

Predictive values for procalcitonin in the diagnosis of neonatal sepsisAbdel Hakeem Abdel Mohsen¹, Bothina Ahmed Kamel²¹ MD, Assistant Professor, Department of Pediatrics, Faculty of Medicine, El Minya University, Minya, Egypt² MD, Lecturer, Departments of Biochemistry, Faculty of Medicine, El Minya University, Minya, Egypt**Type of article:** Original**Abstract**

Background: Early diagnosis of neonatal sepsis followed by appropriate treatment decreases mortality and morbidity in infants. The aim of this study is to assess the role of procalcitonin (PCT) as a marker in the early diagnosis of neonatal sepsis.

Methods: We present a cross sectional study where 35 neonates with early onset sepsis (admitted to the Neonatal Intensive Care Units at El-Minia Children University Hospital from August 2012 to August 2013) were included in the study. Another 35 healthy neonates with no clinical or biological data of infection were included as a control group. Subjects were subjected to a thorough history taking and routine laboratory investigations. Serum PCT and C-reactive protein (CRP) levels were determined by enzyme-linked immunosorbent assay (ELISA).

Results: Mean levels of PCT and CRP in neonates with sepsis were significantly higher than in the control group ($p=0.0001$). There was a moderate, but significant, positive correlation between PCT and C-reactive protein ($p=0.001$, $r=0.55$) and an insignificant correlation between procalcitonin and total leukocytic count among the neonates with sepsis ($p=0.2$, $r=0.2$). In addition, procalcitonin had high sensitivity, specificity, a high positive predictive value, and a high negative predictive value (80%, 85.7%, 84.8%, and 81.1% respectively). Procalcitonin showed higher sensitivity when compared to CRP.

Conclusion: Procalcitonin is a sensitive, independent, and useful biomarker in comparison to CRP in early diagnosis of neonatal sepsis.

Keywords: Procalcitonin, C-reactive protein, Neonatal sepsis

1. Introduction

Neonatal sepsis is the most common cause of morbidity and mortality in the neonatal period. The disease is classified into early- onset sepsis (<7 days of birth) and late-onset sepsis (>7 days) (1). Early diagnosis and treatment of sepsis are essential for neonates and infants since a delay in treatment may lead to neonatal death (2). The clinical picture of sepsis is variable in newborn infants and these findings may be associated with multiple conditions complicating the infection. Therefore, treatment should be started early and without delay in newborns that have findings of sepsis and continued until the final results of the blood culture are obtained (3). The results of blood culture may be negative despite bacterial infection. Therefore early diagnosis of neonatal sepsis is difficult, despite advanced bacteriologic techniques, so different investigative techniques were assessed for usefulness, either singly or in combination, for the early prediction of neonatal sepsis. Assessment of procalcitonin (PCT) level in serum may be helpful in rapid diagnosis of sepsis (4). In 1993, Assicot et al. observed that procalcitonin is produced in response to bacterial and fungal infections (5). PCT is the precursor of calcitonin and does not demonstrate hormonal activity. It is a 116 amino acid peptide with a molecular weight of 14.5k Da (6). PCT is synthesized in the C cells of the thyroid gland of healthy individuals. The level of procalcitonin in a healthy person is undetectably low. However, in severe bacterial, fungal, parasitic infections with systemic manifestations, a significant rise in procalcitonin levels is observed. In such a situation, PCT is produced by extra thyroid tissue (7, 8). After injection of small amount of bacterial endotoxins in healthy volunteers, PCT is detectable in the plasma two hours, increases

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rapidly at 6-8 hours, and reaches a plateau between 12 and 48 hours (9). PCT levels increase in severe infections and concentrations correlate to the patient's clinical condition and the severity of microbial invasion (10). C-reactive protein (CRP) is an acute-phase reactant protein, which is synthesized by the liver. It is a classical and sensitive marker of inflammation; however, it cannot be used to differentiate between bacterial and other infections. Also the increase of CRP level occurred after PCT. Several authors have opined that it is important to remain cautious with the interpretation of CRP levels in children with fever lasting less than 12 hours, because tests may remain negative despite the presence of sepsis (6). High levels of CRP may be observed in conditions other than sepsis, including perinatal asphyxia, respiratory distress syndrome, brain hemorrhage, meconium aspiration syndrome, and during the post-surgical period (11, 12). However, slight increases in PCT levels were found for localized bacterial infections, severe viral infections, and inflammatory reactions of noninfectious origin (13). The PCT levels increase before any observable rise in CRP concentrations (6). The PCT levels are significantly increased in bacterial and fungal infections when compared to viral infections and other inflammatory diseases. This makes PCT is a potential diagnostic variable for the diagnosis of bacterial infection (14). The present study is aimed at investigating the validity of establishing early diagnosis of neonatal sepsis via measurement of PCT versus CRP measurement.

