

## Procalcitonin as a marker of neonatal sepsis

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**Abstract:** *Introduction:* Neonatal sepsis is one of the commonest causes of neonatal mortality in the developing world. Procalcitonin (PCT) has emerged as the most studied and promising sepsis biomarker. *Objective:* To assess the role of procalcitonin (PCT) as a marker in the early diagnosis, treatment and follow-up of neonatal sepsis. *Methods:* Twenty five neonates with clinical (n=5), suspected (n=13) and proven sepsis (n=7) were evaluated. The PCT levels were measured by immunoluminoassay before and on day 5 of treatment. PTC levels of 0.5-2 ng/ml, 2.1-10 ng/ml and >10 ng/ml were considered as weakly positive, positive and strongly positive, respectively. *Findings:* The levels of PCT in proven sepsis group were higher than that in other groups. Strongly positive PCT level was seen in 2 cases of proven sepsis, 5 cases of suspected sepsis and in 1 case of clinical sepsis. PCT levels were dramatically decreased in three groups on day 5 of treatment. *Conclusion:* The results show that the serum procalcitonin levels seem to be significantly increased in proven sepsis and decrease dramatically in all types of sepsis after appropriate treatment.

**Keywords:** Neonatal sepsis, Procalcitonin, Marker, Infection, Infancy.

### Introduction

Neonatal sepsis is one of the major health problems throughout the world; every year an estimated 30 million newborns acquire infection and 1-2 millions of them die [1]. Since the clinical signs and symptoms of sepsis in neonates are non - specific and associated with high (28-50%) morbidity and mortality, early suspicion and treatment before blood culture confirmation of it is crucial [2]. An inflammatory marker such as C-reactive protein (CRP) does not reliably differentiate between the systemic inflammatory response and sepsis [2-3].

Procalcitonin (PCT), a precursor of calcitonin is a 116 amino acid protein secreted by the C cells of thyroid gland in normal situation but its levels may increase during septicemia, meningitis, pneumonia and urinary tract infection [3-4]. This marker also is produced by macrophage, and monocyte cells of various organs in severe bacterial infection and sepsis [5-6]. The results of recent studies suggest the usefulness of PCT for early diagnosis of neonatal sepsis [7-9], although other investigations have observed lack of accuracy for this marker [10-11]. Since a kit for quantization of PCT is available for rapid

quantitative measurement, we carried out this study to evaluate the serum level of PCT on neonatal sepsis in relation to our classification of neonatal sepsis.

### Material and Methods

This prospective study was conducted on neonates admitted for sepsis work up to newborn service and neonatal intensive care unit (NICU) at Al Ameen Medical college hospital, Bijapur, Karnataka, India. Sepsis work up including complete blood count (CBC), blood culture, erythrocyte sedimentation rate (ESR), CRP, urine analysis (UA), urine culture (UC), chest X-ray, cerebrospinal fluid (CSF) analysis and culture was performed in all neonates. Three distinct groups were defined; proven sepsis, suspected sepsis and clinical sepsis (table 1).

Exclusion criteria were administration of antibiotic therapy prior to admission, birth asphyxia, aspiration syndromes, laboratory finding suggestive of inborn error of metabolism and congenital anomalies. The sample size was calculated 25 neonates when considering confidence interval 95% power

80% and error in serum PCT estimation of 0.1 nanogram. Before starting the antimicrobial therapy, blood samples (sample 1) for complete blood count, CRP, ESR, PCT and culture were collected. This procedure was repeated at day 5 after treatment with antibiotics (sample 2). CSF, urine, tracheal and gastric aspirate cultures were obtained. Serum PCT level was measured using quantization immuno-luminometry method by lumitest kit (Brahms Diagnostic, Berlin, Germany).

respectively. The study protocol was approved by the ethical committee of hospital. Informed parental consent was obtained for all infants. We used SPSS version 15 for statistical analysis. Correlation between variables and statistical differences were analyzed using Fisher exact, ANOVA, Monte Carlo and Wilcoxon tests. P values of <0.05 were considered to be significant.

**Results**

Twenty five neonates were eligible for the study. These neonates are classified into three groups; proven sepsis (7 neonates), suspected sepsis (13 neonates) and clinical sepsis (5 neonates) according to the study protocol. The mean gestational age, birth weight and the sex of the patients in these three groups were similar (P-value 0.096). Early onset sepsis was confirmed in 16 (65.8%), late onset sepsis in 6 (23.7%) and nosocomial sepsis in 3 (10.5%) patients. Causative pathogens and site of involvement were as follows: CSF in one patient positive for Escherichia coli, blood culture in five patients positive for Staphylococcus, Escherichia coli and Klebsiella; urine in two neonates for Staphylococcus and Escherichia coli; and culture of the tip of chest tube was positive for Pseudomonas. Table 2 shows the results of sepsis screening tests including PCT in relation to three classified groups of patients.

