Research Article

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Comparative study of C-reactive protein versus procalcitonin as an early marker of neonatal sepsis

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ABSTRACT

Background: Neonatal sepsis is one of the important causes of neonatal morbidity and mortality particularly in the developing countries. In order to avoid unnecessary NICU admissions and antibiotic therapies, it is very important to make early diagnosis of neonatal sepsis with utmost accuracy. Blood culture though gold standard requires lot of time for diagnosis, hence it's necessary to rely on early diagnostic markers such as blood counts, micro-ESR, CRP, Procalcitonin. Out of the early diagnostic markers available, CRP and pro-calcitonin has the highest sensitivity and specificity rates.

Methods: The present study was conducted for a period of one year from January 2014 to December 2014 on neonates admitted to NICU, GSL Medical College, Rajahmundry, Andhra Pradesh, India. Proper consent was taken from the parents of all neonates. Specimens of blood obtained from each neonate with proper aseptic conditions and prior to commencement of antibiotics.

Results: Total of 60 neonates satisfying the inclusion criteria are taken in the study group, based on the above criteria, they are grouped into 3 categories, 20/60 neonates had clinical sepsis, 22/60 had suspected sepsis and confirmed sepsis was found in 18/60 neonates. Appropriate investigations were done. Blood culture was positive in 18 neonates. Procalcitonin was negative in 32 neonates, weakly positive (0.5-2ng/ml) in 5 neonates, positive (2-10ng/ml) in 15 neonates, and strongly positive (>10ng/ml) in 7 neonates. Total no. of cases positive for procalcitonin are 28/60. The sensitivity of procalcitonin is 88.88%, specificity is 75%, Positive predictive value is 61.5%, and negative predictive value is 93.75%. PCT is positive in 16/18 blood culture positive cases. CRP was positive in 22/60 cases, and negative in 38/60 cases. CRP was positive in 12/18 blood culture positive cases. The sensitivity of CRP was 66.66%, specificity 76.19%, PPV 54.54%, NPV 84.21%.

Conclusions: Higher sensitivity and negative predictive value of PCT, Pro-calcitonin surely scores a way more compared to CRP in early diagnosis of neonatal sepsis.

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

INTRODUCTION

Neonatal sepsis is one of the important causes of neonatal morbidity and mortality particularly in the developing countries.¹

Neonatal sepsis is classified into early or late according to the different ages at onset of infection during the neonatal period. The clinical relevance of this distinction is that earlyonset disease is often due to organisms acquired during delivery while, late-onset disease is more frequently caused by organisms acquired from nosocomial or community sources.

Because of variable presentation and non-specific clinical features of neonatal sepsis, it is difficult to make early diagnosis of neonatal sepsis.

Diagnosis of neonatal sepsis is always a challenge. Blood culture though "gold standard", takes a lot of time for diagnosis.² Unnecessary antibiotic administration may cause problems of antibiotic resistance; hence it's necessary to rely on early diagnostic markers such as blood counts, micro-ESR, CRP, Procalcitonin.

Out of the early diagnostic markers available, CRP and Pro-calcitonin has the highest sensitivity and specificity rates.³ As little information available based on comparison between these two potential markers, this present study was conducted.

The aim of this study is to determine the accuracy of CRP and pro-calcitonin as early diagnostic marker in detection of neonatal sepsis, taking blood culture as the gold standard.

METHODS

The present study was conducted for a period of one year from January 2014 to December 2014 on neonates admitted to NICU, GSL Medical College, Rajahmundry, Andhra Pradesh, India.

Proper consent was taken from the parents of all neonates. Specimens of blood obtained from each neonate with proper aseptic conditions and prior to commencement of antibiotics.

Investigations were sent for total leukocyte count, absolute neutrophil count, micro ESR, immature neutrophils to total neutrophil count, CRP and PCR. Blood culture and antibiotic sensitivity tests were also carried out.

Inclusion criteria

Any suspected case of neonatal sepsis with maternal risk factors for sepsis e.g.:

- Prolonged labour.
- PROM >18 hours.
- Maternal intrapartum fever, urinary tract infection (UTI), chorioamnionitis.

Clinical signs and symptoms of the new-born having sepsis related clinical signs:

Temperature instability, apnea, bradycardia, tachycardia, hypotension/hypo perfusion, feeding intolerance, abdominal distension, necrotizing enterocolitis.

Exclusion criteria

- Neonates who had prior antibiotic treatment
- birth asphyxia
- babies with major congenital anomalies

Specimens and tests performed

The specimens of blood were obtained from each neonate prior to the commencement of the antibiotics for the sepsis work up, which included TLC, ESR, ANC, the immature neutrophils to total neutrophil count ratio (I/T ratio), platelet count, degenerative changes in the neutrophils, blood culture and antibiotic sensitivity, PCT and C-reactive protein (CRP) estimation.

Serum pro-calcitonin

- The serum PCT level was measured by using a quantitative immuno-luminometry method using the Limits' kit (BRAHMS Diagnostic, Berlin, Germany).
- PCT level
- >0.5 to 2ng/ml weakly positive
- 2 to 10ng/ml positive
- >10ng/ml strongly positive

Serum CRP

- Serum CRP level was measured by using the A-15 CRP Kit (Bio-system, Costa Brava, Barcelona, Spain). CRP from the serum was measured by an immunoturbidimetric method in the laboratory according to the manufacturer's instructions.
- Value >6mg/dl was taken as cut off.
- Total of 60 neonates were included in our study group. And they are classified into 3 categories

Clinical sepsis

- 1. Clinical signs suggestive of sepsis are present.
- 2. Less than 2 parameters for sepsis screen positive.
- 3. Blood culture negative.

