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DİAGNOSTIC RELIABILITY OF CRP AND PROCALCITONIN IN EARLY-ONSET NEONATAL SEPSIS AND THE IMPACT OF FETAL DISTRESS

Erken Başlangıçlı Yenidoğan Sepsisinde CRP ve Prokalsitonin'in Tanısal Güvenilirliği ve Fetal Distresin Etkisi

Running Title: The reliability of CRP and procalcitonin

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Özet

Amaç: Yenidoğanlarda yapılan çalışmalar C-reaktif protein (CRP) ve prokalsitoninin (PCT) sepsis tanı ve tedavisinde güvenilir bir belirteç olarak kullanılabileceğini göstermektedir. Bununla birlikte bu belirteçlerin serum düzeylerinde enfeksiyon dışı nedenler ile de yükselme görülebilmektedir. Bu çalışmanın amacı fetal distress, doğum sonrası fizyolojik faktörler ve sepsisin CRP ve PCT serum seviyeleri üzerine ne düzeyde etki ettiğini tespit etmek ve karşılaştırmaktır.

Materyal ve Metot: Çalışmaya 88 bebek alındı. Tüm bebeklerden başlangıç anında hemogram, CRP, PCT ve kültür için kan örneği alındı (T0), sepsis tanılı bebeklerde tetkikler 3. (T3) ve 7. günlerde (T7) tekrarlandı.

Bulgular: Klinik ve laboratuvar bulguları sepsis ile uyumlu olan hastalar sepsis grubu (Grup 1), fetal distresi olan ve olmayan sağlıklı bebekler birlikte kontrol grubu olarak alındığında (Grup 2+Grup 3) T0'da duyarlılık ve özgüllük sırası ile CRP için %82 ve %86, PCT için %64 ve %49 bulundu. Yalnızca fetal distress yaşamayan sağlıklı bebekler kontrol grubu olarak alındığında ise bu değerler CRP için %82 ve %93, PCT için ise %71 ve %47 olarak bulundu.

Sonuç: Doğum sonrası fizyolojik artışın yanı sıra fetal distress nedeni ile de CRP ve PCT'in her ikisinin de serum düzeylerinde artış görülebilmektedir. Ancak bu iki faktörün etkisi PCT üzerinde çok daha fazladır.

Anahtar Kelimeler: Yenidoğan, Sepsis, C-reaktif protein, Prokalsitonin

Abstract

Aim: The studies in neonates suggest that C-reactive protein (CRP) and procalcitonin (PCT) can be used as a reliable marker for both diagnosis and follow-up of neonatal sepsis. However, their serum levels may also increase in some conditions without infection. The aim of this study was to determine and compare the effects of fetal distress, postnatal physiological factors and sepsis on serum levels of CRP and PCT.

Materials and Methods: A total of 88 infants were included in this study. Before initiating therapy, blood samples for whole blood count, CRP, PCT and culture were obtained from all neonates (T0). This procedure was repeated two times at 72 h (T3) and day 7 (T7)

Results: The group that included infants with clinical and laboratory findings of sepsis considered as a sepsis group (Group 1) and the groups with and without fetal distress were combined as a control group (Group 2+Group 3), so CRP and PCT were evaluated in terms of the sensitivity and specificity. The sensitivity and specificity at T0 were found to be 82%, 86% for CRP and 64%, 49% for PCT, respectively. Additionally, when the healthy term infants without fetal distress were considered as a control group; the sensitivity and specificity at T0 were found to be 82%, 93% for CRP and 71%, 47% for PCT, respectively.

Conclusion: Consequently, we found that PCT and CRP levels are affected by fetal distress as well as physiological increase after birth. However, we found that their effects was greater on the PCT levels.

Keywords: Neonatal, Sepsis, C-reactive protein, Procalcitonin

INTRODUCTION

Despite all the advances in diagnosis, neonatal sepsis continues to be one of the major causes of morbidity and mortality. Although, the incidence in neonatal period has been reported between 1-10 per 1000 live births, it is higher in developing countries [1-4].

