Role Of C-Reactive Protein In Early Onset Neonatal sepsis

M Himayun, S Ahmad, A Rasool

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Abstract

Objective: To evaluate the role of C-Reactive Protein (CRP) in the diagnosis of early onset sepsis (EOS) in neonates Design: Prospective study Settings: intensive care unit of a tertiary level teaching hospital in India subjects: 225 neonates at risk of / or with clinical features of EOS Methods: CRP levels were measured semi-quantitatively (at value of 8 mg /L) at the time of admission and 8-24 hours later on the next morning. Results: of 225 neonates 30 had positive blood cultures. The sensitivity, specifity, PPV and NPV of CRP at 0 hours were 40%, 87.7%, 33.3%and 90.4% respectively, the corresponding values at 24 hours were 70%, 72.3%,28% and 94% respectively Conclusions: a single CRP value done at the time of admission lacks sensitivity. The sensitivity is increased by serial testing. A negative CRP value is more important than a positive CRP value in that it excludes infection with a high certainty

INTRODUCTION

Neonatal sepsis has a high mortality and morbidity[1]. Timely detection and treatment will help in decreasing mortality and morbidity. Diagnosis of neonatal sepsis is suspected in high risk neonates or in those with clinical features of sepsis. Confirmation of diagnosis is done by growing organism from blood. The main drawback of blood culture is that it takes 24-48 hours for the results to come, which has prompted the evaluation of surrogate markers of inflammation as possible tools for diagnosis of bacterial sepsis. Cytokines and C - reactive protein (CRP) levels have been evaluated in this respect [2-8]. Although several studies confirm that CRP levels are useful, there are reports to the contrary[9-12]. It has been suggested that serial levels may be more useful diagnostically[15-18].

We designed this study with the aim of evaluating the role of CRP in early onset sepsis (EOS) of neonates.

METHODS

This prospective study was done in the department of neonatology SKIMS Soura from January 2006 to October 2007. Neonates with birth weight >1000 grams, gestational age >28 weeks and born within 48 hours were included in the study if they had Risk factors for EOS &/or Clinical features of sepsis.

At the time of admission a complete septic screen was done which included total and differential leukocyte count, absolute neutrophils count, platelet count, CRP, chest X ray and blood culture. CRP was measured at the time of admission and 8-24 hours later, on the next morning, using a semi-quantitative technique with a detection limit of 8 mg/L (Biocientifica S.A. iturri, Buenous Aires, Argentina).

Newborn babies were classified as having sepsis if they had signs suggestive of sepsis and a positive blood culture. Probable sepsis was diagnosed if they had a negative blood culture with signs suggestive of sepsis and no sepsis if there were no clinical features of sepsis with a negative blood culture. Babies with sepsis or probable sepsis received antibiotics for about 14 days. The remaining newborns were classified as at risk of infection and received antibiotics for an average of 5 days.

Positive blood culture was considered the “gold standard” against which the performance of CRP was compared.

RESULTS

A total of 225 neonates were enrolled for the study. The demographic characteristics of these neonates are shown in table1.

Figure 1

TABLE 1: DEMOGRAPHIC CHARACTERISTICS

Age at admission , mean (range)	11.74 hours (0-72 hrs)
Gestational age ,mean / range	37 weeks (28-40 weeks)
Male female	1.5:1
Birth weight ,mean /range	2.49 kgs. (0.9-3.7 kgs.)
PREMATURATIY	34% (84)
LOW BIRTH WEIGHT	
<1500 gms.	(42)
1500-2500 gms.	(87)
>2500 gms.	(96)
INTRA MURAL DELIVERIES	(138)
EXTRA MURAL DELIVERIES	(87)
PRIMI	(102)

Klebsiella pneumoniea was the commonest organism isolated. Majority of the babies were term deliveries. Perinatal asphyxia was present in a significant no. of cases. The commonest risk factor was premature rupture of membranes. Refusal to feed and temperature instability were the commonest presentations (table2).

