Original Article

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Evaluation of Diagnostic Value of Procalcitonin as a Marker of Neonatal Bacterial Infections

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Abstract

Objective: This study tried to assess sensitivity, specificity, positive and negative predictive value of procalcitonin for diagnosis of neonatal bacterial infections.

Methods: This prospective cross sectional study was carried out during an 18-month period in NICU and neonatal wards of Besat Hospital in Hamedan province, Iran. 39 symptomatic infants with clinical and laboratory findings in favor of bacterial infection with a positive blood, CSF, and/or supra pubic urine culture entered the study; 32 newborns without any bacterial infection served as control group. Quantitative procalcitonin level ≥0.5 ng/ml was accepted as pathological. Finally sensitivity, specificity, positive (PPV) and negative predictive value (NPV) were calculated for procalcitonin test.

Findings: 20 blood cultures, 17 urine cultures and 8 CSF cultures were positive. Sensitivity, specificity, PPV and NPV for procalcitonin test was 76.9%, 100%, 100% and 78% respectively. Diagnostic value of procalcitonin test in accordance with blood culture for mentioned items was 85%, 100%, 100% and 91.4% respectively. Its diagnostic value according to urine culture was: sensitivity 70.6%, specificity 100%, PPV 100% and NPV 86.4%, and according to CSF culture was: sensitivity 75%, specificity 100%, PPV 100% and NPV 94.1% respectively.

Conclusion: The results show that the procalcitonin test has high sensitivity, specificity, PPV and NPV for diagnosis of neonatal infections.

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Key Words: Infection; Newborn; Procalcitonin; Sensitivity; Specificity; Predictive Value of Tests

Introduction

Early diagnosis of neonatal infections and appropriate treatment lead to decrease of mortality and morbidity in affected newborns. Clinical manifestation of sepsis in newborns is usually nonspecific and it also can be observed in other diseases and conditions. Positive blood culture is the most important and reliable test in neonatal sepsis, but it may be positive due to contamination. Furthermore it may be under-diagnosed, if the obtained blood volume is too small (less than 0.5 ml)[1,2]. Other suitable tests for confirmation of bacterial infections in newborns are body fluids culture, leukocyte count, acute phase proteins (CRP, Haptoglobin–Fibrinogen)

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and procalcitonin (PCT) measurement[3-20]. PCT is precursor of calcitonin, it does not have hormonal effect. Recent studies reveal increased level of PCT in early phase of bacterial infections that decline after appropriate antibiotic therapy[4-20,22].

Neonatal sepsis and bacterial infections are one of the most important health problems in the world. Since the symptoms and signs of bacterial infections are nonspecific and have high mortality rate, early suspicion and treatment before confirmed blood culture is of great importance[1-5]. CRP as an inflammatory marker is not reliable in distinction between the systemic inflammatory response and sepsis[4,6].

Early and correct diagnosis of neonatal sepsis is a major national health criterion in diminishing neonatal death. Early manifestations of sepsis and other diseases in neonates are similar, therefore, delayed blood culture results or negative cultures, make sepsis diagnosis very difficult[7-11]. Since the clinical signs and symptoms of sepsis, urinary tract infection and meningitis in neonates are non-specific and associated with high morbidity and mortality, early suspicion and treatment before blood culture confirmation of it is crucial[8-12].

Based on recent literature, PCT is a reliable test for diagnosis of meningitis, bacterial infection and sepsis in newborns[3-14,20,22].

This study was designed for evaluation of sensitivity, specificity, PPV and NPV of procalcitonin test for diagnosis of sepsis, meningitis and urinary tract infection in newborns.

Subjects and Methods

This prospective cross sectional study was carried out during an 18-month period from April 2009 to September 2010 in the NICU and neonatal wards of Besat Hospital in Hamadan province, Iran. The research protocol was approved by Ethics Committee of Hamadan University of Medical Sciences.

Inclusion criteria were newborns with clinical and laboratory findings in favor of bacterial infection (before antibiotic therapy) and a positive blood, CSF, and/or urine culture. Clinical criteria in favor of bacterial infection consisted of hypothermia or fever, lethargy, convulsion, poor feeding, abdominal distension, organomegaly, apnea, tachypnea, cyanosis, respiratory distress, brady- or tachycardia.

