.

Table (3): Distribution of patients according the mood of delivery.

Mode of delivery	***No.***	***%***
Caesarian section	43	43
Vaginal delivery	57	57
Total	100	100%

Table (4) after the categorization of neonatal sepsis into two groups; early and late, the early neonatal sepsis represent (79%) of the patients in the group study while (21%) of patients had late sepsis.

87 patients (87%) discharged from the hospital after finishing the course of chemotherapy and 11patients (11%) was died.

Table (4): Distribution of neonates according to the onset of sepsis.

Neonatal sepsis	**No.**	**%**
Early	79	79
Late	21	21
Total	100	100%

Table (5) show the diagnosis of neonatal sepsis was suggested by the clinical data the CRP level correlate with the diagnosis of sepsis as 86 patients (86%) had a positive result versus 14 patients (14%) who had negative results.

Table (5): Distribution of neonates according to CRP value.

CRP value	**No.**	**%**
CRP positive	86	86
CRP negative	14	14
Total	100	100%

Table (6) show 14 patients (14%) had conditions that have a similar effect on CRP value such as asphyxia Birth injury pneumothorax as shown in the following table 6.

Table (6): Conditions that increased CRP level without sepsis.

Conditions	No.	%
Asphyxia	8	8
Birth injury	5	5
Pneumothorax	1	1
Total	14	14

Table (7) show that the maternal illness effect on the incidence of neonatal sepsis we found that there is a correlation between early neonatal sepsis and maternal infections such as UTI, fever, and skin rash. Thirty five patients (44%) with early neonatal sepsis had a maternal history of infections.

Table (7): Maternal illness that correlate with early neonatal sepsis.

Maternal conditions	No of patients	Percent %
UTI	22	28
Fever	11	13
Skin rash	2	3
Total	35	44%

Discussion

C-reactive protein is the most extensively studied acute-phase reactant so far; its wide availability and its simple, fast, and cost-effective determination make it one of the preferred indices in many neonatal intensive care units [21-24].

Neonatal gender and sepsis might show some difference, in our study we found that out of the 100 patients, males were represented 56 (56%), and females were represented 44 (44%), with a male to female ratio of 1.2:1.; Which agree to *Chirico et al 2011*. in whom study on 2000 neonate infant who had sepsis as guided by clinical and laboratory aid in 2011 in Denmark in their study that they found that male to female ratio 1.3:1[25].

C-reactive protein is particularly useful for monitoring the response to treatment and for ruling out an infection. *Hofer et al (2012).* A repeated determination of CRP 24-48 h after the initiation of antibiotic therapy has been reported to carry a 99% negative predictive value in accurately identifying uninfected neonates, though nothing replaces a clinical impression and the gold standard [26].

Imhof et al 2003. who did a study on a distributions of C-reactive protein measured by high-sensitivity assays in apparently healthy men and women from different populations in Europe in 2003 they found that the percentage of caesarian section is (23%) while the rest represent vaginal delivery (78%). Which partly due to availability of close follow up to the patients and good antenatal care. While in this study 43 patients (43%) were delivered by caesarian section and the

remaining 57 patients (57%) were delivered by normal vaginal delivery [12].

In this study the early neonatal sepsis represent (79%) of the patients while (21%) of patients had late sepsis; While in *Escobar et al 2003.* in France on 1000 neonate infants he found that the early neonatal sepsis represent (61%) of the patients and (39%) of patients had late sepsis; which was differ to that of our study, which could be also attributed to good anti natal care that discover the perinatal infections such as UTI and fever. [27].

As we assumed that the diagnosis of neonatal sepsis was made on a clinical data the CRP level was positive in 86 patients (86%) while14 patients (14%) who had negative which is similar to that results of *Hengst 2003.* in his study on the role of C-reactive protein in the evaluation and management of infants with suspected sepsis [16].

Regarding the maternal illness effect on the incidence of neonatal sepsis it was found that 35 patients (44%) with early neonatal sepsis had a maternal history of infections that support the evidence of the correlation between early neonatal sepsis and maternal infections such as UTI ,fever, and skin rash. This agrees with the results that had been reached by *Rifai et al 2003* [11].

Benitz et al 1998. Found that a raised CRP is not necessarily diagnostic for sepsis, as elevations may also occur due to the physiologic rise after birth or no infection-associated conditions such as asphyxia Birth injury pneumothorax. In this study fourteen patients had a conditions that have a similar effect on CRP value such as asphyxia Birth injury pneumothorax as we said previously [18].

In conclusion, the CRP is a sensitive, cheap and available test that aid in the diagnosis of neonatal sepsis. Early neonatal sepsis is more prevalent than late one and it had correlation with maternal illness. There are some neonatal conditions unrelated to infections are associated with increased CRP value and should be excluded in order to CRP be more sensitive to sepsis. We and other previous studies recommend serial CRP level measurement to evaluate response to therapy.

Regular usage of CRP value with titer for the diagnosis and follow up of neonate with sepsis. Usage of blood culture and sensitivity is a gold standard way to establish the diagnosis of neonatal sepsis in addition to other samples like cerebrospinal fluid, stool and urine, if necessary. Early treatment of maternal infections and good antenatal care with follow up is crucial for decreasing early neonatal sepsis. The importance of blood culture and sensitivity is to exclude the non-septic conditions that resembling sepsis in that having a similar effect on CRP.

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