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Original Article

Significance of Serum Procalcitonin Level in the Early Diagnosis of Neonatal Sepsis

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ABSTRACT

Background: Sepsis in neonates presents itself with non-specific clinical features which makes early diagnosis difficult. However, procalcitonin (PCT) and other inflammatory markers have recently been considered as sensitive markers for the early detection of neonatal sepsis. Therefore, the present study aimed to determine the diagnostic value of PCT in the early detection of neonatal sepsis and compare it with C-reactive protein (CRP) and white blood cells count.

Methods: This case-control study was conducted on 40 neonates who were divided into two groups. The case or sepsis group consisted of 18 neonates with the clinical symptoms of sepsis and positive culture. On the other hand, the control group contained 22 healthy neonates with negative culture. Demographic characteristic of all the participants was recorded during the clinical follow-up. Moreover, blood samples were collected from each neonate for hematological analysis, blood culture, serum CRP measurement, and PCT analysis. Finally, all the collected data were statistically analyzed in SPSS software (version 17).

Results: Based on the findings, the mean value of the procalcitonin level was significantly higher in the sepsis group (866.60±480.51 pg/ml), compared with that of the control group (P<0.001). Moreover, the CRP was positive in 66.7% of sepsis patients and 22.7% of the control group (P=0.006). The procalcitonin level shows higher sensitivity (94%) than CRP (66%) with the same specificity but a higher positive and negative predictive value.

Conclusion: Procalcitonin level was elevated in neonates with sepsis in comparison to normal neonates and it is more sensitive than CRP. The PCT could be used as a routine test for the early diagnosis of neonatal sepsis which also leads to a reduction in the use of antibiotics.

Keywords: C-reactive protein, Diagnosis of sepsis, Neonatal sepsis, Procalcitonin

Introduction

Despite the advances and developments in the field of neonatology, bacterial sepsis in neonates remains one of the most important reasons for neonatal mortality and morbidity around the world, especially in developing countries (1). Given the high mortality rate of neonatal bacterial sepsis and its nonspecific signs and symptoms, its early detection and treatment before positive culture are of great importance (2).

A definitive diagnosis of neonatal sepsis can only be made by blood culture which takes at least 24-48 h with a high false negative rate. This leads to the misuse of antibiotics and the treatment of many newborn infants who are clinically suspected to have bacterial sepsis (3). This method is non-sensitive, non-specific, and usually associated with a substantial time delay (2, 3).

Inflammatory mediators, such as C-reactive protein (CRP), serum amyloid A, interleukins (IL-6, IL-8), and procalcitonin (PCT), were investigated as biomarkers of neonatal sepsis with various sensitivity and specificity. Despite the fact that these mediators were used in the diagnosis of bacterial neonatal sepsis, no single investigation has provided early and reliable detection of early bacterial infection and a combination of biomarkers was the best prediction used in the diagnosis (4).

A PCT is a peptide secreted in response to pro-

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inflammatory stimuli, especially bacteria-induced inflammatory mediators (5). The actual biological role of PCT is still largely unknown; however, recent experimental studies show that it may have a pathogenic role in sepsis (6).

The PCT has the highest diagnostic accuracy and its level rises rapidly (within 6–12 h) after an infectious insult with systemic consequences. Beyond its value for the diagnosis of sepsis, PCT has also proved to be useful in monitoring the course and severity of the systemic inflammatory response (7).

Many studies have investigated the potential roles of PCT in the diagnosis and management of local and systemic infections. There is some evidence that PCT is highly specific for bacterial infections, with levels rising at the onset of infection and falling rapidly as the infection resolves by treatment, compared to other markers (8).

Recently, PCT has been increasingly used for the early detection of infection in adult and pediatric populations due to its sensitivity, specificity, rapid response, and short half-life (9).

It is mainly used in hospitals and seems to have a more diagnostic value than other known biomarkers of inflammation (10). It has attracted attention as a potential means for guidance on antibiotic stewardship, decrease of inappropriate antimicrobial use, and associated resistance (11).

The present case-control study aimed to determine the diagnostic value of PCT in the early detection of neonatal sepsis and compare it with CRP and WBC count.

