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Original Article

Study On C-Reactive Protein And Procalcitonin Levels In Neonatal Sepsis

Dr. Sandeep Rama Thute[1*]

[1*]Assistant Professor, Dept. Of Pediatrics, Rama Medical College, Hospital & Research Centre, Hapur, U.P.

***Corresponding Author:** Dr. Sandeep Rama Thute

*****Assistant Professor, Dept. Of Pediatrics, Rama Medical College, Hospital & Research Centre, Hapur, U.P.

Abstract

Background: In newborn infants, neonatal sepsis is one of the major causes of morbidity and mortality. There are two different patterns of the disease associated with neonatal sepsis, which start to appear, early- onset (<7 days of birth) and late-onset (>7 days). Identifying the symptoms and diagnosing it early and subsequent treatment of systemic bacterial infection by anti-biotics is very important in neonate and infants, to prevent mortality, since a delay in treatment of severe bacterial infection may not lead to a proper outcome and essential for preventing the possibilities of antibiotics resistance from the use of unnecessary antibiotic prescriptions

Aim and Objectives: To estimate and compare the concentration of CRP and PCT in neonatal sepsis and normal neonates and to evaluate the diagnostic value of PCT in neonatal sepsis.

Materials and Methods: The study was a prospective hospital based type undertaken among the 87 neonates who were admitted to Neonatal Intensive Care Units (NICU) at our tertiary care hospital. We measured c-reactive protein and procalcitonin levels in all the neonates included in our study.

Discussion and Conclusion: The results of our study indicate that the sensitivity of procalcitonin (76%) was higher than CRP (57%) for the diagnosis of neonatal sepsis and PCT appears to be a useful marker for the severity of infection.
The findings of our study support the important role of the PCT to support an early diagnosis of neonatal sepsis. Results from this study indicates that any increase in PCT in an ill neonate suggests the possibility of a septicemic infection. However, PCT is not sufficiently reliable to be the sole marker of neonatal sepsis and would be useful as part of a full sepsis evaluation. A negative PCT test finding is not exclusively sufficient to rule out sepsis, but needs to be evaluated further. PCT also has very high advantages where prediction of severity and mortality is concerned.

Key-words: c-reactive protein, procalcitonin, neonatal sepsis, diagnostic value and sepsis

INTRODUCTION:

In newborn infants, neonatal sepsis is one of the major causes of morbidity and mortality. There are two different patterns of the disease associated with neonatal sepsis, which start to appear, early-onset (<7 days of birth) and late-onset (>7 days). Identifying the symptoms and diagnosing it early and subsequent treatment of systemic bacterial infection by anti-biotics is very important in neonate and infants, to prevent mortality.

In the general clinical practice, the diagnosis of neonatal sepsis, rapidly and accurately is difficult due to the reason that, clinical characteristics of neonatal sepsis gets confused with other non-infectious disorders. Also, sepsis has an acute onset, so the clinical process could get subsided quickly. So, by improving the accuracy of diagnosing tests, the outcomes of treatment and pro-diagnosis in those having real sepsis will improve and the use of anti-biotics indiscriminately in those who don't have sepsis [1]. For diagnosis of neonatal sepsis, isolating the microorganisms through conventional blood culture is still the gold standard. However, this conventional blood culture has a very low sensitivity, as it was able to detect the pathogen in only around 25% of cases. It can give both false-negative and false positive results, especially due to the use of antibiotics and contamination, respectively. [2]
Apart from doing blood culture, polymerase chain reaction (PCR) is also done to amplify the conserved DNA sequences present in all bacteria, which will allow fast and sensitive detection of bacteria present in blood samples. But its results may still be positive even after antibiotic treatment because it does not depend on the bacterial viability. [3-5]
Many recent studies conducted by authors has found that the bio-markers procalcitonin (PCT) & C-reactive protein (CRP) are very highly effective markers for the diagnosis of neonatal sepsis. Procalcitonin (PCT) is the precursor of the hormone calcitonin which is produced by the C cells of the thyroid gland in very low concentrations under normal conditions. It is specially induced as an acute-phase reactant in bacterial sepsis. [4] C-reactive protein (CRP) is an acute-phase protein which is synthesized by liver when there is any inflammation and infection. [6] So, overall, neonatal sepsis is a very challenging problem, and physicians all over the world require new and accurate methods of predicting it and also diagnosing sepsis early to also start the therapy at early to reduce the negative health impact on the patient. So, we have conducted our study to establish the better markers, PCT & CRP for the neonatal sepsis diagnosis.

AIM AND OBJECTIVES:

To estimate the concentration of CRP and PCT in neonatal sepsis and to evaluate the diagnostic value of PCT in neonatal sepsis.

