Indian Journal of Basic and Applied Medical Research; September 2017: Vol.-6, Issue- 4, P. 606-613

Original article:

The diagnostic and prognostic values of Procalcitonin in neonatal sepsis: a review of current evidence

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Abstract

Background: Neonatal sepsis continues to be a contributor to morbidity and mortality in newborns, particularly amongst preterm infants.

Rapid diagnosis is difficult because the initial signs of sepsis are quite non-specific, in addition, bacterial cultures are time-consuming, have low yield and sometimes not feasible.

The most widely used test in clinical practice is the C-reactive protein (CRP), however its drawbacks include its delayed rise and inability to reliably differentiate between the systemic inflammatory response and sepsis.

Another biomarker that has been the subject of several studies is Procalcitonin (PCT), with diverse feedbacks.

Aim: This article evaluates the findings from several studies to assess the accuracy of PCT in the diagnosis and prognosis of neonatal sepsis.

Method: a search of several published studies and review articles, highlighting the methods, results and drawbacks of these works.

Conclusion: Procalcitonin is a useful marker in detecting EONS as part of sepsis evaluation. It is reliable in excluding babies who do not have sepsis. Further studies are needed to assess its prognostic value.

Keywords: Prognostic, Diagnostic, sepsis, procalcitonin.

Introduction

Neonatal sepsis remains a major problem associated with high morbidity and mortality in newborns, particularly amongst preterm infants.[1-4] Mortality rate is between 11-68 per 1000 live birth in developing countries and 5 per 1000 live birth in developed countries.[5,6] Neonatal Sepsis is implicated in 25-40% of neonatal mortality in Nigeria.[7,8]

Rapid diagnosis is problematic because the early signs of this disease may be subtle, and are similar to those of various non-infectious processes; furthermore, bacterial cultures are time-consuming, have low yield and sometimes not feasible, especially in low resource settings. Other laboratory tests are either not available for routine use or lack sensitivity or specificity.[9,10]

The clinical course of neonatal sepsis can be fulminant and fatal if treatment is not commenced promptly.[11] In such settings, neonates with risk factors for infection or clinical suspicion of infection are empirically treated with antibiotics.[12-14] When such empirical antibiotics are given, another challenge is when to stop such treatment. The practice of prolonged empirical treatment of newborns with suspected sepsis has far reaching implications. In order to avoid the unnecessary treatment of uninfected patients,

an early, sensitive and specific laboratory test would be helpful to guide clinicians in neonatal units in deciding whether or not to start administering antibiotics.[12]

The most widely used test in clinical practice is the C-reactive protein (CRP), however its drawbacks include its delayed rise and inability to reliably differentiate between the systemic inflammatory response and sepsis.[15,16]

Another biomarker that has been the subject of several studies is Procalcitonin (PCT), with diverse feedbacks.

This article evaluates the findings from several studies to assess the accuracy of PCT in the diagnosis and prognosis of neonatal sepsis.

Procalcitonin (PCT) has been reported as a measurable laboratory marker in the inflammatory response to infection in some studies. It is a 116-amino acid protein, a precursor of calcitonin which is produced by the thyroid. In sepsis, macrophages and the monocytic cells of the liver are involved in the synthesis of PCT. A number of studies have reported on the usefulness of the quantitative measurement of PCT for an early diagnosis of sepsis in newborns.[17]

In healthy persons Procalcitonin levels are undetectably low, however in bacterial, fungal, parasitic infections with systemic manifestations, a significant rise is seen. In this condition the production sites are the extra thyroid tissues.[18]

In healthy individuals, production of PCT and subsequently calcitonin occurs solely in the thyroid C-cells. Bacterial infections selectively induce an increase in the concentration of PCT; because both endotoxins released from the bacterial cell wall as well as the host responses to infection activate the production of PCT mainly in parenchymal tissues.[19,20]

In1993, PCT was first described as a marker of the extent and course of systemic inflammatory response to bacterial and fungal infections. The advantage of PCT as compared to C□reactive protein is that the increase of the former in bacterial infection and its restoration to normal is more rapid. It can therefore help in deciding the duration of antibiotics administration.[21,22]

