Caspian Journal of Pediatrics
Non-communicable Pediatric Diseases Research Center
e-ISSN: 2383-3106
Babol University of Medical Sciences

Umbilical cord serum procalcitonin, as an early diagnostic marker of early neonatal sepsis

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Article Info

Article type:
Research Article

Received: 10 Jan 2021
Revised: 26 Feb 2021
Accepted: 3 March 2021

Keywords:
Neonatal Sepsis,
Procalcitonin,
Umbilical Cord

ABSTRACT

Background and Objective: The prognosis of early neonatal sepsis is significantly associated with rapid diagnosis and appropriate antibiotic therapy. Since blood culture has been reported positive in less than 16% of neonatal sepsis cases, various biochemical markers have been evaluated. This study was performed to evaluate the umbilical cord blood procalcitonin (PCT) as an early diagnostic marker of early neonatal sepsis.

Methods: This cross-sectional study included 100 neonates in two groups of case and control. The case group consisted of three separate groups, including proven, suspected and clinical sepsis groups. The PCT level of umbilical cord blood was measured by immunoluminoassay method, and PCT 0.5-2ng/ml, 2-10 ng/ml and >10ng/ml were considered weakly positive, positive and strongly positive, respectively. Sepsis screening tests and a culture taken from blood or other sterile fluids were studied in the case group.

Findings: The PCT mean was 1.39±1.52 and 0.17±0.05ng/ml in the case (sepsis) and control groups, respectively. Finally, the PCT level was significantly higher in all cases in the proven sepsis group than in other sepsis groups.

Conclusion: The result of this study showed that the mean value of PCT level in umbilical cord blood was higher in the sepsis group, and it was higher in the proven sepsis group than in the other two groups of sepsis.

Cite this article: Akbarian-rad Z, Ehsani Sh, Hajiahmadi M, Haghshenas-Mojaveri M. Umbilical Cord serum Procalcitonin, an early diagnostic marker of early neonatal sepsis. *Caspian J Pediatrs* March 2021; 7(1): 502-8.

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Publisher: Babol University of Medical Sciences

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[Downloaded from caspianjp.ir on 2025-08-31]

[DOI: 10.22088/CJP.BUMS.7.1.509]

Introduction

Sepsis is a critical clinical condition caused by bacterial infections and impairs the function of vital organs [1]. This condition is considered to be one of the major life-threatening causes during infancy and is associated with high mortality (28-50%) [2]. Thus, a rapid diagnosis and proper treatment before confirmation of diagnosis with cultures are needed [2]. Since positive blood culture is seen in only <16% of neonates with sepsis, [3] a rapid diagnosis of sepsis is considered a daily challenge in a neonatal intensive care unit (NICU). To do so, several biochemical markers have been proposed. Procalcitonin (PCT) is a calcitonin pheromone that is naturally produced by C-Cells of the thyroid gland and is a peptide with 116 amino acids that has no known hormonal activities [4]. The PCT serum level is increased after exposure to endotoxin bacteria, its half-life is 25-30 hours and the gestational age does not affect its serum level [5]. PCT is the most reliable biochemical parameter in distinguishing bacterial infections from viral and prevents the unnecessary consumption of antibiotics in viral infections [6, 7].

Moreover, this marker is secreted from the thyroid cells in the physiological conditions of healthy people but its secretion increases under sepsis conditions, meningitis, urinary tract infection and pneumonia [8-10]. Therefore, this marker also stems from monocytes and macrophages of various tissues under conditions of infection or severe bacterial sepsis [11, 12]. Different opinions have been formed concerning the diagnostic value of the umbilical cord PCT in the early diagnosis of neonatal septicemia.

However, several studies have shown that the PCT as a useful marker has been suggested in some umbilical cords for early detection of neonatal sepsis [13-17], contradictory results have been achieved in other studies. In addition, it has been stated that the neonatal umbilical cord PCT has a limited diagnostic value [18, 19]. The current study was designed and performed to evaluate an umbilical cord blood PCT as an early diagnostic marker of early neonatal sepsis.

Methods

This cross-sectional study was conducted in the NICU of Ayatollah Rouhani Hospital in Babol, North of Iran from September 2016 to June 2017. This hospital is a referral center for high-risk mothers and neonates which provide health services to a significant population of Mazandaran, especially the West of Mazandaran.

Inclusion criteria included infants admitted to the NICU during the first 3 days of life with symptoms and findings similar to sepsis and with gestational age <34 weeks or weight <2500 grams. Maternal factors also predict pre-term neonatal infection (fever during childbirth, symptoms of chorioamnionitis, premature rupture of membrane and prolonged labor).

Exclusion criteria were neonates with asphyxia at birth, meconium aspiration syndrome, childbirth trauma, congenital anomalies, positive clinical and laboratory results for inherited metabolic diseases as well as heart diseases.

The sample size for each group was 50 neonates considering the PCT difference in the two groups as one unit and dispersion in each group was 4 and 0.04 $(0.2)^2$, respectively. Though 95% confidence and 80% test power were registered, a total of 100 neonates were studied.