MATERIALS AND METHODS:

The study was a prospective hospital based type undertaken among the 87 neonates who were admitted to Neonatal Intensive Care Units (NICU) at our tertiary care hospital from October 2017 to November 2018. A detailed antenatal history, consanguinity, geographical area of mother, birth order, mode of delivery, gestational age, birth injuries and blood group were recorded in each baby by interviewing the mother after taking consent in prescribed proforma. Written consent was obtained from the families of all the investigated neonates.
Study design: Prospective hospital based study.
Sample size: We included a total of 87 neonates.
Clinical criteria indicative of sepsis:

The clinical criteria taken as indicative of sepsis were:

I. Maternal risk factor such as fever, prolonged rupture of amniotic membrane >24 hr
II. Neonatal history: low birth weight (< 2500 grams), premature birth (<37 weeks).
III. Signs and symptoms of sepsis: feeding intolerance, lethargy, temperature instability, apnea, respiratory distress, poor perfusion, seizures, tachypnea, bradycardia, abdominal distension or vomits.

Neonates who had any features from I and II associated with two or more clinical symptoms of sepsis would warrant a septic screen. Before initiation of antibiotic therapy in infants suspected of

sepsis, blood samples for blood culture (1-2 ml), PCT and CRP measurements (1-2 ml) were obtained by peripheral venous puncture. Serum was separated from blood cells by centrifugation and stored in 2 plastic tubes at -20 °C for measurements of PCT and CRP. The results of spinal fluid culture were obtained from the hospital laboratory. Finally, according to clinical symptoms of sepsis, microbiologic and laboratory results, neonates classified in to three groups: 1) Proven sepsis (n= 25): positive blood culture and clinical symptoms of sepsis. 2) Suspected sepsis (N= 43): with clinical symptoms but negative blood culture. 3) Control group (n= 19): healthy neonates with physiological hyperbilirubinemia (referred to the hospital for bilirubin determination) and no clinical and biological data of infection were selected as the control group.

Laboratory Investigations*:* Serum C-reactive protein and PCT in serum (detection limit 0.10 ng/ml) were measured as per the instructions of the manufacturer. The Apgar score is used as an indicator of the infant's condition in the first and fifth minutes after birth that include: appearance, heart rate, muscle tone, respiratory effort. Apgar score is measured by nurse-midwife or specialist.

Microbiological examination*:* One to two ml of blood was added to blood culture media (Biphasic) and incubated at 37 °C for 5-7 days. Bottles with positive results were sub cultured on blood agar and EMB media. The isolated microbes were identified by standard bacteriological methods.

RESULTS:

In the present study, 87 neonates who were admitted to Neonatal Intensive Care Units (NICU) at our tertiary care hospital from October 2017 to November 2018 were included. Proven sepsis (n= 25): positive blood culture and clinical symptoms of sepsis. 2) Suspected sepsis (N= 43): with clinical symptoms but negative blood culture. 3) Control group (n= 19).

Table 1: Shows the demographic characteristics

Features	Proved sepsis (n=25)	Suspected sepsis (n=43)	Control (n=19)	P value
GA (week)	31.45±3.7	34.7 ±3.6	37.4 ±7.64	S
Birth weight (g)	2056±528	2226±726	2760±521	S
Apgar Score 1	6.25±2.0	6.71±2.81	8.6±1.42	NS
Apgar Score 5	7.83±1.48	8.32±1.62	9.5±0.92	NS

*The Apgar score is used as an indicator of the infant's condition in the first and fifth minutes after birth that include: appearance, heart rate, muscle tone, respiratory effort.

Table 2: Shows the concentration of CRP and PCT in different groups

Parameters	Proved sepsis (n=25)	Suspected sepsis (n=43)	Control (n=19)	P value
CRP (mg/L)	29.2±29.23	10.5 ±11.8	4.51 ±2.72	S
PCT (ng/mL)	7.23±7.34	3.67±4.77	0.84±0.49	S

The mean of CRP and PCT in studied groups are shown in Table 2. There was a significant difference between the mean of CRP level in healthy controls and septic infants ($P< 0.05$). In addition, it was observed a significant difference between septic and suspected newborns ($P< 0.05$).

PCT level was significantly higher in septic and suspected infants in comparison with the normal infants ($P< 0.05$). PCT level in 22% of proved sepsis group and 31% of suspected sepsis was located lower than the cut-off value, but in 89.4% of infants in the control group it was located

lower than the cut-off value. The optimum cut-off value was found to be 14 mg/l for CRP and 1.2 ng/ml for PCT. At a cut-off value, 14 mg/L CRP was found to have a sensitivity of 57%, specificity of 95%, positive predictive value (PPV) of 40%, negative predictive value (NPV) of 40% for the diagnosis of neonatal sepsis. We found 76% sensitivity, 80% specificity, 80% PPV and 78% NPV for procalcitonin as a marker for the early diagnosis of neonatal sepsis.

DISCUSSION:

Neonatal sepsis remains a diagnostic and treatment challenge for the neonatal health care providers. This challenge leads to the over treatment of large number of neonates who present with clinical suspicion of sepsis.