Furthermore, the finding that PCT is released into the circulation within 3 h after endotoxin injection, plateaus at 6 h, and remains elevated for 24 h, makes PCT a promising new agent for early and sensitive identification of infected patients.[23]

The results of recent studies on the usefulness of PCT for early diagnosis of neonatal sepsis have been inconclusive.[24-31]

There are two types of PCT assays available:

1. Qualitative tests: rapid test strips for point-of-care testing (results available in < 30 minutes)
2. Quantitative tests: use luminescence immunoassay (results available in a few hours)

It is not known if quantitative testing yields similar results to semi-quantitative testing.[32]

Blood or plasma samples are used with, a minimum volume of 20-50 microliters. The lowest detection limit is 0.1 – 0.3 ng/ml.[33]

The sensitivity of PCT in initial determinations for the diagnosis of early-onset neonatal sepsis has been reported to vary from 61% to 85%, increasing to 72–100% within the subsequent 24 h.

Some authors have reported markedly increased concentrations during the first 48 h of life in newborn infants without bacterial infection. In these studies, PCT sensitivity in the early diagnosis of neonatal sepsis was found to be 83-100% while the specificity was 70-100%.

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Sastre et al evaluated 317 newborns in a multicentre Spanish study (confirmed vertical sepsis: 31, vertical clinical sepsis: 38, non-infectious diseases: 79). In asymptomatic neonates, PCT values at 12–24 h were significantly higher than at birth and at 36–48 h of life. Neonates with confirmed vertical sepsis showed significantly higher PCT values than those with clinical sepsis. PCT thresholds for the diagnosis of sepsis were 0.55 ng/mL at birth (sensitivity 75.4%, specificity 72.3%); 4.7 ng/mL within 12–24 h of life (sensitivity 73.8%, specificity 80.8%); and 1.7 ng/mL within 36–48 h of life (sensitivity 77.6%, specificity 79.2%). Active resuscitation at birth was independently associated with high PCT values.[12]

Ali et al in a study of 70 Neonates admitted in NICU, 31.4%, 42.9% and 25.7% were categorized as proven sepsis, suspected sepsis and clinical sepsis respectively. Procalcitonin was positive in 100% compared to the CRP positivity in 63.6% of the proven sepsis cases.[34]

Chiesa et al determined reference ranges for PCT across the range of postnatal hours from 0 to 48 h and posited that PCT sensitivity and specificity were greater than those of CRP or interleukin 6 if different cutoff points at birth, 24 h and 48 h of life were used.[35]

In these studies, it was reported that serum levels had also increased in non-infected neonates with maternal chorioamnionitis, GBS colonization, perinatal asphyxia, intracranial hemorrhage, pneumothorax, or after resuscitation, and these conditions had negatively affected the specificity of PCT.

Janota et al reported a significant increase in serum PCT concentrations within 72 h of age in preterm infected and uninfected newborns born to mothers with chorioamnionitis. Gendrel and Bohuon suggested that hypoxemia may be responsible for increased PCT values in neonates. They also found that neonates born to mothers with preeclampsia had higher PCT concentrations at both 24 and 48 h of life.[36,37]

Adib et al in a study of 69 at risk neonates in Iran reported found 75% sensitivity, 80% specificity, 80%, positive predictive value and 75% negative predictive value for procalcitonin as a marker for the early diagnosis of neonatal sepsis. Their cut-off value was 1.1 ng/ml.[38]

In a Nigerian study in 2015, Arowosegbe et al evaluated 85 infants with suspected sepsis and elevated PCT levels were recorded in 84.2%, 66.7%, 57.4% and 16.7% of neonates in the proven, suspected, clinical and control groups respectively. At a cut-off value of 0.5 ng/ml, the negative predictive value (NPV) of PCT was 80% and the positive predictive value (PPV) 39%.[39]

Nazeer et al in an Indian study (2016) assessed 25 neonates with clinical (n=5), suspected (n=13) and proven sepsis (n=7). The PCT levels were measured by immunoluminoassay before and on day 5 of treatment. PCT 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. The levels of PCT in proven sepsis group were higher than that in other groups. It remained positive however in 50% of babies with proven sepsis and was negative in all those with clinical sepsis after 5 days of antibiotics. Infants with asphyxia and meconium aspiration were excluded from this study.[40]

