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ORIGINAL ARTICLE

Diagnostic Value of Serum Procalcitonin and C-reactive Protein Levels in Neonatal Sepsis

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Abstract

Introduction: Rapid and early diagnosis in neonatal sepsis is of great importance in reducing morbidity and mortality. An increase in acute phase reactants before the causative agent is shown in the hemoculture supports the diagnosis. Monitoring of C-reactive protein (CRP) levels is used for this purpose in clinical applications. In recent years, the use of procalcitonin (PCT) in neonatal sepsis has come to the fore. PCT increase occurs earlier than CRP. In this study, we aimed to compare CRP and PCT levels in the diagnosis and follow-up of neonatal sepsis.

Methods: The study was carried out with 40 patients hospitalized in the neonatal intensive care unit (NICU) with the diagnosis of sepsis and 40 control subjects.

Results: Pre-treatment PCT and CRP values of the study group were significantly higher than the control group ($p<0.05$). When the pre-treatment CRP and PCT values were compared with the CRP and PCT values after the 72nd hour of the treatment, a statistically significant decrease was found ($p<0.05$).

Discussion and Conclusion: As a result, PCT has been found to be as useful as CRP, which is routinely used in the early diagnosis of sepsis and in monitoring the response to treatment.

Keywords: C-reactive protein; neonatal sepsis; procalcitonin.

The term neonatal sepsis refers to systemic and symptomatic bacterial, viral, fungal infections in the first month of life. Neonatal sepsis occurs in 0.1-0.8% of term infants. In premature babies, the rate of sepsis rises up to 30%. In neonatal sepsis, the rate of invasion of the meninges is 15-20%, and the rate of neurological sequelae is around 20-50%[1]. The gold standard in the diagnosis of sepsis is isolation of the causative agent in blood culture. However, it is not always possible to isolate the causative agent in blood culture and auxiliary diagnostic methods are also used in the clinic. The main auxiliary diagnostic methods are white blood cell count and related indicators and acute phase reactants. The main acute phase reactants are C-reactive protein, fibrinogen, ceruloplasmin, sedimentation, transferrin, fibronectin, prealbumin, haptoglobin, serum amyloid A, orosomucoid, procalcitonin, (PCT) antigens of various bacteria and PCT, which has been used frequently in recent years. Follow-up of increased CRP values with serial measurements is a useful method in neonatal sepsis. It is also used in follow-up to understand the effectiveness of treatment[2]. PCT, on the other hand, has been used in neonatal sepsis in recent

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years. PCT increase occurs within four hours after sepsis. There are studies suggesting that PCT may be a screening test and even a diagnostic criterion in neonatal sepsis. In this study, we aimed to compare CRP and PCT elevation, which are used in the diagnosis and treatment follow-up of neonatal sepsis[2,3].

Materials and Methods

This study was carried out on 40 patients hospitalized in our NICU with a prediagnosis of sepsis and 40 control subjects between September 2008 and September 2009, with the approval of our hospital's educational board. Term and preterm newborns with suspected sepsis were included in the study. Before starting empirical antibiotic therapy, 1 cc of blood was collected for CRP and PCT analysis from newborns with suspected sepsis. In addition, blood culture and, if required by the patient's clinic, urine, CSF and other cultures (belly button swab, rectal, tracheal aspirate, etc.) were collected from each patient. Lumbar puncture was performed in patients with signs and symptoms of meningitis. Chest X-ray was obtained in patients with suspected sepsis and respiratory system symptoms. In addition, a complete urinalysis was performed. As the control group, 40 term and preterm healthy newborns were randomly assigned. Sepsis occurring within the first 4 postnatal days was considered as early sepsis, and sepsis occurring between 4 days and 30 days after birth was considered as late sepsis. Empirical therapy was continued until the culture results were obtained of the patients who were started on antibiotic therapy.

CRP and PCT were measured again 72 hours after the start of antibiotic therapy to evaluate the response to treatment. CRP and PCT values taken before starting antibiotics for diagnosis and CRP and PCT values taken to evaluate response to treatment at 72 hours were compared. CRP levels were determined quantitatively by immunonephelometric method using the appropriate kit on the Arctitect 16200 device. Values above 5 mg/dl were considered significant. PCT measurements were performed from serum using Minividas Cobas e 411(Hitachi) analyzer and PCT kit (B.R.A.H.M.S. Diagnostica, Berlin, Germany). Values above 2 ng/ml were considered significant.