In recent years' measurement of procalcitonin and other inflammatory mediators have been reported as sensitive parameters for the early diagnosis of neonatal sepsis and evaluating its outcome. The aim of this study was to evaluate PCT as diagnostic marker for neonatal sepsis. The incidence of culture-proven sepsis was low (28.7%), this finding was similar to the studies conducted by Adeleke and Belonwu which showed 20% and 25.7% respectively and finally concluded low sensitivity of blood culture in neonatal sepsis [8]. PCT levels were high in the neonates with proven and suspected sepsis cases. This finding was similar with reports of some studies [7-11]. Two neonates in the proven sepsis group had PCT lower than 0.5ng/ml. These neonates were preterm and had very low birth weights. Three neonates had procalcitonin higher than 0.5 ng/ml in control group. This may be due to physiological increase of procalcitonin, reported up to 21-48 hr postpartum, even in the absence of infection.

PCT has been intensively investigated for its diagnostic role in neonatal sepsis. It has been reported that high concentration of plasma PCT was found in infants with severe infection, while PCT levels were very low in those with no infections. Many authors found that procalcitonin is a promising marker for the diagnosis of neonatal sepsis [12, 13]. In these studies, PCT sensitivity in the early diagnosis of neonatal sepsis was found to be 83-100% while the specificity was 70-100% [12, 13]. But some investigators questioned the diagnostic accuracy of PCT in detecting of neonatal sepsis. In these studies, it was reported that serum levels had also increased in non-infected neonates with perinatal asphyxia, intracranial hemorrhage, pneumothorax, or after resuscitation, and these conditions had negatively affected the specificity of PCT.

CONCLUSION:

The results of our study indicate that the sensitivity of procalcitonin (76%) was higher than CRP (57%) for the diagnosis of neonatal sepsis and PCT appears to be a useful marker for the severity of infection.

The findings of our study support the usefulness of the PCT to support an early diagnosis of neonatal sepsis. Results from this study suggest that any increase in PCT in an ill neonate suggests the possibility of a septicemic infection. However, PCT is not sufficiently reliable to be the sole marker of neonatal sepsis and would be useful as part of a full sepsis evaluation. A negative PCT on presentation is not exclusively sufficient to rule out sepsis, but needs to be evaluated further. PCT is also of great advantages where prediction of severity and mortality is concerned.

REFERENCES:

1. M. Adib, Z. Bakhshiani, F. Navaei, F. Saheb Fosoul, S. Fouladi, and H. Kazemzadeh, "Procalcitonin: a reliable marker for the diagnosis of neonatal sepsis," *Iranian Journal of Basic Medical Sciences*, vol. 15, no. 2, p. 777, 2012.

2. Ugarte H, Silva E, Mercan D, De Mendonca A, Vincent JL. Procalcitonin used as a marker of infection in the intensive care unit. Crit Care Med. 1999;27(3):498–504.

3. N. I. Draz, S. E. Taha, N. M. Abou Shady, and Y. S. Abdel Ghany, "Comparison of broad range 16S rDNA PCR to conventional blood culture for diagnosis of sepsis in the newborn," *Egyptian Journal of Medical Human Genetics*, vol. 14, no. 4, pp. 403–411, 2013..

4. Çetinkaya M, Özkan H, Köksal N, Çelebi S, Hacimustafaoğlu M. Comparison of serum amyloid A concentrations with those of C-reactive protein and procalcitonin in diagnosis and follow-up of neonatal sepsis in premature infants. J Perinatol. 2009;29(3):225–31.

5. Palmiere C, Mangin P. Postmortem chemistry update part II. Int J Legal Med. 2012;126(2):199–215.

6. Bréchot N, Hékimian G, Chastre J, Luyt C-E. Procalcitonin to guide antibiotic therapy in the ICU. Int J Antimicrob Agents. 2015;46:S19–S24.

7. Adib M, Bakhshiani Z, Navaei F, Saheb Fosoul F, Fouladi S, Kazemzadeh H. Procalcitonin: a reliable marker for the diagnosis of neonatal sepsis. Iran J Basic Med Sci. 2012;15(2):777–782

8. Adeleke, SI, and Belonwu, RO. Bacterial Isolates in Neonatal Septicaemia in Kano, Nigeria. Pinnacle Int. J. Med. Sci.2006;1(1): 17-20

9. Naher, HS, Khamael, AB. Neonatal Sepsis; The Bacterial Causes and the Risk Factors. Int. J. Res. Med. Sci. 2013; 1 (6): 19-22.

10. Carrol ED, Thomson AP, Hart CA. Procalcitonin as a marker of sepsis. Int J Antimicrobe Agents. 2002;20:1–9

11. Gendrel D, Raymond J, Coste J. Comparion of procalcitonin with C-reactive protein, interleukin-6 and interferon-alpha for differentiation of bacterial vs. viral infections. Pediatr Infect Dis. 1999;18:875–881.

12. Monneret G, Labaune JM, Isaac C, Bienvenu F, Putet G, Bienvenu J. Procalcitonin and C-reactive protein levels in neonatal infections. Acta Paediatr. 1997;86:209–212.

13. Janota J, Stranak Z, Belohlavkova S, Mudra K, Simak J. Postnatal increase of procalcitonin in premature newborns is enhanced by chorioamnionitis and neonatal sepsis. Eur J Clin Invest. 2001;31:978–983.