The diagnosis is usually difficult as the sign and symptoms are non-specific in early stages of neonatal sepsis and this results with delayed or unnecessary treatment. The blood culture is gold standard for diagnosis of neonatal sepsis but the factors such as emergence of the earliest cultures 24-48 hours, insufficient

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quantity of sample, contamination and inability to produce of microorganism may lead to delay in diagnosis [1,2]. Therefore, in addition to blood culture, bacterial antigen tests, complete blood count, and several biomarkers such as C-reactive protein (CRP) have been widely used in diagnosis of neonatal sepsis [(4-6)]. Although CRP is the most widely used acute phase protein, procalcitonin (PCT) has also been reported as an reliable and accurate marker [4,7,8.]

CRP is an acute phase protein synthesized by hepatocytes in response to infectious stimuli. CRP production begins in 4-6 h, detectable in the serum within 12 h and reaches to peak values between 36 to 50 h. Its' plasma level begin to fall along with the regression of inflammation. As CRP may increase in several conditions, it is preferably used in combination with other biomarkers. Serial CRP measurements that taken 24-48 h after the onset sign and symptoms can increase the sensitivity [4,5,8-10.]

PCT is the precursor protein of calcitonin. It is produced by macrophages and hepatocytes. Its' serum levels increase after 2-4 h of bacterial endotoxin release. It reaches a peak level after 6-8 h and begins to decrease after 24 h. Serum value is compatible with the severity of the infection and fall after treatment. PCT begins to increase earlier than CRP in case of infection and also falls quicker after treatment [4,7-9,11].

The studies in neonates suggest that CRP and PCT can be used as a reliable marker for both diagnosis and follow-up of neonatal sepsis. However, their serum levels may also increase in some conditions without infection such as fetal distress. This may lead to misinterpretation for the early diagnosis of sepsis [7,8,10,11].

Intrauterine meconium passage in near-term or term fetuses has been associated with fetomaternal stress factors, whereas meconium passage in postterm pregnancies has been attributed to gastrointestinal maturation. The finding of meconium stained amniotic fluid (MSA) is associated with multiple markers of fetal distress, as meconium-stained infants have in general lower scalp and umbilical cord artery pH in comparison with infants born through clear amniotic fluid. However, no major problems occur in the majority of infants born through MSA [12,13].

In this study, MSA was accepted as a sign of fetal distress and healthy neonates were divided into two groups as neonates with and without fetal distress. Thus, the aim of this study was to determine the effects of fetal distress and postnatal physiological factors on serum levels of CRP and PCT. We also aimed to compare CRP and PCT levels of these infants with those who had early onset sepsis (EOS).

MATERIAL AND METHODS

This study was performed in the neonatal intensive care unit (NICU) of Medicine Hospital between October 2015 and March 2016. Although 40 term infants diagnosed as EOS were initially included, 11 infants were excluded from the study because of parents rejected inclusion of their babies. Therefore, a total of 88 infants (29 term infants with EOS group, 27 healthy term infants with fetal distress group, 32 healthy term infant with control group) were included in this study. The

study protocol was approved by the ethic committee of Biruni University and informed consent was obtained for all infants from their family.

The EOS group (Group 1) included infants with clinical and laboratory findings of sepsis in the first 72 h, whereas MSA was accepted as a sign of fetal distress and newborns without clinical and laboratory findings of sepsis divided into two groups according to with and without fetal distress (Group 2 and Group 3, respectively). Gestational age, gender, birth weight, mode of delivery, Apgar score, history of premature rupture of membranes (PROM), chorioamnionitis and prenatal demographics were all recorded.

The diagnosis of EOS was made according to the presence of the clinical and laboratory parameters or culture screen. The Töllner scoring system was used for clinical signs. According to this scoring system, a score of ≥10 indicates clinical sepsis, a score of ≤ 5 indicates no sepsis, and a score of 5-10 indicates possible sepsis [14].