Figure 2

TABLE 3: CLINICAL CHARACTERISTICS

PERINATAL ASPHYXIA	195
MECONIUM	54
RUPTURE OF MEMBRANES	
12-24 hours	84
>24 hours	39
INTRA PARTUM FEVER	45
FOUL SMELLING LIQOUR	03
UTI	30
REFUSAL TO FEED	204
TEMPERATURE INSTABILITY	192
JAUNDICE	27
APNOEA	180
TACHY/BRADYCARDIA	186
SHOCK	183
BLEEDING	15
SEIZURES	96

PERFORMANCE OF SCREENING TEST

The calculated sensitivity, specifity, positive predictive value (PPV) and negative predictive value (NPV) were as follow: 0 hour CRP: 40%, 87.7%, 33.3% and 90.4% respectively and 24 hour CRP: 70%, 72.3%, 28% and 94% respectively. The sensitivity of CRP at 0 hours was low (40%), which increased to70% at 24 hours. NPV was more than 90% both at the time of initial and subsequent evaluation. PPV was low at all times.

DISCUSSION

Serum concentrations of CRP increase several hundredfold in response to bacterial infection, making it an attractive diagnostic test for neonatal sepsis. Several hours are needed for CRP levels to increase in serum (including activation of neutrophils, elaboration of interleukin-6, and induction of hepatic synthesis of CRP) therefore limiting the sensitivity of this test in diagnosing NNS. CRP levels are consistently elevated 24 to 48 hours after the onset of infection[20]; therefore serial normal levels may be useful for identification of infants who do not have bacterial infection.

Our findings demonstrates that a single CRP level at the beginning of evaluation lacks sensitivity (40%), which was improved by delaying testing for 24 hours, attesting to the fact that serial levels are better than a single level. Similar findings have been reported by Nuntnarumit P[15] and others who, in a series of 76 neonates with late onset sepsis (LOS), reported a high sensitivity (100%) and NPV (100%), for serial CRP levels done initially and 24-48 hours later. Jankovic B[16] also pointed out the diagnostic accuracy of serial measurements. In the largest series of 1136 neonates, William E benitz[17] showed serial levels to be diagnostically superior. Elizabeth Mathai[19] and others in 250 neonates with risk factors for EOS did not find serial levels to be diagnostically useful. This conclusion could be due to variations in the population studied with respect to age (cord blood vs. neonatal blood) different cut off point (6 mg vs. 8 mg) and selecting only babies with risk factors etc.

Various factors apart from sepsis can cause a rise in CRP levels esp. Meconium aspiration syndrome, perinatal asphyxia, surgery, etc. therefore limiting its Positive Predictive Value. But a negative CRP rules out infection with high certainty i.e. it has a high Negative Predictive Value. Our study also shows a high NPV for CRP of > 90% at all times. This is in agreement with studies of Ehl S[13] and others who in a group of 176 neonates with suspected sepsis showed that CRP at a cut off value of 10 mg/l had a negative predictive value of 99%. Similar results have also been shown by Jankovic B[14] and others.

Therefore, in conclusion, a single CRP value done at the time of admission may not identify all neonates with sepsis; serial levels done 24 hours apart increase the sensitivity of CRP determinations. A negative CRP is more important than a positive CRP in that it excludes infection with a high degree of certainty.

References

1. The WHO young infants study group, Bacterial etiology of serious infections in young infants in developing countries: results of a multicentric study, Pediatr Infect Dis J 1999; 18: S17-22.
2. Zuppa AA, Calabrese V, D'Andrea V, Fracchiolla A, Scorrano A, Orchi C. Evaluation of C reactive protein and others immunologic markers in the diagnosis of neonatal sepsis. Minerva Pediatr2007; 59(3):267-74
3. Chan D.K.L, Ho L.Y. Usefulness of C-reactive protein in