2. Material and Methods

2.1. Study population

In this descriptive cross-sectional study, the study group consisted of 35 neonates with early onset sepsis admitted to the Neonatal Intensive Care Units (NICU) at El-Minia Children University Hospital from August 2012 to August 2013. Written consent was obtained from the families of all the investigated neonates.

2.2. Inclusion criteria

This study included any suspected case of neonatal sepsis with maternal risk factors for sepsis, e.g. prolonged labor, premature rupture of membrane (PROM) or prolonged PROM (>18 hours), maternal intrapartum fever, urinary tract infection (UTI), chorioamnionitis, and any clinical signs and symptoms of the newborn for sepsis: temperature instability, apnea, need for supplemental oxygen, need for ventilation, bradycardia, tachycardia, hypotension/hypoperfusion, feeding intolerance, abdominal distension, and necrotizing enterocolitis.

2.3. Exclusion criteria

The exclusion criteria for this study are as follows: administration of antibiotic therapy prior to admission, birth asphyxia, aspiration syndromes, laboratory finding suggestive of inborn errors of metabolism, and congenital anomalies. Another apparently healthy 35 neonates were cross matched with age and sex and used as a control group. Before initiation of antibiotic therapy in infants suspected of sepsis, blood samples were obtained by peripheral venous puncture and the samples for complete blood count, blood culture (1-2 ml), and PCT and CRP measurements (1-2 ml). Serum was separated from blood cells by centrifugation and stored in 2 plastic tubes at -20 °C for PCT and CRP measurements.

2.4. PCT measurement

PCT assays were completed using a commercial enzyme-linked immunosorbent assay kit. Readings of more than 1.1pg/ml are considered positive (Procalcitonin in Human EIA Kit, EK-031-30; Phoenix Pharmaceuticals, Inc., Belmont, CA, USA).

2.5. CRP measurement

Serum CRP concentration was determined by the standard nephelometric method. Levels more than 12 mg/dl is considered positive.

3. Results

In this study, 35 neonates with positive blood cultures and clinical sepsis (group 1) were enrolled as cases and 35 healthy neonates were enrolled as controls (group 2). Table 1 shows a higher incidence of sepsis among males compared to females. It also shows that neonates born by CS had a significant higher reading than neonates born vaginally ($p=0.04$). Neonates with sepsis had a significant higher total leukocytic count, bilirubin (total and direct) level than the control group ($p=0.001$). Also, CRP and PCT levels were significantly higher among group 1 than group 2 ($p=0.0001$) (Table 2). Regarding the sensitivity and specificity values, PCT had higher sensitivity, higher negative predictive value (NPV) than CRP, while CRP had higher specificity, higher Positive predictive value (PPV) in comparison to PCT (Table 3). Our findings showed that CRP had a significant moderate positive correlation with

PCT ($r=-0.55$, $p=0.001$). In addition, there was an insignificant correlation between PCT and total leukocytic count (TLC) among group I ($r=-0.20$, $p=0.2$).