Exclusion criteria included antibiotic therapy at admission, serious congenital malformation, admission after first 72 h of life and refusal of parental consent. The hematologic parameters were processed according to the Manroe and Rodwell scoring systems [15,16]. Leukopenia was defined as leukocyte count <5000/mm^3, leukocytosis was defined as leukocyte count >25000/mm^3 at birth, >30000/mm^3 at 12 to 24 h and >21000/mm^3 after the second day. Normal absolute neutrophil count was accepted as 7800 to 14500/mm^3 in the first 60 h and 1750 to 5400/mm^3 after 60 h. Thrombocytopenia was defined as platelet count <150000/mm^3. Before initiating therapy, blood samples for whole blood count, CRP, PCT and culture were obtained from all neonates (T0). This procedure was repeated two times at 72 h (T3) and day 7 (T7). Whole blood count, CRP, PCT, cultures were studied immediately. CRP levels (reference range: <6 mg/l) were studied by an immunoturbidimetric method using Cobos integra 400 plus (Roche Diagnostics, Rotkreuz, Switzerland). PCT level (reference range: <0.5ng/ml) were determined by an immunoassay method using i-Chroma (Boditech Med. Inc., Korea). Whole blood count was performed by using a Sysmex XT-1800i (Sysmex Corporation, Japan). Cultures were analyzed using fully automated BACTEC method by BacT/Alert (Biomeriux, France).

SPSS Statistics 22 program was used for data analysis. Descriptive statistics were given as mean, median, standard deviation, minimum, maximum and percentage. The significance between groups were evaluated with χ^2-test for qualitative data and with Wilcoxon test for quantitative data. Values of $p < 0.05$ were considered to be statistically significant.

RESULTS

Eighty eight term infants were included in this study. No significant differences were found in gestational age, gender, birth weight, mode of delivery, presence of PROM, chorioamnionitis, acidosis, hypoxia, jaundice and support of mechanical ventilation ($p > 0.05$). The mean Apgar scores at minute 1 were found to be significantly higher in group 2 and 3 than in sepsis group (Group 1) ($p = 0.03$) but there are no differences Apgar scores at minute 5 among three groups (Table 1).

Table 1: Clinical characteristics of study groups.

	Grup 1	Grup 2	Grup 3	*p*
	Mean±SD(median) (n=29)	**Mean±SD (median) (n=27)**	**Mean±SD (median) (n=32)**	
Gestational age (week)	39.38±0.90 (39)	39.52±1.05 (40)	38.69±1.53 (39)	[1]**0.724**
Gender				
Female	14 (%48.3)	13 (%48.1)	15 (%46.8)	[2]**0.804**
Male	15 (%51.7)	14 (%51.9)	17 (%53.2)	
Age (day)	1.55±0.57 (2)	1 ±0 (1)	1 ±0 (1)	[1]**0.00***
Birth weight (gr)	3376.21±522.33 (3450)	3289.26±486.59 (3380)	3216.25±513.92 (3335)	[1]**0.439**
Delivery route				
Normal	6 (%20.7)	13 (%48.1)	8 (%25)	[2]**0,06**
Cesarean delivery	23 (%79.3)	14 (%51.9)	24 (%75)	
Apgar min. 1	7.57±0.87 (8)	8.04±0.76 (8)	8.53±0.57 (9)	[1]**0.03***
Apgar min. 5	8.86±0.64 (9)	9.11±0.51 (9)	9.56±0.50 (10)	[1]**0.11**
PROM	0 (%0)	1 (%4)	3 (%9)	
Choriamnionitis	0 (%0)	0 (%0)	0 (%0)	
Acidosis	0 (%0)	1 (%4)	1 (%1.8)	
Hypoxia	0 (%0)	1 (%4)	0 (%0)	
Invasive ventilation	0 (%0)	0 (%0)	0 (%0)	
Jaundice	2 (%7)	0 (%0)	0 (%0)	

*[1]One-way ANOVA [2]Ki-Kare Test, Continuity (Yates) correction ve Fisher's Exact Test *p<0.05 **p<0.01*

Initial leukocyte counts were higher in group 1 compared with the group 2 and 3 but there were no statistically differences. The leukocyte counts in sepsis group decreased significantly at both 72 h and day 7 (p = 0.02). The initial platelet counts were significantly higher in the groups 2 and 3 compared with group 1 (p = 0.00). In addition, platelet counts in sepsis group significantly increased at day 7 compared with initial count (p = 0.001) (Table 2).