Results

As seen in Table 1, the most abundant microorganism in the blood culture in the sepsis group was found to be coagulase-negative staphylococcus (CoNS) with 10 cases (25%). Enterobacter, Streptococcus epidermidis, Candida albicans were seen in two cases (5%) and MRCNS, E.coli, Klebsiella pneumoniae, P.aeuriginosa in one case (2.5%). Early sepsis was detected in 14 of 20 newborns and late sepsis in 6 of 20 newborns with growth in blood culture (Table 2). CoNS was found to be the most isolated factor in early sepsis with 8 cases. S.epidermidis was detected as an early sepsis agent in 2 cases, and Klebsiella pneumonia, Pseudomonas, Enterobacter and MRSA in 1 case each. The most common factor detected in late sepsis was CoNS and Candida with 2 cases. Enterobacter and E. Coli were detected as late sepsis agents in one case each. CRP and PCT levels of the sepsis group before and after treatment were statistically significantly higher than the control group ($p<0.01$) (Table 3). In the study group, the decrease in the post-treatment CRP level compared to the pre-treatment CRP level was statistically significant ($p<0.01$) (Table 4).

Table 1. Distribution of acute phase reactant levels and hematological parameters in groups

Parameter	Study group n (n=40) %	Control group n (n=40) %
PCT increased	31 (77.5)	12 (30)
CRP increased	31 (77.5)	5 (12.5)
I/T increased	17 (42.5)	0 (0)
Leukocytosis or leukopenia	14 (35)	10 (25)
Thrombocytopenia	5 (12.5)	0 (0)

PCT: Procalcitonin; CRP: C-reactive protein.

Table 2. Evaluation of CRP and PCT in study and control groups

	Study group Mean±SD (Median)	Control group Mean±SD (Median)	+p
CRP			
Before treatment	31.817±37.3 (17.8)	6.77±7.49 (1.16)	0.001
After treatment	10.80±19.02 (5.00)	0.62±1.38 (0.19)	0.001
++p	0.001	0.003	
PCT			
Before treatment	10.77±12.13 (7.6)	2,72±4.22 (5,00)	0.001
After treatment	2.75+7.09 (1.00)	0.17+0.24 (0.10)	0.001
++p	0.001	0.001	

PCT: Procalcitonin; CRP: C-reactive protein.

Table 3. Evaluation of CRP and PCT Positivity

	Study group n (%)	Control group n (%)	+p
CRP			
Positive	31 (77.5)	5 (12.5)	0.001
Negative	9 (22.5)	35 (87.5)	
PCT			
Positive	31 (77.5)	12 (30)	0.001
Negative	9 (22.5)	28 (70)	

PCT: Procalcitonin; CRP: C-reactive protein.

Table 4. Comparison of sensitivity and specificity of CRP and PCT

	Sensitivity	Specificity Predictive Value	Positive	Negative Predictive Value
PCT	77.5%	70%	72%	69%
CRP	77.5%	87.5%	86%	79%

PCT: Procalcitonin; CRP: C-reactive protein.

Discussion

CRP is a frequently used test in the diagnosis of neonatal sepsis. CRP does not cross the placental barrier and its concentration does not change with gestational age[4]. It starts to increase 4-6 hours after infection and peaks at 24-48 hours. And when the inflammation regresses, its amount decreases. Benitz et al. showed that the incidence of proven sepsis is 10% when CRP is >5 mg/dL[5]. Since non-infectious causes such as meconium aspiration, respiratory distress syndrome, perinatal asphyxia, maternal fever, premature rupture of membranes and intraventricular hemorrhage also cause an increase in CRP, its specificity decreases[4,5].

The sensitivity of CRP in neonatal sepsis varies between 75 and 93%, and its specificity varies between 62% and 95% in different studies[3,6,7]. In our study, while the sensitivity was 77.5%, the specificity was 87.5%. These values seem to be compatible with the literature.

PCT is an acute phase reactant that has been studied frequently in neonatal sepsis in recent years and seems very valuable. Studies have revealed that bacterial endotoxin (lipopolysaccharide) is the strongest stimulus for PCT production[8, 9]. However, viral diseases, autoimmune diseases, oncological diseases, local and limited infections do not cause PCT increase. Therefore, PCT is most commonly used in differentiation of bacterial diseases and non-bacterial diseases. In addition, serum PCT levels were found to be high in sepsis, bacteremia, meningitis, and fungal infections that cause serious systemic infections[8, 10].