the Diagnosis of neonatal sepsis. Singapore medical journal1997; 38: 252-55
4. Jincharadze N, Abelashvili D, McHedlishvili M, Kacharava M. Diagnostic value of C-reactive protein test at early-onset sepsis in preterm infants. Georgian Med News 2006; 130:87-91.
5. Laborada G, Rego M, Jain A, Guliano M, Stavola J, Ballabh P et al. Diagnostic value of cytokines and C-reactive protein in the first 24 hours of neonatal sepsis. Am J Perinatol 2003; 20(8):491-501
6. Khassawneh M, Hayajneh WA, Kofahi H, Khader Y, Amarin Z, Daoud A. Diagnostic markers for neonatal sepsis: comparing C-reactive protein, interleukin-6 and immunoglobulin M. Scand J Immunol. 2007; 65(2):171-5
7. Sl□ncheva B, Vakrilova L, Emilova Z, Iar□kova N, Shishkova R, Popivanova A. Inborn bacterial infections during neonatal period. Akush Ginekol (Sofiia) 2006; 45(4):42-8.
8. Ng PC, Cheng SH, Chui KM, Fok TF, Wong MY, Wong W, et al. Diagnosis of late onset neonatal sepsis with cytokines, adhesion molecule, and C-reactive protein in preterm very low birth weight infants. Arch Dis Child Fetal Neonatal Ed. 1997;77(3):F221-7
9. Hajiehe Borna, M.D. Sedigheh Borna, M.D. Value Of Laboratory Tests And C - Reactive Protein In The Detection Of Neonatal Sepsis. The Internet Journal of Pediatrics and Neonatology TM ISSN: 1528-8374
10. Janota J, Stranák Z, B□lohlávková S. Interleukin-6, procalcitonin, C-reactive protein and the immature to total neutrophil ratio (I/T) in the diagnosis of early-onset sepsis in low birth weight neonates. Ceska Gynekol 2000; 65 Suppl1:29-33.
11. Mustafa S, Farooqui S, Waheed S, Mahmood K. Evaluation of C-reactive protein as early indicator of Blood culture positivity in Neonates. Pak J Med Sci. 2005; 21(1):69-73.
12. Kocabaş E, Sarikçioğlu A, Aksaray N, Seydaoğlu G, Seyhun Y, Yaman A. Role of procalcitonin, C-reactive protein, interleukin-6, interleukin-8 and tumor necrosis factor-alpha in the diagnosis of neonatal sepsis. Turk J Pediatr. 2007; 49(1):7-20
13. Ehl S, Gering B, Bartmann P, Hogel J, Pohlandt F.C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. Pediatrics1997; 99(2):216-21
14. Janković B, Pasić S, Marković M, Veljković D, Milicić M. C-reactive protein concentrations during initial (empiric) treatment of neonatal sepsis. Srp Arh Celok Lek. 2001; 129 Suppl 1:17-22.
15. Nuntnarumit P, Pinkaew O, Kitiwanwanich S. Predictive values of serial C- Reactive protein in neonatal sepsis. J Med Assoc Thai 2002; S1151-8.
16. Janković B, Veljković D, Pasić S, Rakonjac Z, Jevtić D, Martic J.C-reactive protein and cytokines in the diagnosis of neonatal sepsis. Med Pregl. 2006; 59(11-12):545-9
17. William E. Benitz, Michael Y. Han, Ashima Madan, and Pramela Ramachandra Serial. Serum C - reactive protein Levels in the Diagnosis of Neonatal Infection. Pediatrics 1998; 102(4): e41
18. Wagle S, Grauaug A, Kohan R, Evans SF. C-reactive protein as a diagnostic tool of sepsis in very immature babies. J Paediatr Child Health. 1994; 30 (1):40-4.
19. Elizabeth Mathai, Usha Christopher, Matthews Mathai, Atanu Kumar Jana, Dolly Rose, Staffan Bergström. Is C - reactive protein Level useful in Differentiating Infected from Uninfected Neonates among those at Risk of Infection? Indian pediatrics 2004; 41: 895-99
20. Ehl S, Gering B, Pohlandt F. A detailed analysis of changes in serum C-reactive protein levels in neonates treated for bacterial infection. Eur J Pediatr 1999; 158:238-42.

Author Information

Mohmmad Himayun, MD
Senior resident, Department of neonatology, SKIMS

Sheikh Mushtaq Ahmad, MD
Additional professor, Department of neonatology, SKIMS

Akhtar Rasool
Post Graduate student, Department of neonatology, SKIMS