Table 2: Table showing mean levels at 0, 72 h and 7 days.

		Grup1	Grup 2	Grup 3	*p*
		Mean±SD	**Mean±SD**	**Mean±SD**	
Leukocyte (mm^3)					
	T1	18808.62±5814.69	18812.22±3629	16616.8±3464.5	
	T3	10985.47±4001.14			[1]**0.57**
	T7	11702.41±2632.68			
	[2]***p***	**0.021***			
Platelet (mm^3)					
	T1	233344±50612	236777±42525	261062.5±70201.5	
	T3	233655±54906			
	T7	328931±110260			[1]**0.00****
	[2]***p***	**0.001****			
CRP (mg/l)					
	T1	21.47±11.58	4.33±5.5	0.30±0.62	
	T3	12.27±19.58			[1]**0.002****
	T7	1.72±1.70			
	[2]***p***	**0.002****			
PCT (ng/ml)					
	T1	6.44±17.56	2.63 ±2.3	0.54 ±1.43	
	T3	0.71±1.1			[1]**0.014***
	T7	0.16±0.06			
	[2]***p***	**0.005****			

*[1]One-way ANOVA Test [2]One-way Repeated Measures ANOVA *p<0.05 **p<0.01*

Initial levels (T0) of CRP and PCT in group 1 were significantly higher than in group 2 and 3 (p = 0.002, p = 0.014, respectively). Similarly, CRP and PCT values in the group 2 were significantly higher than in the group 3. CRP and PCT levels at T0 declined throughout the study period and these changes are statistically significant (p = 0.002, p = 0.005) (Table 2).

In the sepsis group, 8 patients (28%) had positive blood culture (3 Staphylococcus epidermidis, 2 Alpha-hemolytic streptococcus, 2 Staphylococcus aureus, 1 Escherichia coli) and no patients died from sepsis. No statistically differences were found when the patients that with and without culture positive were compared to in terms of values of CRP and PCT (p = 0.77, p = 0.56).

The groups with and without fetal distress were combined as a control group (Group 2+Group 3), so CRP and PCT were evaluated in terms of the sensitivity and specificity in all neonates. The sensitivity and specificity at T0 were found to be 82%, 86% for CRP and 64%, 49% for PCT, respectively. The area under the curve (AUC) calculated from the receiver operating characteristic curve (ROC), so we evaluated the performance of biomarkers. AUC for CRP and PCT were 0.85 (95% confidence interval (CI): 0.74-0.96) and 0.53 (%95 CI: 0.41-0.66), respectively (p< 0.01). The comparison of CRP, PCT in terms of sensitivity, specificity, PPV, NPV and AUC are all shown in Table 3 and Figure 1.

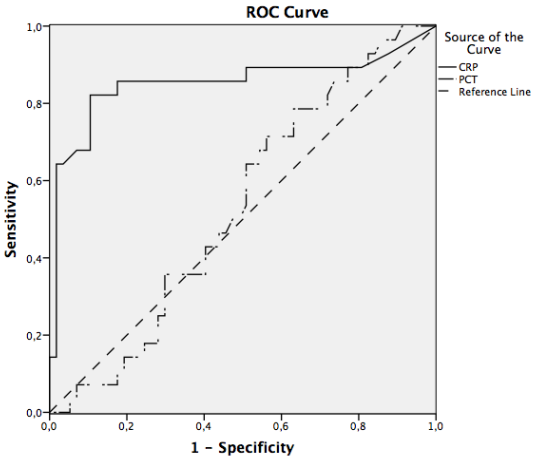

Figure 1. ROC curve of CRP, PCT values at T0 in the EOS group.