Two-milliliter umbilical cord blood samples were taken by a 2 cc syringe (Supa, made in Iran) from all the neonates born in the maternity hospital or operating room of Ayatollah Rouhani Hospital during the project, and then the serum was separated and frozen at -80 ° C in the laboratory of Ayatollah Rouhani Hospital. Then, 50 neonates who were not hospitalized during the first month after birth in NICU were included in the study as the control group and 50 neonates who had symptoms of sepsis during the first 7 days after birth or neonates who were hospitalized in NICU were entered into the study as the case group. Furthermore, newborns who were hospitalized in NICU with clinical findings in favor of sepsis before starting antibiotics, sepsis workup (w/u) including complete cell blood count (CBC), blood culture, erythrocyte sedimentation rate (ESR), C-reactive

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protein (CRP), urine analysis and culture (U/A, U/C), Chest X-ray (CXR) and cerebral spinal fluid (CSF) analysis was performed. Then, CRP, CBC and blood culture were repeated on the fifth day and the PCT level of the umbilical cord was quantitatively measured by the immunoluminoassay method with an ichroma PCT kit (Boditech Company made in England).

In this study, the PCT level ≥0.5 ng/ml was to be considered pathologic. The PCT levels about 0.5-2ng/ml, 2-10ng/ml and >10ng/ml were considered weakly positive, positive and strongly positive, respectively. The present study was approved by the Ethics Committee of the Babol University of Medical Sciences and the written consent forms were obtained from all parents of the ongoing study. Demographic data such as delivery methods, gestational age and birth weight of both groups were prepared using the checklist. Then, SPSS 18 was used to analyze the data. T-test and Chi-Square tests were also used for quantitative and qualitative variables. A value of P <0.05 was considered significant. Three separate groups for neonatal sepsis were proven sepsis (Clinical signs and symptoms plus a positive bacteria culture), suspected sepsis (Clinical signs and symptoms with negative bacteria culture but at least with 2 positive screening tests (ESR, CRP, CBC or CXR)) and clinical sepsis (clinical signs and symptoms with negative bacteria culture and negative screening test) [3], (table 1).

Results

Out of 100 neonates included in the study, 42 neonates (84%) in the case group and 21 newborns (42%) in the control group were born by cesarean delivery, 44 neonates (88%) in the case group and 10 infants (20%) in the control group were preterm and 26 neonates (52%) in the case group and 23 neonates (46%) in the control group were female. In both case and control groups, there was a significant relationship between sepsis with delivery method, gestational age and birth weight (p<0.05). However, there was no significant relationship between sepsis and neonate's gender (p=0.548). In addition, the present study indicated that the highest risk factors for early neonatal sepsis were premature birth and low birth weight (table 2).

The PCT mean was 1.39±1.52 and 0.17±0.05 ng/ml in the case and control groups, respectively, and this difference was statistically significant (p<0.001). Moreover, the PCT mean based on gender, gestational age and birth weight was significantly higher in the case group than in the control group (p<0.001).

Out of the 50 neonates in the case group, 7 (14%), 16 (32%) and 27 (54%) neonates were in the proven sepsis, suspected sepsis and clinical sepsis groups, respectively. Out of the 7 infants in the proven sepsis group, E-Coli and staph epidermis in 5 (71.4%) and 2 (28.6%) ones of blood culture had grown and in all cases, the CSF analysis was normal. Its cultivation was negative, and blood culture was negative in all neonates on the fifth day after treatment. The PCT level of the umbilical cord was >0.5ng/ml (100% sensitivity) in all positive blood culture cases (proven sepsis group). The PCT level in 14 out of 16 neonates was >0.5 ng/ml (87.5% sensitivity) in the suspected sepsis group. However, the PCT level in 10 out of 27 neonates was >0.5 ng/ml (37% sensitivity) in the clinical sepsis group, 85.7% of neonates had the PCT level between 2-10ng/ml in the proven sepsis group while no neonates had a PCT level > 2 (table 3) in the clinical sepsis group. Furthermore, there were significant correlations between gestational age and PCT with 3 groups of sepsis (p<0.001 and p=0.025, respectively).

A significant difference was seen in CRP level and white blood cell counts (WBC) in the three sepsis groups between the first and fifth days after treatment and birth so that they had a higher average on the first day (p<0.001). The WBC and CRP levels were significantly higher in the proven sepsis group than the other two groups of sepsis, averagely (p<0.001).

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Table 1. Criteria for the three sepsis groups

Groups		Criteria
I	**Proven Sepsis**	Clinical signs and symptoms plus a positive bacteria culture.
II	**Suspected Sepsis**	Clinical signs and symptoms with negative bacteria culture but at least with 2 positive screening tests (ESR, CRP, CBC, or CXR).
III	**Clinical Sepsis**	Clinical signs and symptoms with a negative bacteria culture and negative screening test.