Table 1. Demographic and clinical characteristics of the studied cases (n=35) and controls (n=35)

Characteristics		Group 1 (Cases)	Group 2 (Controls)	Chi-square	P
Gestational age	Full term	21 (60%)	25 (71.4%)	1.01	0.4
	Pre term	14 (40%)	10 (28.6%)		
Sex	Male	19 (54.3%)	13 (37.1%)	2.07	0.1
	Female	16 (45.7%)	22 (62.9%)		
Gestational weight	Range	750-3700	1400-3500	0.49	0.6
	Mean \pm SD	2575.1 \pm 842.5	2665.7 \pm 685.3		
Mode of delivery	Normal	15 (42.6%)	26 (74.3%)	7.12	0.04
	CS ^a	20 (57.4%)	9 (25.7%)		
Apgar	Score 1	6.29 \pm 2.3	8.1 \pm 1.3	0.5	0.18
	Score 5	7.8 \pm 1.57	9.13 \pm 0.8		
Blood culture	Positive	35(100%)	0	70.000	0.0001
	Negative	0	35 (100%)		

CS: caesarian section

Table 2. Comparison between neonates with sepsis and control neonates with regards to laboratory findings

Characters		Cases	Controls	t-test	P
Total leukocytic count (μ l)	Range	9.5-20.1	8-11	13.8	0.001
	Mean \pm SD	16.06 \pm 2.9	9.2 \pm 0.5		
Hb (g/dl)	Range	11.3-18.4	11-14	0.48	0.5
	Mean \pm SD	16.4 \pm 1.7	12.5 \pm 1.4		
Total bilirubin (mg/dl)	Range	7.6-20	2-8	8.68	0.001
	Mean \pm SD	12.5 \pm 4.1	5.6 \pm 2.3		
Direct bilirubin (mg/dl)	Range	1-2.3	0.5-1	2.71	0.001
	Mean \pm SD	1.03 \pm 0.6	0.7 \pm 0.3		
CRP	Range	52.5-151.1	5.6-11.6	10.22	0.0001
	Mean \pm SD	85.6 \pm 44.4	8.09 \pm 11.1		
Procalcitonin level (pg/ml)	Range	52.5-556.3	5.6-110.6	5.51	0.0001
	Mean \pm SD	185.6 \pm 144.4	48.09 \pm 31.1		

Hb: Hemoglobin level, CRP: C-reactive protein

Table 3. The sensitivity, the specificity, PPV, and NPV of PCT and CRP

	Cut-off value	Sensitivity	Specificity	PPV	NPV
CRP	12 mg/l	72.9%	100%	93.2%	69.7
Procalcitonin	1.1 pg/ml	80%	85.7%	84.4%	81.1%

CRP= C-reactive protein, PPV= Positive predictive value, NPV= Negative Predictive value

4. Discussion

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteraemia in the first month of life. This constellation of signs and symptoms is caused by micro-organisms or their toxic products in the blood (15). The diagnosis of neonatal sepsis is difficult due to the clinical signs of sepsis often overlapping with other non-infectious causes of systemic inflammation (16). There is no single reliable test for an early definitive diagnosis of neonatal sepsis and, therefore, there is a continuing search for a new marker to differentiate between sepsis and non-infectious conditions. PCT is a promising molecule for the diagnosis of neonatal sepsis (17). In this study the incidence of sepsis was more common in male (62%) than female (38%) infants, which is in agreement with the previous findings of Washburn et al. (18). This is due to the fact that male babies receive medical services at a higher rate than female babies in this region. Also, infection was found to be more common in low birth weight babies compared to babies of normal birth weight in studies reported from India and Bangladesh, which is in agreement with this study (19). As regard to mode of delivery, 57.4% of infants with