In a study conducted in our country by Yıldız et al. in 47 sepsis (+) and 50 (-) newborn cases in 2001, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined as 92.15%, 94.33%, 94%, 92.5%, respectively, for PCT (cutt off: 2 ng/ml), and as 87.03%, 86.20%, 90%, 74.6%, respectively, for CRP (cutt off: 8 mg/dl)[11]. CRP and PCT values in the group with sepsis were found to be significantly higher than the values of healthy newborns, and were found to be significantly higher than the values of sepsis (-) healthy newborns in the control group ($p<0.01$). The values and results found in this study were statistically the same, although PCT and CRP values were found to be 15-20% higher compared to our study. In our study, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined as 77.5%, 70%, 72%, 75% for PCT (cutt off: 2 ng/ml), while as 77.5%, 87.5%, 86%, 79% for CRP (cutt off: 5 mg/dL). The specificity, sensitivity, PPV, NPV values that are strong compared to our study can be attributed to the fact that the gestational week of the study group was between 38 and 42 weeks and the cases that completed the postnatal two days were included in the study.

Köksal et al., in their study in 2002, found CRP and PCT to be diagnostically significant in neonatal sepsis. However, the sensitivity and specificity for PCT (cutt off: 2 ng/ml) were 48% and 100%, respectively, while it was 48% and 87%, respectively, for CRP (cutt off: 1 mg/dL)[11]. While the sensitivity values are quite low, there is a 10-15% difference in favor of PCT in terms of specificity, as in our study. In other words, it is a very powerful study in terms of excluding the diagnosis of sepsis when PCT is negative. The reason why its strong specificity compared to our study may exclude the diagnosis of sepsis, can be attributed to the characteristics of the patients in the selected study group. While the study groups were formed as high, intermediate and low risk sepsis, the control group consisted of healthy newborns. Again, whether or not the CRP was above 1 mg/dl determined that the patients were in any of these risk groups. These reasons may explain the low sensitivity and very high specificity.

PCT (cutt off 2 ng/mL) and CRP (cutt off 1 mg/dL values were evaluated in 87 newborns, 18 of whom were confirmed (blood culture positive), by Boo et al. (2008). Sen-

sitivity, specificity, PPV, NPV values for PCT were 88.9%, 65.2%, 40%, 95.7%, respectively and 55.6%, 89.9%, 58.8%, 88.6% for CRP, respectively. PCT has been found to be more valuable from a diagnostic point of view. In our study, however, no difference was found. Considering our results, it was seen that there was no difference between the reliability of PCT and CRP in the diagnosis of sepsis. As mentioned above, the sensitivity and specificity of PCT have been reported in the literature as 60-100% and 70-100%, respectively[12, 13]. In this context, we believe that the different results regarding sensitivity and specificity in some studies are due to the number of cases included in the study, week of gestation, age, sepsis definition criteria, different structure of the control groups, and different cutt-of values for PCT and CRP.

In the study conducted by Bozkaya et al.[14], the positive predictive value of PCT was found to be more significant than CRP in the early diagnosis of congenital pneumonia. In this study, the positive predictive value of PCT level was found to be significantly higher in cases whose samples were taken in the first 31 hours of life. In our cases, the first PCT measurement was performed after the clinical signs of sepsis were observed and between the 1st and 7th day of life. We think that the positive predictive value of the PCT value being similar to the positive predictive value of the CRP level is due to the fact that we had cases whose first blood sample was taken in the late neonatal period. Similarly, in the study of Canpolat et al.[15], it was shown that the positive predictive value of PCT levels was high in the early neonatal period. The positive predictive value of PCT levels in cord blood was also found to be high in the diagnosis of early onset neonatal sepsis[16]. Evaluation of PCT level was found useful in the management of early neonatal sepsis in meta-analysis studies[17].

Conclusion

In conclusion, PCT is at least as valuable as CRP in the early diagnosis of sepsis and in monitoring the response to treatment. In the light of these findings and the literature, it can be said that the use of PCT in neonatal sepsis is as beneficial as routinely used CRP. In fact, its early rise (within 4 hours) compared to CRP and its early fall in response to treatment are its advantages. Therefore, it has been found to be useful in the early diagnosis and management of pneumonia and sepsis, especially in the early neonatal period. In addition, PCT's superiority over CRP is that it does not increase in non-infectious conditions such as trauma, burns and operations. As a result of the data obtained, we believe that PCT should be used as an indicator of infection, especially in the diagnosis of pneumonia and sepsis in the early neonatal period.

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