Laboratory criteria in favor of bacterial infection were luekocytosis (WBC >25000/mm^3), leuko-penia (WBC <5000/mm^3), thrombocytopenia (PLT <150000/mm^3) and positive quantitative CRP.

Newborns with antibiotic therapy before starting the study, expired infants during study, exchange transfusion due to hyperbilirubinemia, direct or hemolytic hyprbilirubinemia were excluded from the study.

The case group consisted of 39 hospitalized neonates with at least three clinical signs of infection, at least one laboratory finding consistent with infection and a positive culture of body fluids (blood, supra pubic urine, CSF).

The control group consisted of 32 healthy newborns with indirect, non hemolytic jaundice without clinical and laboratory findings in favor of infection, who were treated with phototherapy.

An informed written parental consent was obtained according to Ethics Committee regulations.

Body weight, sex and age of all newborns were recorded. Blood was collected for complete blood count (CBC), platelet count, CRP, blood culture and PCT. CSF analysis and culture as well as urinalysis and urine culture were also performed. The urine was obtained by supra pubic puncture. In control group, after confirmation of indirect, non hemolytic hyperbilirubinemia, PCT ttest was done with a second blood specimen, in addition for blood and urine culture.

Serum PCT level was measured using quantittative immuno-luminometry method by lumitest kit (Brahms Diagnostic, Berlin, Germany). A PCT level of ≥0.5 ng/ml was accepted as pathological. PCT level 0.5-2 ng/ml, 2-10 ng/ml and >10 ng/ml was considered as weakly positive, positive, and strongly positive, respectively.

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A minimum sample size of 71 infants was required in order to achieve the lowest acceptable sensitivity (75%) and specificity (72%).

PLR (confirmed positive likelihood ratio)=1.5; α=0.05; sensitivity=75%[10]; Specifity=72% [10]

Finally, we calculated sensitivity, specificity, positive and negative predictive values for PCT test.

Findings

During the study period, 39 symptomatic infants involving bacterial infection with clinical and laboratory findings, including a positive blood, CSF, and/or supra pubic urine culture and 32 newborns without any bacterial infection entered the study. In case group 17 (43.6%) were females and 22 (54.3%) were males, whereas in control group 14 (42.8%) were females and 18 (56.2%) males.

The majority of newborns in case group (76.9% or 30 out of 39) were term and remaining was preterm. In control group (81.3% or 26 out of 32) were term, 5 (15.6%) were preterm and one newborn (3.1%) was post term.

In case group 10.3% (4 out of 39) had body weight less than 2500 gr, 28 (71.8%) newborns weighed between 2500-4000 gr, and remaining were heavier than 4000 gr. In control group 8.88% (6 out of 32) were less than 2500gr, 19 (59.4%) newborns weighed between 2500-4000 gr and remaining had a weight more than 4000 gr.

In case group 20 newborns had positive blood culture, 17 cases had positive supra pubic urine culture and 8 cases had positive CSF culture. The statistical analysis showed relatively high diagnostic value of PCT test. Its sensitivity was 76.9%, specificity 100%, positive predictive value (PPV) 100% and negative predictive value (NPV) 78%. Diagnostic value of PCT test according to blood culture, urine culture and CSF culture was shown in Table 1.

Discussion

Neonatal bacterial infection is one of the most important health problems in the world. Since the symptoms and signs of neonatal bacterial infections are nonspecific and have high mortality rate, early suspicion and treatment before positive culture is of great importance[1-5]. CRP as an inflammatory marker is not reliable in distinction between the systemic inflammatory response and bacterial infections[4-6].

Procalcitonin (PCT) is precursor of calcitonin, produced in C cells of thyroid, it is overproduced in the process of sepsis, meningitis, pneumonia and urinary tract infection (UTI)[7-10]. It is also secreted from monocytes and tissue macrophages in severe bacterial infections[11-13]. Recent studies proposed PCT for early diagnosis of bacterial infections[6-14,20-22]. There are also contrary reports in this field[21].