Table 3: Comparison of CRP and PCT according to sensitivity, specificity, PPV, NPV and AUC (When the groups with and without fetal distress were combined as a control group)

	Cut-off Point	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
CRP	>6.10	0.82 (0.70-0.94)	0.86 (0.79-0.93)	0.97 (0.90-1)	0.46 (0.43-0.49)	0.853** (0.74-0.96)
PCT	>1.37	0.64 (0.59-0.70)	0.49 (0.41-0.57)	0.59 (0.49-0.69)	0.55 (0.48-0.62)	0.532 (0.41-0.66)

Abbreviations: AUC, area under the curve; CI, confidence interval; NPV, Negative Predictive Value; PPV, positive predictive value.
**p < 0.05 **p < 0.01*

Additionally, when the healthy term infants without fetal distress were considered as a control group; the sensitivity and specificity at T0 were found to be 82%, 93% for CRP and 71%, 47% for PCT, respectively. AUC for CRP and PCT were 0.88 (95% confidence interval (CI): 0.78-0.99) and 0.58 (%95 CI: 0.43-0.73), respectively (p< 0.01). The comparison of CRP, PCT in terms of sensitivity, specificity, PPV, NPV and AUC are all shown in Table 4.

Table 4. Comparison of CRP and PCT according to sensitivity, specificity, PPV, NPV and AUC (When the healthy term infants without fetal distress were considered as a control group)

	Cut-off Point	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
CRP	>6.15	0.82 (0.78-0.86)	0.93 (0.90-0.96)	0.98 (0.92-1)	0.41 (0.34-0.48)	0.883** (0.78-0.99)
PCT	>1.25	0.71 (0.65-0.77)	0.47 (0.40-0.54)	0.65 (0.59-0.71)	0.42 (0.36-0.48)	0.580 (0.43-0.73)

Abbreviations: AUC, area under the curve; CI, confidence interval; NPV, Negative Predictive Value; PPV, positive predictive value.
**p < 0.05 **p < 0.01*

DISCUSSION

Sepsis is an important cause of morbidity and mortality in neonatal period. Early diagnosis is essential in sepsis but the sign and symptoms are nonspecific. Although blood culture is gold standard for the diagnosis, false negative results and long incubation period limits the use of blood culture in neonatal sepsis [1,2]. Therefore, auxiliary markers are needed to confirm the diagnosis of sepsis, but a reliable identification test has not been provided for this purpose.

CRP is the most commonly used marker for diagnosis and follow-up of neonatal sepsis. CRP levels increase with bacterial infections but it may also show a physiological increase after birth or non-infection associated conditions such as perinatal asphyxia, fetal distress, meconium aspiration syndrome, respiratory distress syndrome (RDS), traumatic and ischemic tissue damage, hemolysis, maternal fever. In addition, serum CRP levels begin to rise 10-12 h after an inflammatory stimulus. Therefore, there have been concerns about the reliability of CRP during the early stage of the disease [5,8,10,17]. In previous studies, the sensitivity and specificity values for CRP has been reported to 25-89% and 59-100%, respectively [8,17,18,19].

The mean CRP value of neonates with fetal distress (Group 2) was found 4.33 ± 5.5 mg/l and CRP levels were higher than cut off value in 6 of them (22%). However, in neonates without fetal distress (Group 3), mean CRP value was found 0.30 ± 0.62 mg/l and CRP levels of 3 patients (9%) were higher than cut off value. The difference between the two groups was considered to be related with fetal distress. The mean CRP value in EOS group 21.47±11.58 mg/l and CRP levels were higher than cut off value in 24 of them (83%). In our study, when all healthy neonates that with and without fetal distress is considered as a control group, the sensitivity and specificity values for CRP were found 82% and 86% for 6 mg/l as a cut off value. However, we found 65% sensitivity and 93% specificity for 10 mg/l as a cut off value. This difference results in previous studies may be related with different cut off level, testing methodologies, diagnostic criteria and patient characteristics. When neonates that without fetal distress is considered as a control group, the sensitivity and specificity for CRP were found 82%, 93%, respectively. The increasing specificity of CRP suggests that fetal distress affects the performance of the test.