Table 2. The mean of umbilical cord serum procalcitonin based on sex, delivery method, gestational age and birth weight

Variables		Case Group Procalcitonin (ng/ml) Mean ± SD	Control Group Procalcitonin (ng/ml) Mean ± SD	P-value
Sex	Girl	1.41±1.65	0.18±0.06	<0.001
	Boy	1.37±1.40	0.17±0.05	<0.001
Delivery method	Cesarean section	1.4±1.58	0.16±0.30	<0.001
	normal	1.35±1.28	0.18±0.07	<0.001
Gestational age	term	3.18±2.21	0.18±0.06	<0.001
	preterm	1.14±1.25	0.14±0.03	<0.001
Weight of birthday	Less than 2500 grams	1.11±1.23	-	-
	More than 2500 grams	2.26±2.03	0.17±0.05	<0.001

Table 3. The Frequency of three sepsis groups based on sex, delivery method, gestational age, birth weight, and procalcitonin

Variables		Proven Sepsis Number(%)	Suspected Sepsis Number(%)	Clinical Sepsis Number(%)	P-value
Sex	Girl	2(28.6)	8(50)	14(51.9)	0.537
	Boy	5(71.4)	8(50)	13(27)	
Delivery method	Cesarean section	6(85.7)	11(68.8)	25(92.6)	0.118
	normal	1(14.3)	5(31.3)	2(7.4)	
Gestational age	term	3(42.9)	1(6.2)	2(7.4)	0.025
	preterm	4(57.1)	15(93.8)	4(92.6)	
Birth weight (grams)	Less than 2500	4(57.1)	12(75)	4(57.1)	0.403
	More than 2500	3(42.9)	4(25)	3(42.9)	
procalcitonin (ng/ml)	<0.5	-	-	13(48.1)	<0.001
	0.5-2	1(14.3)	11(68.8)	14(51.9)	
	2-10	6(85.7)	5(31.3)	-	

Discussion

The current study demonstrated that the PCT level of umbilical cord blood in neonates with early sepsis was higher than that in the control group (without sepsis evidence). Meanwhile, the present study suggested that the PCT level of umbilical cord blood was significantly higher in the proven sepsis group than that in the other two groups of sepsis (suspected and clinical).

Oria De Salaguero et al. in 2017 found that the sensitivity of the umbilical cord PCT was 100% in diagnosing neonatal sepsis. In the ongoing study, the sensitivity of the umbilical cord PCT was 100% [20] in the proven sepsis group, too.

Chauhan et al. (2017) reported that the PCT markers, serum amyloid-A and CRP of the umbilical cord were useful in the early diagnosis of neonatal sepsis [15].

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Moreover, like the present study, Lopez et al. [21] and Perez et al. [22] stated that umbilical cord blood PCT could detect a significant proportion of neonates with sepsis.

Another study conducted by Altunhan et al. in 2011 represented that measuring umbilical cord blood PCT could be normal at birth, but its serum level measuring 24 hours after birth was more sensitive to CRP [23].

Pierrakos et al. reviewed various sepsis biomarkers and PCR. In their review article, it was mentioned that the PCT level was extensively used in the study of sepsis, but this level did not appear to be reliable in distinguishing between sepsis and other inflammatory conditions [18].

In the study of Santuz et al. [19] in 2008, it was reported that umbilical cord blood PCT could not be helpful in the diagnosis of sepsis, which was the same as those of Dessi et al. in 2014 [24].

Perhaps, the difference between the results of these studies and those of the current study was due to the sample size and different criteria to diagnose the sepsis so that in the last two studies, patients with severe sepsis leading to acute life-threatening conditions were considered as study samples. Similarly, in the study of Altunhan et al., the number of samples was different in the community of the neonates.

Another result of the present study was the sepsis prevalence in preterm neonates, this result was also found in Fesharaki et al.' study [25].

However, the present study represented that the mean CRP level and serum WBC increased in neonates with proven sepsis and significantly decreased on the fifth day after treatment, which is similar to the Pastor Pridio et al.'s results [26]. In addition, Jia et al. in 2017 suggested that the PCT marker with serum CRP could be useful in the early diagnosis of neonatal sepsis [27].

In the study of Zahedpasha et al. in 2009, it was revealed that the serum PCT of neonates was significantly higher in the proven sepsis group and decreased in all sepsis groups with treatment [28], which agreed with the result of the present study although the serum PCT was used in their study.

The limitation of this study was a low number of positive cultures.

In conclusion, the ongoing study showed that the PCT level of umbilical cord blood in neonates with early sepsis was higher than that in those without evidence of sepsis. Meanwhile, it had a higher sensitivity in the proven sepsis group so that in all cases of proven sepsis, its level increased and in most cases, its level was in the positive range. This finding supports the usefulness of the PCT level of the umbilical cord in the early diagnosis of early neonatal sepsis.

Acknowledgments

The authors would like to thank the Clinical Research Development Unit of Ayatollah Rouhani Hospital for its utmost cooperation in the realization of this study.

Ethical Code

This study was approved by the Ethics Committee of the Babol University of Medical Sciences (No. MUBABOL.HRI.REC.1395.47) and the written consent forms were obtained from all parents of the ongoing study.

Funding

The present study was financially supported by Babol University of Medical Sciences.

Conflicts of interest

The authors declare that there is no conflict of interest.

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