Methods

The present case-control study was conducted on the neonatal care unit of a secondary hospital in Iraq, from the first of April 2013 to the end of October 2013. In total, 60 neonates who were referred to the hospital due to suspicion of sepsis or hyperbilirubinemia were enrolled in the study. The demographic and clinical characteristics of the patients were recorded at the time of admission. Complete family and maternal histories were obtained and a thorough physical examination was performed by a trained senior house officer. Newborns with birth asphyxia, obvious or suspicious congenital anomalies, chromosomal anomalies, or any other dysmorphic features were excluded from the study.

Blood samples were obtained from each neonate prior to the commencement of the antibiotic treatment for the sepsis. Subsequently, the samples were sent for workup (complete blood count (CBC), differential leucocyte count, blood cultures, cerebrospinal fluid (CSF) analysis and culture, and CRP and procalcitonin analysis), and radiological test if needed.

The CBC and white blood cell (WBC) differentiation were performed using the Sysmex automated hematology analyzer (KX-21N, manufactured by KOBE-JAPAN). The blood cultures were collected by adding one ml of blood to a blood culture media (screw caps) which contained bacterial activator (brain-heart infusion) and incubated at 37 °C for 3-5 days by Lab incubator (Termaks, Sweden). Containers with positive growth were re-cultured on blood agar and Macconkey agar for 24 h. The isolated organisms were identified by standard bacteriological methods.

Serum CRP was measured by enzymatic heterogeneous sandwich immunoassay which is a latex agglutination test for qualitative and semi-quantitative determination of CRP in serum.

Serum Procalcitonin level was measured by immunoluminometric assay (ELIZA M6, USA). The PCT levels of > 250 pg/ml were considered positive. The CSF was collected from the patients and sent for cytology test, glucose level measurement, protein level measurement, and culture test.

According to the clinical signs and symptoms of sepsis and microbiological results of blood culture, 20 neonates with clinical suspicion of sepsis who had negative culture were excluded from the study. In total, 18 neonates with clinical signs and symptoms of sepsis and positive culture were enrolled in the study as the sepsis group. Moreover, 22 neonates who were healthy and visited the hospital for jaundice management or routine visit who had negative culture were allocated to the control group.

Informed consent was obtained from the parents of each patient. The study protocol was proved by the scientific and ethical committees of the hospital and the Faculty of Medicine at the University of Kufa, Najaf, Iraq.

Statistical data analysis

Continuous variables were represented as the mean±SD and categorical variables were represented as frequency and percentages. The data were statistically analyzed in the SPSS software (version 17) using the t-test for the mean difference and chi-square ($\chi 2$) and Mann-Whitney U tests for percentage differences and the odd ratio of categorical variables. Furthermore, sensitivity, specificity, positive predictive value

(PPV), and negative predictive value (NPV) were used for diagnostic efficiency. In addition, receiver operating characteristic (ROC) curves and the area under the curve were used to compare the sensitivity and specificity of the diagnostic procedures. A P-value of less than 0.05 was considered statistically significant.

Results

The mean age of the sepsis group was 10.88±11.5 days while that of the control group was 4.0±6.49 days (P=0.022). Moreover, 61% and 18% of the members in the sepsis and control groups were born through vaginal delivery, respectively (P=0.006). Other characteristics show no significant difference as shown in Table 1. Irritability, temperature instability, convulsion, bulging fontanelle, poor reflexes, pallor, distress, cyanosis, and the number of deaths were significantly more in the sepsis group, compared to the control group as shown in Table 1.

Procalcitonin level was significantly higher in the sepsis group (866.60±480.51 pg/ml) compared with the control group (P<0.001). Furthermore, the CRP was positive in 66.7% and 22.7% of the sepsis and control groups, respectively (P=0.006). While the white blood cell count and neutrophil percentage and lymphocyte percentage show no statistical difference as shown in (Table 2).

