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Serum Procalcitonin and C Reactive Protein in as early markers neonatal sepsis- A prospective study

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ABSTRACT

Neonatal sepsis is one of the commonest causes of morbidity and mortality in neonates in India compared to the developed countries. Aim: To evaluate the Procalcitonin level this is an early marker in the diagnosis of neonatal sepsis and to assess the suitability of this test in the diagnosis of early-onset sepsis.

Method: The prospective study was conducted in the Neonatal Division of Department of Pediatrics, Prathima Institute of Medical Sciences over a period of one year. The blood samples from 100 babies meeting the inclusion and exclusion criteria constituted the material for study.

Result: Among the n=100 cases n=39 were procalcitonin positive, compared with gestational age 10 (43.5%) cases were positive with a gestation of <37 weeks and 24 (31.2%) cases positive of cases >37 weeks and there was no statistical significance concerning gestational age the association of material characteristics with procalcitonin positive and CRP positive levels. Blood culture was positive in n=9 (9%) of babies with (90% CI, 5.3-14.9) and negative in n=91 (91%) of babies with (90% CI, 85.2-94.7).

Conclusion: A positive blood culture is the only definitive and gold standard for confirming a case of sepsis. Since the culture and sensitivity test requires a minimum period of 48 hours which is a precious time in deciding on the treatment of sepsis in the newborn. Rapid diagnosis by using Procalcitonin and CRP gives a reasonable degree of accuracy in diagnosing neonatal sepsis and will also guide antibiotic therapy. Procalcitonin in comparison with CRP has better sensitivity and hence can detect most cases of neonatal sepsis and better negative predictive value.

Keywords: Procalcitonin, C Reactive Protein, Neonatal sepsis.

Introduction

It is one of the four leading causes of morbidity and mortality in the developing nations among the neonates due to delivery and postnatal follow up in an unhealthy environment and low socio-economic state leading to maternal infections and premature delivery. [1] It is necessary to diagnose early neonatal sepsis and its cause, using clinical signs and rapid diagnostic method so that no time is wasted to start the appropriate treatment. If not recognized early, it can cause septicemia leading to, multiple organ dysfunction and invariably death. The neonates who develop sepsis often die rapidly. Although this approach is reasonable given the dire consequence of a missed diagnosis, improvement in our diagnostic accuracy should diminish the exposure to the risk of avoiding antibiotic therapy, excess financial and emotional cost to the parents. [2] There are various diagnostic tests used for the rapid diagnosis of neonatal sepsis. These rapid diagnostic tests that differentiate infected from non-infected neonates, particularly in the first few days, have the potential to make a significant impact on neonatal care. Early diagnostic tests for infection would have 100% sensitivity and specificity. [3] However, such a test is yet to be discovered. For infection, a neonate is more likely to suffer if an infection is under diagnosed and not treated, than if the infection is over-diagnosed and treated, so the desirable characteristic of the diagnostic test is high sensitivity than high specificity. Hence, this study was done to differentiate the infected from non-infected neonates among the risk of infection by using various blood tests. To evaluate the levels of Procalcitonin and CRP as rapid diagnostic tests, to identify those with infection at the earliest and compare between the two tests.

Material and methods

The prospective study was conducted in the Neonatal Division of Department of Pediatrics, Prathima Institute of Medical Sciences over a period of one year. The blood samples from 100 babies meeting the inclusion and exclusion criteria constituted the material for study.

Inclusion Criteria: Neonates born to mothers with at least one of the following risk factors were included:

1. Premature rupture of membranes (PROM) > 12 hours.
2. More than 3 vaginal examinations after the rupture of membranes.
3. Intrapartum fever (>38ºC).
4. Foul-smelling liquor.
5. Meconium stained liquor.
6. Maternal UTI within 2 weeks before delivery.
7. Prolonged and difficult delivery with instrumentation.

Exclusion Criteria

1. Newborn babies with gestational age < 28 weeks.
2. Neonates with birth weight less than <1000 gm.

3. Neonates with lethal congenital anomalies.
4. Stillborn and fetal deaths.
5. Post-dated neonates.

The following are considered as signs and symptoms suggestive of sepsis:

General: Hypothermia/poor feeding/sclerema/mottling/ lethargy.

CVS: Bradycardia/tachycardia/CFT>2 seconds.

RS: Apnea/RDS/chest retractions/cyanosis/grunting.

CNS: Hypotonia/irritability/seizures/high pitched cry.

GIT: Vomiting/ abdominal distension/hepatomegaly.

Hematology Jaundice with serum bilirubin <15mg% in the absence of blood group abnormality/pallor/petechiae/ bleeding diathesis.