Suspected sepsis

- 1. Clinical signs suggestive of sepsis are present.
- 2. At least 2 parameters for sepsis screen must be positive.
- 3. Blood culture negative.

Confirmed sepsis

- 1. Clinical signs suggestive of sepsis are present.
- 2. At least 2 parameters of sepsis screen must be positive.
- 3. Blood culture positive.

Statistical analysis

Data were expressed as mean±sd. Statistical significance was assessed by chi-square test.

Sensitivity and specificity, PPV, NPV of CRP and PCT were calculated taking blood culture as gold standard.

RESULTS

Total of 60 neonates satisfying the inclusion criteria mentioned above are included in our study group.

Based on above criteria they are divided into 3 categories:

- 1. Clinical sepsis 20
- 2. Suspected sepsis 22
- 3. Confirmed sepsis 18

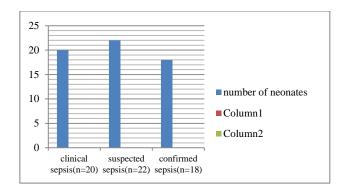


Figure 1: Mean and statistical significance of different variables in neonatal sepsis.

Table 1: Mean and statistical significance of different variables in neonatal sepsis.

Variable	Clinical sepsis	Suspected sepsis	Confirmed sepsis	P VALUE
Number	20	22	18	_
Weight (gm)	2850 <u>+</u> 40	2360 <u>+</u> 50	2010 <u>+</u> 40	P<0.05
Gestational Age	36.7	33.5	30.4	P<0.05
CRP(g/dl)	6.62 <u>+</u> 0.4	7.08 <u>+</u> 0.7	18.25 <u>+</u> 4.69	P<0.05
PCT	0.75 <u>+</u> 0.12	2.71 <u>+</u> 1.63	6.9 <u>+</u> 3.8	P < 0.05

Out of 20 neonates with clinical sepsis 18 had negative PCT (0.5ng/ml) and 2 had PCT weakly positive (0.5-2ng/ml).

Out of 18 blood culture positive/confirmed sepsis cases, PCT was found to be positive in 16 cases, with a sensitivity of about 88.8 percent.

The levels of PCT are also in the higher range >10ng/ml in neonates with confirmed sepsis or blood culture positive.

Out of 18 neonates with confirmed sepsis, CRP was found to be positive in only 12 neonates, with a sensitivity of about 66.6% which is lower compared to sensitivity of PCT. CRP levels above 6mg/dl were taken as cut off.

CRP positive:

- 1. Clinical sepsis 4/20 cases
- 2. Suspected sepsis 6/22 cases
- 3. Proven sepsis 12/18 cases

DISCUSSION

Early diagnosis of neonatal sepsis is a great challenge to many paediatricians.

Through early diagnosis, we can avoid usage of unnecessary antibiotics and its related complications.

CRP and procalcitonin are the important early markers in neonatal sepsis which came into light during the recent years.

Table 2: Distribution of sepsis groups in relation to PCT levels.

	PCT(ng/ml)	Total no. of cases	Clinical sepsis	Suspected sepsis	Confirmed sepsis
Negative	<0.5ng/ml	32	18	12	2
Weakly positive	0.5-2 ng/ml	6	2	4	0
Positive	2-10 ng/ml	15	0	6	9
Strongly positive	>10ng/ml	7	0	0	7

Table 3: Comparison of validity tests of CRP and PCT.

Validity tests	PCT	CRP
1.Sensitivity	88.8%	66.66%
2.Specificity	75%	76.19%
3. PPV	61.53%	54.54%
4.NPV	93.75%	84.21%
5. Accuracy	72.5%	62.3%

CRP mediates its action by activation of immune system through opsonisation of bacteria and elicits further inflammatory response, but the problem with CRP is that after it increases up to certain value it reaches a plateau and does not come back to normal after the infection.

Advantages of Pro-calcitonin (PCT) over CRP from our study shows:

- PCT rises quickly compared to CRP after an infection and comes back to normal limits after the infection has been subsided, whereas CRP increase is rather slow after an infection 12-24hrs and thus it negatively affects its sensitivity.
- CRP values can increase in certain non-clinical conditions such as MAS, PROM and they can affect the specificity of the test. PCT values are not affected by such non clinical conditions, similar to Hisamuddin and Hisam study.⁴
- 3. PCT values allow a more sensitive and specific discrimination of bacterial versus viral infections compared to CRP and other parameters. This is similar with Delevaux Andre study.⁵

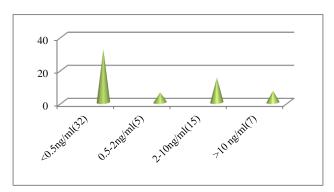


Figure 2: Distribution of sepsis groups in relation to PCT levels.

In our study all the patients that presented positive cultures had PCT levels were greater than 2mg/dl. The correlation of PCT with culture was highly significant and the relative risk was much greater than with CRP values.

This clear determination helps to initiate early and efficient therapy prior to the infectious process being evident or having a positive culture. Thus, the sepsis related morbidity and mortality could be greatly reduced.

Another important finding noticed in our study was mortality rate was significantly increased in neonates having PCT levels >10ng/ml, so it's possible to predict the prognosis.⁶

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 without infections. Hence we can say procalcitonin is a promising marker for the diagnosis of neonatal sepsis in coming years.

CONCLUSION

From the above advantages, higher sensitivity and negative predictive value of PCT, Pro-calcitonin surely scores a way more compared to CRP in early diagnosis of neonatal sepsis. PCT can in turn predict the prognosis too. But the only drawback of PCT is its higher cost.

Nevertheless we recommend usage of these newer diagnostic markers in diagnosis of neonatal sepsis and avoid unnecessary antibiotic usage in young neonates.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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