Table 1. Demographic characteristics and clinical features of the studied groups

Parameters	Sepsis, N=18 N(percent)	Control, N=22 N(percent)	OR (95% CI)	p-value
Age (day) (Mean ±SD)	10.88±11.5	4.0±6.49	-	0.022*
Birth wt (kg) (Mean ±SD)	2.60±0.61	2.93±0.56	-	0.88
Gender: Male	11(61)	11(50)	1.57(0.44 – 5.56)	0.488
Preterm	6(33)	4(18)	2.25(0.52 – 9.70)	0.277
Delivery: NVD	11(61)	4(18)	7.07(1.68 – 29.83)	0.006
CS	7(39)	18(82)		
lethargy	13 (72.2)	9 (40.9)	3.77(0.99 – 14.29)	0.051
Irritability	4 (22.2)	0 (0)	2.57(1.70 – 3.87)	0.021
Poor feeding	17 (94.4)	19 (86.4)	2.68(0.25 – 28.31)	0.4
Fever/cold	17 (94.4)	4 (18)	10.0(1.77 – 55.98)	0.004
Convulsion	6 (33.3)	0 (0)	2.83(1.80 – 4.47)	0.004
Bulging fontanelle	7 (38.9)	0 (0)	3.0(1.85 – 4.86)	0.001
Poor reflexes	6 (33.3)	2 (9.1)	5.0(0.87 – 28.86)	0.06
Pallor	5 (27.8)	0 (0)	2.69(175 – 4.14)	0.009
Jaundice	3 (16.7)	4 (18.2)	0.90(0.17 – 4.67)	0.9
Dyspnea	8 (44.4)	2 (9.1)	8.0(1,43 – 44.92)	0.011
Cyanosis	4 (22.2)	0 (0)	2.57(1.70 – 3.87)	0.021
Skin rash	1 (5.6)	0 (0)	2.29(1.6 – 3.28)	0.27
Death	3(16.7)	0(0)	2.47(1.67 – 3.64)	0.049

CS: cesarean section, NVD: normal vaginal delivery, N: number, OR: odd ratio, SD: standard deviation, *: independent sample t-test, other analysis used Mann-Whitney U test

Table 2. Hematology and blood tests of the study groups

Parameters	Sepsis (N=18) Mean± SD	Control (N=22) Mean± SD	p-value
Procalcitonin pg/ml	866.60±480.51	321.61±315.39	<0.001
WBC count×10^9/L	15.08±5.95	15.62±2.19	0.722
Neutrophils (percent)	55.67±15.06	61.17±9.77	0.192
Lymphocytes (percent)	31.86±14.07	31.17±8.31	0.855
CRP Positive, N(percent)	12 (66.7%)	5 (22.7%)	0.006*

CRP: C-reactive protein, N: number, SD: standard deviation, WBC: white blood cell, *: Mann-Whitney U test, others used independent sample t-test.

The procalcitonin level shows higher sensitivity (94%) than CRP (66%) with the same specificity but more positive and negative predictive values as shown in Table 3.

The PCT level in the sepsis group shows a significantly higher area under the curve in the ROC curve than CRP, WBC count, and differential count (P=0.038) as shown in Table 4 and Figure 1.

Table 3. Comparison of Validity tests of CRP and PCT with blood culture

Validity test	CRP	Procalcitonin
Sensitivity	66 %	94 %
Specificity	75 %	77 %
PPV	70 %	75 %
NPV	73 %	85 %

CRP: C-reactive protein, NPV: negative predictive value, PPV: positive predictive value

Table 4. Receiver operating characteristic test and area under the curve for the sepsis group

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	p value	95% Confidence Interval	
				Lower Bound	Upper Bound
PCT	0.884	0.054	0.000	0.778	0.990
CRP	0.280	0.084	0.018	0.116	0.44
WBC count	0.429	0.099	0.447	0.236	0.623
Neutrophils (percent)	0.578	0.092	0.399	0.399	0.758
Lymphocytes (percent)	0.562	0.096	0.511	0.375	0.750