The following are considered as abnormal laboratory parameters:

1. Total leukocyte count <5000/mm^3.
2. Absolute neutrophil count <1000/mm^3.
3. Band cell count >20%.

The blood samples from neonates born to mothers with risk factors for neonatal sepsis were collected and sent for analysis. Detailed birth events, Apgar score, sex of the baby, the weight of the baby will be recorded on the pre-coded proforma made available. Gestational age was assessed by using a modified Ballard scoring system. Neonates were followed up for up to 72 hours from the time of birth for the development of any symptoms and signs suggestive of neonatal sepsis and if the present were recorded

The blood sample will be collected from the neonate and will be sent for:

1. Procalcitonin levels.
2. CRP levels.
3. Blood culture and sensitivity.
4. Total count, absolute neutrophil count, and band cell ratio.

Results on categorical measurements are presented in Number (%). Significance is assessed at a 5% level of significance. Chi-square/Fisher Exact test has been used to find the significance of study parameters on a categorical scale between two groups. Diagnostic statistics viz. Sensitivity, Specificity, PPV, NPV, Accuracy was computed and a 90% confidence interval computed in the study.

Results

In this study, a total of n=100 cases were included based on the inclusion and exclusion criteria. Among the n=100 babies, there were n=55 (55%) males and n=45 (45%) females. The birth weight was <2.5Kg in 28% cases and >2.5 Kg in 72% cases. There were n=23 (23%) with gestational age < 37 weeks and n=77 (77%) with gestational age of > 37 weeks.

Table 1: Shows distribution of cases according to risk factors (n=100)

Maternal risk factors	No. of cases (n=100)	Percentage	90%CI
Meconium stained liquor	60	60	51.8-61.7
PROM	25	25.0	18.6-32.7
Prolonged or Inst Del	12	12.0	7.6-18.4
Maternal UTI	5	5.0	2.5-9.9
> 3 Vaginal examination	5	5.0	2.5-9.9
Foul-smelling liquor	2	2.0	0.7-5.9
Intrapartum fever(>38*C)	2	2.0	0.7-5.9
Maternal infections	0	0.0	-

Among n=100 babies who developed signs of sepsis, n=53 (53%) had developed

respiratory problems with, n=27 (27%) had developed general signs with (90% CI, 20.4-34.8), n=25 (25%) developed gastrointestinal tract related problems with (90% CI 18.6-32.7), n=13 (13%) babies had CNS related problems with (90% CI, 8.4-19.5), 7 (7%) babies had cardiovascular problems with (90% CI, 3.8-12.4) and n= 4 babies had hematological problems with (90% CI, 1.8-8.6).

Among the cases with procalcitonin positive, compared with gestational age10 (43.5%) cases were positive with the gestation of <37 weeks and 24 (31.2%) cases positive of cases >37 weeks and there was no statistical significance concerning gestational age the association of material characteristics with procalcitonin positive and CRP positive levels is shown in table 2.

Table 2: Association of Maternal characteristics Procalcitonin positive and CRP positive

Risk factors	Procalcitonin positive		p-value	CRP positive		p-value
	No. of cases (n=100)	No. of Procalcitonin positive		No. of cases (n=100)	Number of CRP positive	
Foul-smelling liquor	2	2	0.049*	2	100.0	0.008*
> 3 Vaginal examination	5	3	0.219	5	2	0.331
PROM	25	9	0.832	60	13	0.955
Prolonged OR Inst Del	12	4	0.957	25	5	0.809
Meconium stained liquor	60	20	0.908	12	2	0.657
Maternal UTI	5	1	0.509	5	0	-
Intrapartum fever	2	0	0.544	2	0	-

*Significant

Blood culture was positive in n=9 (9%) of babies with (90% CI, 5.3-14.9) and negative in n=91 (91%) of babies with (90% CI, 85.2-94.7). The various organisms found with blood culture in the cases are given in table 3. The WBC picture among the n=100 babies, Total count < 5000 mm3 was noted in n=10(10%) of patients, and the remaining 90(90%) was > 5000 mm^3. Absolute neutrophil count < 1000/mm^3 was not observed in any of the cases and all the cases it was >1000. Band cell ratio >20% was noted in n=4(4%) of cases and n=96(96%) of cases had a ratio of <20%. There was no sepsis observed in n=67 (67%) of cases, probable sepsis was observed in n=24 (24%) of cases and definite sepsis was observed in n=9 (9%).

Table 3: Distribution of Blood culture cases

Blood culture findings	Number (n=100)	%	90%CI
No growth	91	91.0	85.2-94.7
Coag Neg staph	1	1.0	0.2-4.4
E. coli	2	2.0	0.6-5.9
Klebsiella	4	4.0	1.8-8.6
Pseudomonas	2	2.0	0.6-5.9

In n=100 cases, compared with blood culture, Procalcitonin was true positive in n=5 cases, false positive in n=29, false negative in 4, and true negative in n=62. CRP was true positive in n=5, false positive in n-17, false negative in 4, and true negative in n=74 cases.