**Table-1: Criteria employed for defining the sepsis score**

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

In this assay a PCT level of  $\geq 0.5$  ng/ml was accepted as pathological. PTC level 0.5-2 ng/ml, 2-10 ng/ml and >10 ng/ml considered as weakly positive, positive, and strongly positive,

**Table-2: Relation between elevated procalcitonin levels with normal sepsis screening tests**

Test	Clinical Sepsis N= 7	Suspected Sepsis N= 13	Proven Sepsis N= 5
Normal ESR	5	5	5
Normal CRP	4	5	3
Normal WBC count	6	6	5
Normal Chest X-ray	5	8	4
Elevated PCT levels	7	10	3

WBC: White Blood Cell Count; CRP: C Reactive protein; ESR: Erythrocyte sedimentation rate

**Table-3: Serum procalcitonin level (ng/ml) between groups before and after treatment**

Group	Clinical Sepsis		Suspected Sepsis		Proven Sepsis	
	Before	After	Before	After	Before	After
Negative(PCT<0.5ng/ml)	0	5	3	9	2	3
Weakly Positive (PCT 0.5-2ng/ml)	0	2	1	1	0	1
Positive(PCT 2-10ng/ml)	5	0	5	3	2	1
Strongly Positive(PCT>10ng/ml)	2	0	4	0	1	0

In neonates with proven sepsis in spite of negative result for sepsis screening test, the result of PCT was positive. This result was seen also in some patients with clinical sepsis. Table 3 shows the serum concentrations of PCT in the studied groups. Comparison of serum PCT level before and after treatment reveals significant changes in clinical sepsis (P=0.001) and proven sepsis (P=0.003) groups of patients.

### Discussion

In the present study the PCT levels were remarkable high in neonates with proven and the levels dropped dramatically after treatment with antibiotics. Also in some cases of proven and suspected sepsis the levels of PCT were high in spite of negative results for other sepsis screening tests. Previous studies had shown high PCT levels in all neonates with proven or clinically diagnosed various types of neonatal sepsis [10-12]. In a recent study Koksai et al concluded that serum procalcitonin level was superior to serum CRP level in terms of early diagnosis of neonatal sepsis, in detecting the severity of the illness and in evaluation of the response to antibiotic treatment [13-15].

In our study the serum PCT level was high in most of the patients before the initiation of therapy, but there was not a significant correlation between the serum PCT level and the type of sepsis. In Koksai study, unlike our study, the level of serum PCT had a significant difference between the four study groups (no sepsis, probable sepsis, highly probable sepsis and possible sepsis). This difference may be due to the small sample size of our study. The serum PCT level in our study decreased significantly in all three sepsis groups which were most evident in proven sepsis group and like the same finding reported in other studies [16-18].

Athhan et al in their study revealed that at 7th day of therapy neonates who had achieved clinical recovery had a significant decrease of procalcitonin levels compared to the initial values (P=0.000) [19]. This finding was reported also by Viallon and coworkers in 50 patients presenting with bacterial meningitis at day 2 after appropriate antibiotic treatment [20-22]. Carol et al in their study showed that procalcitonin is more sensitive than the CRP in the diagnosis of septicemia, meningitis and urinary tract infection [23]. The usefulness of PCT was assessed by Lopez Sastre and their colleagues as a marker of neonatal sepsis of nosocomial origin in neonates admitted to the 13 neonatology services of 13 acute-care teaching hospitals in Spain over one year. They concluded that serum PCT concentration showed a moderate diagnostic reliability for the detection of nosocomial sepsis from the time of infection [24].

Four of all culture positive neonates in our study had nosocomial sepsis and all of them had elevated PCT levels. One of the limitations of the present study was the shortage of culture positive neonatal standard for sepsis to determine the sensitivity and specificity. For this reason we classified the neonatal sepsis into three groups and assessed the PCT level in relation to the class of sepsis before and after treatment.

### Conclusion

The PCT concentration in our study was elevated in culture positive neonates and decreased with appropriate antibiotic therapy. In some cases of culture positive babies other sepsis screening tests were negative but the level of PCT was elevated. These findings support the usefulness of the PCT to establish an early diagnosis of neonatal sepsis.

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