CRP: C-reactive protein, PCT: procalcitonin, WBC: white blood cells

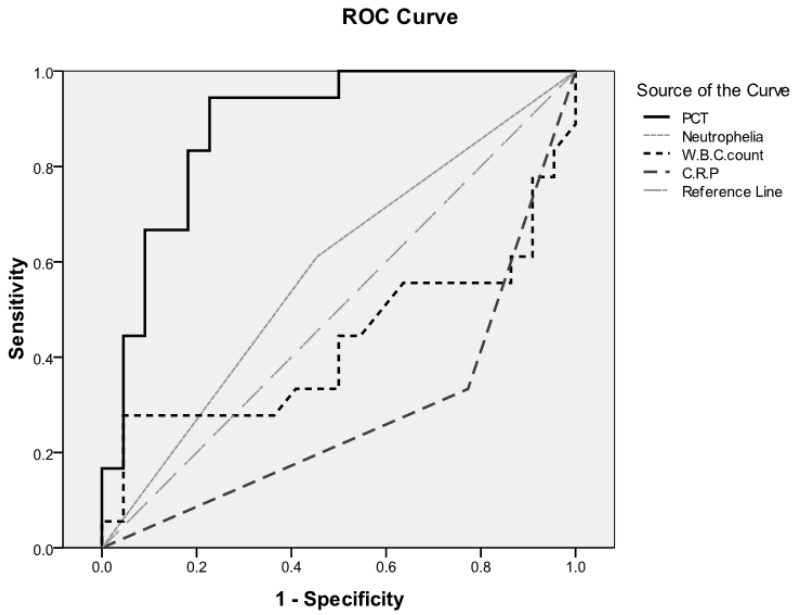

Figure 1. Receiver operating characteristic curve and area under the curve for the laboratory parameters of the sepsis group

Discussion

The CRP and PCT are only two examples of many mediators of infection which were investigated in severely ill neonates aiming to distinguish sepsis from noninfectious clinical presentation (12). Recently, the measurement of PCT and other biomarkers have been shown as a sensitive indicator for the rapid diagnosis and the outcome of neonatal sepsis (13, 14).

The present study investigated the serum level of PCT as an early diagnostic procedure for neonatal sepsis in comparison with CRP and WBC count and differential diagnosis in neonates with or without proven sepsis. The results revealed that the mean level of PCT in the culture-positive group was higher than that of the normal groups (P<0.001).

This finding was comparable with that of Minoo Adib et al. (15) and Zahedpasha et al. (16) who found that PCT levels were obviously increased in newborns with proven sepsis and the levels decreased rapidly after treatment by antibiotics. Moreover, many investigators had found that PCT is a promising indicator for the early diagnosis of neonatal sepsis (13, 17, 18). These studies revealed that PCT is 83-100% sensitive and 70-100% specific in the early diagnosis of neonatal bacterial sepsis (17-19). In the present study, PCT sensitivity and specificity, PPV, and NPV with a cut-off level of more than 250 pg/ml were 94%, 77%, 75%, 85%, respectively. PCT was significantly more than CRP and WBC count and differential diagnosis (P=0.038) with more area under the ROC curve. These results were in line with those of a study performed by Chin YL et al. (20) who found that the sensitivity and specificity of PCT were 69.5% and 64.5%, respectively. Moreover, according to the above-mentioned study, the sensitivity and specificity of CRP were 67.25% and 93.9%, respectively. Adib M et al. (15) also found that the sensitivity and specificity of PCT were 75% and 80% respectively, while those of CRP were 45% and 95%, respectively.

Earlier studies had shown that there were

higher PCT levels in all neonates with proven or clinically suspected various types of neonatal sepsis (21-25). In a recent research Koksal et al. found that serum PCT level was superior to serum CRP level regarding the early diagnosis of neonatal sepsis, prediction of the severity of the illness, and the evaluation of the response to antibiotic treatment (26). on the other hand, Sakha K. et al. (27) proved that the serum levels of CRP and PCT are statistically different in the sepsis group with the CRP sensitivity and specificity being more than those of PCT.

Recent studies have concluded that PCT is not a perfect marker but it is the best available means for making individualized treatment decisions. The aim of such decisions is to decrease the duration of the antibiotic course of treatment or withhold these antibiotics for non-life-threatening respiratory tract infections (28, 29) and differentiating bacterial from nonbacterial meningitis (30).

Afshari and Harbarth (31) in their study concluded that there was a need for further clinical studies to investigate the procalcitonin and other biomarkers and indicators of sepsis, which will hopefully improve the antibiotic stewardship strategies in intensive-care units.
The limitation of this study was its small scale and focus on one center. Moreover, the culture was falsely negative for clinically suspected sepsis and there was no other confirmatory procedure available to confirm sepsis.

Conclusion

Procalcitonin level was elevated in neonatal sepsis, compared to normal neonates which is more sensitive and specific than CRP. PCT as an adjuvant with clinical signs and symptoms could be used as a routine test for the early diagnosis of neonatal sepsis and reduction of the use of antibiotics and hospital costs.

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Conflicts of interest

The present study was not supported by any grant or fund. The authors declare that there was no conflict of interest in this study.

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