sepsis were delivered by caesarean section, compared to 42.6% cases that were delivered normally. This may be due to an increased number of high risk pregnancies admitted to the hospital, leading to increased number of caesarean section. This is similar to studies by Tuuli and Odibo (20) and Afsharpaiman et al. (21), who reported that neonates delivered via cesarean section had a higher chance of developing neonatal sepsis in comparison to neonates delivered via vaginal delivery. They demonstrated that cesarean section could be associated with several adverse neonatal events, including respiratory complications. This leads to higher rates of NICU admission and higher chances of developing newborn sepsis. Regarding laboratory data of neonates included in the study, there were significant higher levels of total leukocytic count in neonates with sepsis than in the control group ($p=0.001$). This finding was comparable with that of the studies by Basu S et al., (22) and Srinivasan and Harris (23). They concluded that TLC is useful to estimate the probability of sepsis. However, Laurent et al. (24) found that the total leukocytic count had little value in discriminating infection in neonates. In this study, CRP was significantly higher in neonates with sepsis ($p=0.0001$) (Table 2). These results were in agreement with Chiesa et al. (25), Naglaa et al. (26), and Hofer et al. (27). They found that CRP was the most common laboratory test, can be accurate for the diagnosis of neonatal sepsis, is easily measurable and more affordable. CRP can be conveniently used as a marker for the diagnosis of neonatal sepsis, especially with poor resources. However Whicher et al. (6) and Naher et al. (14) have reported that CRP is not necessarily diagnostic for sepsis as elevations may elevate due to the physiologic rise after birth or non-infection associated conditions. With regards to PCT concentration, the current study detected significantly higher levels of PCT in newborns with sepsis compared to the control group ($p=0.001$). This was in agreement with many studies by Koksall et al. (28), Zahedpasha et al. (29), and Sucilathangam et al. (30). Therefore, PCT may be helpful as an independent biomarker and appears to be an improved differentiating biomarker, as it helps differentiate bacterial infection from viral infection. In addition, it correlates well with the progression and severity of infection. For this reason, PCT may be used not only as a marker of infection, but, more importantly, as a reporter of the severity of infection. It has been reported that PCT had beneficial diagnostic value and its measurement is helpful in early diagnosis of neonatal sepsis. Also, Dimple et al. (31) found that PCT level increases rapidly with bacterial infection and is restored to normal more rapidly than CRP and, hence, can be used to guide antibiotic therapy. This study demonstrated that there were insignificant differences between the two studied groups with regard to correlations between PCT and gestational age, weight, and neonatal jaundice. However, there was a significant moderate positive correlation between PCT and CRP, ($r=-0.55$, $p=0.001$). This finding was consistent with that reported by some studies such as Vincent and Mercan (32), Lobo et al. (33), and Mamdouh et al. (34). They found significant correlation between PCT and CRP. In contrast, a study by Wang et al. (35) showed insignificant correlation between PCT and CRP. This study also found insignificant correlation between PCT and TLC among the neonates with sepsis ($r=-0.20$, $p > 0.05$). This finding was in agreement with that of waad Mahmood et al. (36), and Wang et al. (35).

This study showed that the sensitivity of PCT for the diagnosis of neonatal sepsis was 80%, the specificity was 85.7%, its PPV was 84.8%, and NPV was 81.1%. The sensitivity of CRP was 72.9%, the specificity was 100%, its PPV was 93.2%, and its NPV was 69.7%. These results found that PCT was more sensitive than CRP. The higher sensitivity of PCT, in comparison to CRP, was reported by Pavcnik-Arnol et al. (37), and Ivancevic et al. (38), which showed that PCT could be used as a prognostic marker for the diagnosis of sepsis. In contrast, a study by Jimenez et al. (39) reported higher sensitivity for CRP than PCT. Inconsistent with our results, the specificity of PCT was found to be lower than that of CRP in studies by Janota et al. (40), and Mamdouh et al. (34). They concluded that the lower specificity of PCT could be related to the multi-organ dysfunction of the neonates who did not have sepsis. On the other hand, a study by Vazzalwar et al. (41) showed that PCT has higher specificity than CRP. In this study, PPV of CRP was higher than that of PCT, while NPV of PCT was higher than that of CRP. This was in the agreement with Abdollahi et al (42). However, a study by Sakha et al. (43) reported that CRP had a higher NPV than PCT In neonates, an elevated PCT level may help in predicting septicemia; furthermore, low PCT levels were helpful in ruling out septicemia as a diagnosis. The good negative value found suggested that PCT can be tested rapidly and is highly discriminating means to rule out bacteraemia. Therefore, PCT assessment could help physicians limit the number of unnecessary prescriptions for antibiotics.

5. Conclusions

Procalcitonin level is significantly increased in all neonatal cases with sepsis and its level correlates to the severity of the condition. This finding supports the usefulness of PCT to establish an early diagnosis of neonatal sepsis. Also, the increase is more than that observed for CRP levels, and hence PCT is a more sensitive and useful biomarker for the diagnosis of neonatal sepsis. We recommend further studies in a large number of populations to confirm the role of PCT in the diagnosis of neonatal sepsis.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

Both authors contributed to this project and article equally. Both authors read and approved the final manuscript.

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