We programmed this study for evaluating serum PCT in sepsis, UTI and meningitis in newborns. The results revealed overtly elevated levels of PCT in these conditions. Previous studies also showed increased levels of PCT in confirmed

Table 1: Determination of sensitivity and specificity of PCT test according to clinical diagnosis, positive blood, urine or CSF culture in neonatal bacterial infection

Group		PCT test +	PCT test -	Sensitivity	Specificity	PPV	NPV
Bacterial Infected (%)	Positive (n=39)	30 (76.9)	9 (23.1)	76.9%	100%	100%	78%
	Negative (n=32)	0	32 (100)				
Blood Culture	Positive (n=20)	17 (85)	3 (15)	85%	100%	100%	91.4%
	Negative (n=32)	0	32 (100)				
Urine Culture	Positive (n=17)	12 (70.6)	5 (29.4)	70.6%	100%	100%	86.4%
	Negative (n=32)	0	32 (100)				
CSF Culture	Positive (n=8)	6 (75)	2 (25)	75%	100%	100%	94.1%
	Negative (n=32)	0	32 (100)				

PCT: procalcitonin / CSF: Cerebro-Spinal Fluid / PPV: Positive Predictive Value / NPV: Negative Predictive Value

sepsis conditions[6-14,15-20].

The present study confirmed relatively high diagnostic value of PCT test in neonatal bacterial infections. Based on study results, sensitivity of PCT test is 76.9%, its specificity 100%, positive predictive value 100% and negative predictive value 78%, these findings are compatible with similar studies[16-20].

In a study, Koksal et al showed advantage of PCT to CRP in early diagnosis, severity of disease and response to therapy in sepsis. In the mentioned study, PCT level was high in majority of patients before therapy. It is similar to our findings[19].

Carlo et al confirmed high sensitivity of PCT in sepsis, meningitis and UTI[10]; similar results are reported by Viallon et al in 50 newborns with bacterial meningitis[11].

In another study Kowezymksi and Piotrowski, evaluated 48 newborns with nosocomial sepsis for inflammatory parameters. They repeated determination of PCT and CRP serum levels after 24 hours. At the beginning of gram negative sepsis, 14 out of 17 neonates had increased PCT and CRP, whereas at the beginning of gram positive sepsis, only 18 out of 31 cases of positive blood culture had increased CRP, but 28 out of 31 had increased PCT level, it was statistically meaningful[20].

Lopez confirmed the benefit of PCT as a marker for diagnosis of nosocomial sepsis in 13 neonatology wards in 13 acute care educational hospitals in Spain during an annual study program. They reported medium reliability of PCT test in finding of nosocomial sepsis[21].

The present study emphasized diagnostic value of PCT according to blood, CSF and urine cluture results. These findings are in accordance with similar studies[16,18,20].

Based on the results of Zahedpasha et al, PCT level was high in newborns with positive blood culture and it decreased after appropriate antibiotic therapy. On the other hand, in Zahedpasha study other screening tests of sepsis were negative in culture positive cases, whereas PCT level was high. These findings support benefit of PCT in early diagnosis of neonatal sepsis[22].

In the present study, in contrast to Zahedpasha et al, other screening tests for diagnosis of sepsis, meningitis and UTI were positive.

One of the limitations of the present study was selection of icteric neonates as control group. For this reason we propose another randomized double-blinded study for assessment of diagnostic value of procalcitonin as a marker of neonatal bacterial infections. Another limitation of our study was the shortage of culture positive neonates as gold standard for sepsis to determine the sensitivity and specificity. For this reason we propose another study and evaluation the PCT level in relation to the class of sepsis before and after treatment.

Conclusion

Based on the results of the present study the PCT level was high (>2 ng/ml) in newborns with positive blood, urine or CSF culture. The result confirmed high sensitivity, specificity, PPV and NPV for diagnosis of neonatal infections. We recommend antibiotic therapy in newborns suspect to bacterial infections based on clinical features and PCT test results.