PCT level does not increase during viral infections unlike CRP. Furthermore, it rises earlier than CRP during bacterial infections. Therefore, PCT considered to have a higher sensitivity in the early stage of sepsis. PCT levels may be increase in several condition such as hemodynamic instability, RDS, perinatal asphyxia and intracranial hemorrhage. Additionally, a physiological fluctuation is observed in PCT levels in the first 48-96 h of birth [5,17,18,20,21].

In previous studies, the sensitivity and specificity for PCT has been reported to 48-100% and 35-97%, respectively. There are also studies comparing CRP and PCT in diagnosis and fallow-up of neonatal sepsis. There are conflicting results about their superiority to each other in diagnosis of neonatal sepsis in different studies [7,17,22-28].

In our study, when all healthy neonates that with and without fetal distress is considered as a control group, a PCT value of 1.37 ng/ml was established as a cut-off value with 64% sensitivity and 49% specificity. When neonates without fetal distress is considered as a control group, the sensitivity and specificity for PCT were found 71% and 47%, respectively. This result showed that the sensitivity of PCT has been affected fetal distress.

Initial PCT levels of 18 patients (62%) in EOS group is founded higher than cut off value. Similarly, PCT levels were higher than cut off value in 16 healthy neonates (59%) with fetal distress and in 14 healthy neonates (43%) without fetal distress. The mean PCT values for all groups were found higher than reference value that has been reported as 0.5 ng/ml [7,8,18]. It was considered to be related with physiological increase, so we suggest that reference value isn't useful in EOS.

When the all neonates were evaluated, AUC for CRP and PCT were found 0.85 and 0.53, respectively. Additionally, their AUC were found 0.88 and 0.58, respectively, when neonates without fetal distress referred as control group. These results showed that PCT has significantly lower AUC compared with CRP.

Consequently, we found that PCT and CRP levels are affected by fetal distress as well as physiological increase. However, we found that their effects was greater on the PCT levels in 2-3 days after birth, so the reliability of PCT has been reduced. Therefore, we suggest that PCT may not be used as a reliable and accurate marker for both diagnosis and follow-up of EOS. However, to increase the accuracy, CRP and PCT may be used in combination for diagnosis of EOS.

Conflict of Interest: There is no conflict of interest.

REFERENCES

1. Zaidi AKM, Darmstadt GL, Stoll BJ. Neonatal İnfections: A global perspection. In: Wilson CB, Nizet V, Maldonado Y, Remington JS, Klein JO, eds. Remington and Klein's Infectious diseases of the fetus and newborn. 7th ed. Philadelphia: Elsevier Saunders, 2011:25-29.
2. 2- Polin RA, Parravicini E, Regan JA, Taeusch HW. Bacterial sepsis and meningitis. In: Gleason CA, Ballard RA, Taeusch HW, eds. Avery's diseases of the newborn. 8th ed. Philadelphia: Elsevier Saunders, 2005:551-68.
3. Stronati M, Bollani L, Maragliano R, et al. Neonatal Sepsis: New preventive strategies. Minerva Pediatr. 2013;65: 103-10.
4. Cetinkaya M, Ozkan H, Koksal N, Celebi S. Comparison of serum amilod A concentrations with those of C-reactive protein and procalsitonin in diagnosis and fallow-up of neonatal sepsis in premature infants. J Perinatol. 2009;29: 225-31.
5. Shah BA, Padbury JF. Neonatal sepsis: An old problem with new insights. Virulence. 2014; 5: 170-8.
6. Weinberg GA, D'angio CT. Laboratory aids for diagnosis of neonatal sepsis. In: Wilson CB, Nizet V, Maldonado Y, Remington JS, Klein JO, eds. Remington and Klein's Infectious diseases of the fetus and newborn. 7th ed. Philadelphia: Elsevier Saunders, 2011:1132-43.
7. Koksal N, Harmancı R, Cetinkaya M, Hacımustafaoglu M. Role of procalcitonin and CRP in diagnosis and follow-up of neonatal sepsis. Turk J Pediatr. 2007;49:21-9.
8. Hedegaard SS, Wisborg K, Hvas A. Diagnostic utility of biomarkers for neonatal sepsis - a systematic review. Infect Dis. 2015;47: 117-24.
9. Standage SW, Wong HR. Biomarkers for pediatric sepsis and septic shock. Expert Rev Anti Infect Ther. 2011;9: 71-9.
10. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003; 111:1805-12.
11. 11-Machado J, Soave DF, Silva MV, et al. Neonatal sepsis and inflammatory mediators. Mediators