Park et al in a Korean study (2014) of 269 neonates with suspected sepsis compared PCT

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with CRP and reported the following at cutoff of of 0.5 mg/L for PCT and 10 mg/L for CRP (sensitivity, 88.29% vs. 100%; specificity, 58.17% vs. 85.66%; positive predictive value, 13.2% vs. 33.3%; negative predictive value, 98.6% vs. 100%, respectively). They concluded that PCT is very useful for diagnosing neonatal sepsis with high sensitivity and specificity; however, the sensitivity and specificity of CRP were much higher.[41]

Early detection of absence of infection is an important property attributed to PCT.

A single center, prospective study conducted in France in NICU infants with clinical suspicion of late-onset sepsis (after 72 hours of life) found that a PCT cut-off value of 0.6 ng/ml provided a sensitivity, specificity, PPV and NPV of 100%, 65%, 67%, and 100% respectively. Therefore a rapid measurement of PCT could help rule out nosocomial infection in newborn infants.[42]

Another single-center, prospective, randomized intervention study (n =121) conducted in a Switzerland NICU provided moderate evidence that PCT guidance reduces the use of antibiotic therapy for EONS. Antibiotic duration was overall reduced by 22.4 hours (22.0%) and a 27% reduction in neonates on antibiotics for > 72 hours.[43]

Higher concentrations of PCT have been observed in uninfected infants with respiratory disorders (mostly hyaline membrane disease) compared with asymptomatic infants. Because no significant effect related to the severity of RDS could be detected, Monneret et al. suggested that hypoxemia (a common event to each etiology of RDS and which is transient during delivery) could be responsible for these increased PCT values, providing further support for the hypothesis of pulmonary PCT synthesis.[31,44]

Although PCT may cross the placental barrier, the findings of higher PCT concentrations in cord sera compared with maternal samples, with even larger differences at 24 and 48 h of age, cannot be explained on the grounds of maternal transfer alone; therefore, the postnatal surge of PCT may represent endogenous synthesis.[35] This phenomenon might be attributed to direct stress on the baby during the perinatal period or to the adaptation to the extrauterine environment.[45,46]

In addition to detecting infants with sepsis, PCT may be useful in prognostication as follows: < 0.5 ng/ml Systemic infection/sepsis is not likely11, PCT > 0.5 and < 2 ng/ml- Moderate risk for progression to severe systemic infection11), PCT> 2 and < 10 ng/ml- High risk for progression to severe systemic infection11, ≥ 10 ng/ml high likelihood of severe sepsis or septic shock.[11]

Ali et al and Brunkhorst et al reported that the risks of septic shock and mortality rate are significantly increased in proven sepsis if PCT levels are greater than 10ng/ml. Jensen et al in a study in Denmark reported that PCT rise of more than 1mg/dl per day was associated with increased mortality.[34,48,49] There is need for further studies in this regard.

In spite of the promising reports obtained from several studies however, PCT is not yet widely used in clinical practice in the diagnosis of clinical sepsis. This is not unrelated to the contradicting results obtained for EONS diagnosis. Reasons for these contradictions include:

i. Variations in study design

ii. Confounders such as intrapartum antibiotics, postnatal antibiotics, neonatal hypoxemia,

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respiratory distress syndrome (RDS), and intracranial hemorrhage

iii. Lack of uniform definition of clinical septicemia

iv. Different cut-off points used for PCT concentrations.[50,51]

The potential benefits of the clinical use of PCT include early commencement of antibiotics and timely discontinuation of same, thereby reducing the problems arising from prolonged empirical antimicrobial therapy. Furthermore, if found to be prognostically reliable, PCT testing may guide the clinician in determining appropriate level of neonatal intensive care an infant requires.

Conclusions

Procalcitonin is a useful marker in detecting EONS as part of sepsis evaluation. It is reliable in excluding babies who do not have sepsis.

There is clearly a need for uniform protocol, particularly with respect to patient selection and definition of cut-off values to accurately define the role of PCT in the diagnosis of EONS. Further studies are needed to assess its prognostic value.

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