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Conflict of Interest: None

References

1. Afroza S. Neonatal sepsis - a global problem: an overview. *Mymensingh Med J* 2006; 15(1):108-14.
2. Chan YL, Tseng CP, Tsay PK, et al. Procalcitonin as a marker of bacterial infection in the emergency

department: an observational study. *Crit Care* 2004; 8(1):R12-20.

3. Maruna P, Nedelníková K, Gürlich R. Physiology and genetics of procalcitonin. *Physiol Res* 2000; 49 (Suppl 1):S57-61.
4. Müller B, Becker KL, Schächinger et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med* 2000; 28(4):977-83.
5. Lacour AG, Gervaix A, Zamora SA, et al. Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs. *Eur J Pediatr* 2001; 160(2):95-100.
6. Enguix A, Rey C, Concha A, et al. Comparison of procalcitonin with C-reactive protein and serum amyloid for the early diagnosis of bacterial sepsis in critically ill neonates and children. *Intensive Care Med* 2001; 27(1):211-5.
7. Athhan F, Akagunduz B, Genel F, et al. Procalcitonin a marker of neonatal sepsis, *J Trop Pediatr* 2002; 48: 10-4 .
8. Simon L, Gauvina F, Devendra K, et al. Serum Procalcitonin as a marker of bacterial infection in newborn, a systematic review and meta-analysis. *J Clin Infec Dis* 2004; 39:206-17.
9. Koksal N, Harmancı R, Çetinkaya M, Hacımustafaoglu M. Role of procalcitonin and CRP in diagnosis and follow-up of neonatal sepsis. *Turk J Pediatr* 2007; 49(1): 21-9.
10. Carol ED, Thomason AP, Hart CA. Procalcitonin as a marker of sepsis. *Int J Antimicrob Agents* 2002; 20(1):1-9.
11. Viallon A, Guyomarc'h P, Guyomarc'h S, et al. Decrease in serum procalcitonin level over time during treatment of acute bacterial meningitis. *Crit Care* 2005; 9(4):R344-50.
12. Perez Solis D, Lopez Sastre JB, Coto Cotallo GD, et al. Procalcitonin for the diagnosis of bacterial neonatal infections of vertical transmission. *An Pediatr (Barc)* 2006; 64(4):341-8.
13. Cooper P, Perovic O, Ballot D, Galpin J. Serum procalcitonin as an early marker of neonatal sepsis. *S Afr Med J* 2004; 94(10):851-4.
14. Czyzewska M, Lachowska M, Gajewska E. Evaluation of diagnostic value of procalcitonin (PCT) as a marker of infection in newborns, *Przegl Lek* 2002; 59(Suppl 1):46-9.
15. Andrejaitiene J. The diagnostic value of procalcitonin in severe sepsis. *Medicina (Kaunas)* 2006; 42(1):69-78.
16. Pérez Solís D, Roqués Serradilla V, Fernández Colomer B, et al. Evaluation of procalcitonin for diagnosis of neonatal sepsis, *BMC Pediatr* 2007;6: 16.
17. Reinhart K, Karzai W, Meisner M. Procalcitonin - a new marker of the systemic inflammatory response to infections. Intensive Care Med. 2000;26(9):1193-200.
18. Koskenvuo MM, Irjala K, Kinnala A, et al. Value of monitoring serum procalcitonin in neonates at risk infection. *Eur J Clin Microb Infect Dis* 2003; 22(6):377-8.
19. Koksal N, Harmanci R, Getinkaya M, et al. Role of procalcitonin and CRP in diagnosis and follow up of neonatal sepsis. *Turk J Pediatr* 2007;49(1):21-9.
20. Kawezymksi P, Piotrowski A. Procalcitonin and C-reactive protein as a marker of neonatal sepsis. *Cinekol Pol* 2004;75(6):439-44.
21. Lopez Sastre JB, Perez Solis D, Roques Serradilla V, et al. Procalcitonin is not sufficiently reliable to be the sole marker of neonatal sepsis of nosocomial origin. *BMC Pediatr* 2006; 6:16.
22. Zahedpasha Y, Ahmadpour M, Hajiahmadi M, et al. Procalcitonin as a marker of neonatal sepsis. *Iran J Pediatr* 2009;19(2):117-22.