Inflamm. 2014; Available at: http://dx.doi.org/10.1155/2014/269681

12. Khazardoost S, Hantoushzadeh S, Khooshideh M, Borna M. Risk factors for meconium aspiration in meconium stained amniotic fluid. J Obstet Gynecol. 2007;27: 577-9.
13. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2004;60:45-56.
14. Töllner U. Early diagnosis of septicemia in newborn clinical studies sepsis score. Eur J Pediatr. 1982;138: 331-7.
15. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. I.Reference values for neutrophilic cells. J Pediatr. 1979;95: 89-98.
16. Rodwell RL, Leslie AL, Tudehope DI. Early diagnosis ofneonatal sepsis using a hematological scoring system. J Pediatr. 1988;112: 761-7.
17. Delanghe JR, Speeckaert MM. Translational research and bimarkers in neonatal sepsis. Clin Chim Acta. 2015;451: 46-64.
18. Simonsen KA, Anderson-Berry AL, Delair SF, Daviesa HD. Early-Onset Neonatal Sepsis. Clin Microbiol Rev. 2014;27: 21-47.
19. Thermiany AS, Retayasa W, Kardana M, Lila IN. Diagnostic accuracy of septic markers for neonatal sepsis. Paediatr Indones. 2008;48: 299-305.
20. Sachse C, Dressler F, Henke E. Increased serum procalcitonin in newborn infants without infection. Clin Chem. 1998;44: 1343-4.
21. Turner D, Hammerman C, Rudensky B, et al. Procalcitonin in preterm infants during the first few days of life: introducing an age related nomogram. Arch Dis Child Fetal Neonatal Ed. 2006; 91(4): F283–F286
22. Chiesa C, Panero A, Rossi N, et al. Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. Clin Infect Dis. 1998;26: 664-72.
23. Vouloumanou EK, Plessa E, Karageorgopoulos DE, Mantadakis E, Falagas ME. Serum procalcitonin as a diagnostic marker for neonatal sepsis: a systematic review and meta-analysis. Intensive Care Med. 2011;37: 747-62.
24. Park I H, Lee S H, Yu S T, Oh Y K. Serum procalcitonin as a diagnostic marker of neonatal sepsis. Korean J Pediatr. 2014;57: 451-6.
25. Topuz S, Ovalı F. Comparison of C-Reactive Protein and Procalcitonin In The Diagnosis of Neonatal Sepsis. Nobel Med. 2012;8: 72-6.
26. Aygun C, Oran O, Portakal O. Procalcitonin: levels in newborns and as an indicator in the diagnosis of neonatal sepsis. Cocuk Sagligi Hast Derg. 2003;46: 83-9.
27. Yıldız C, Yıldız H, Kavuncuoglu S, Siraneci R. Procalcitonin levels in the diagnosis of early neonatal sepsis. Cocuk Sagligi Hast Derg. 2003;46: 90-7.
28. Altunhan H, Annagur A, Ors R, Mehmetoglu I. Procalcitonin measurement at 24 hours of age may be helpful in the prompt diagnosis of early-onset neonatal sepsis. Int J Infect Dis. 2011;15: e854–e858.