Table 4: Evaluation of Procalcitonin with CRP

Sensitivity & Specificity	Procalcitonin in relation to CRP positivity	CRP with Procalcitonin positivity
True Positive	22	22
False-positive	12	0
False-negative	0	12
True negative	66	66
Sensitivity (%)	100.0	64.7
Specificity (%)	84.6	100.0
PPV (%)	64.7	100.0
NPV (%)	100.0	84.6
Accuracy (%)	88.0	88.00

Discussion

We in the current study evaluated two important markers procalcitonin and CRP in neonatal sepsis. Procalcitonin [PCT] in healthy people, plasma PCT concentrations are found to be below 0.05 ng/ml. PCT concentrations can increase up to 1,000 ng/ml in patients with sepsis, severe sepsis, or septic shock. Usually, PCT concentrations exceeding 0.5 ng/ml are interpreted as abnormal values suggestive of sepsis syndrome. Concentrations greater 10 ng/ml are almost exclusively found in patients with severe sepsis or septic shock. In the current study, we found PCT positive in 39% of cases. In this study male babies were more than the female babies the ratio was 1.3:1, the results are comparable to E Mathai et al; [4] and similar to Tallur SS et al; [5] they also found male preponderance in the neonatal septicemia. It may be linked to the x-linked immunoregulatory gene resulting in the host's susceptibility to the infection in males. In the present study, the higher proportion of cases were with birth weight >2.5 kg. The results of other studies showed a higher proportion of cases with birth weight <2.5 kg. It could be because there were fewer babies with weight <2.5 kg delivered in the hospital hence fewer cases were recorded. [5, 6] The higher proportion of term neonates compared to the preterm neonates in our study probably reflects the difference in the population characteristics and the occurrence of the predisposing factors (preterm incidence) among them. Preterm is more susceptible to infections due to a lack of inherent defensive mechanisms. According to Barbara J. Stoll, [7] the incidence of septicemia is inversely proportional to the gestational age of the neonates. In the present study, maternal fever as a risk factor was observed in 2% of cases which was almost similar to Tallur SS et al; [5] > 3 +VE after ROM as a risk factor was observed in 5% which was less than that observed in other studies. FSL as a risk factor was observed in 2% of cases which was similar to E Mathai et al; [4] and KA Kuruvilla et al; [7] observations. MSL as a risk factor was observed in 60% which was more than that observed in various studies but was similar to results in Raghavan et al; [8] Prolonged labor as a risk factor was observed in 12% of cases which was comparable to results of Tallur et al; [5] and Raghavan et al; [8] UTI as risk factors were observed in 5% of the case which was comparable to Betty Chacko et al; [9] and Kuruvilla et al; [7] PROM as a risk factor was observed in 25% of cases which was higher than that observed in other studies. The variation in the occurrence of intrapartum risk factors probably reflects differences in the rates of occurrence of the predisposing risk factors in various studies. In the present study, blood culture was positive in 9(9%) of cases with maternal risk factors which is comparable to studies done by Rodwell RL et al; [10] and Boyle RJ et al; [11] The success of isolating bacterial pathogens from blood depends upon the quantum of blood cultured, frequency of culture and duration of incubation and the volume of blood required for the isolation of the pathogen depends on the magnitude of septicemia, which is directly related to the age of the patient. All the above reason says why the blood culture positivity is low. In the present study, the sensitivity observed was 64.7%, sensitivity of 100%, PPV was 100%, and NPV of 85.2% which was comparable with Emine et al; [12]. In a cross-sectional by Naher BS et al; [13] confirmed the data of other studies and reported, PCT is a sensitive, independent, and useful biomarker of neonatal sepsis. It correlates with the severity of sepsis and additional measurement of CRP may increase the specificity. Yadolla Z P et al; [14] demonstrated in their study consisting of 126 babies, found that the serum procalcitonin levels seem to be significantly increased in proven sepsis and decrease dramatically in all types of sepsis after appropriate treatment.

Conclusion

Early diagnosis of neonatal sepsis with a reasonable degree of accuracy will help the clinician to decide on the usage of proper antibiotics which will help in reducing the morbidity and mortality. A positive blood culture is the only definitive and gold standard for confirming a case of sepsis. Since the culture and sensitivity test requires a minimum period of 48 hours which is a precious time in deciding on the treatment of sepsis in the newborn. Rapid diagnosis by using Procalcitonin and CRP gives a reasonable degree of accuracy in diagnosing neonatal sepsis and will also guide antibiotic therapy. Procalcitonin in comparison with CRP has better sensitivity and hence can detect most cases of neonatal sepsis and better negative predictive value, which will lead to a decrease in the number of patients treated unnecessarily.

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