



DIAGNOSTIC AND PREDICTIVE VALUES OF SERUM PROCALCITONIN IN COMPARISON WITH ROUTINE SEPSIS WORK UP IN NEONATAL SEPSIS

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ABSTRACT

Neonatal sepsis is one of the commonest causes of morbidity and mortality in the neonates in India compared to the developed countries. It is one of the four leading causes of morbidity and mortality in India among the neonates due to delivery and postnatal follow up in an unhealthy environment and low socio-economic state leading to maternal infection and premature delivery. It is absolutely 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.

Methodology: The prospective study was conducted in Department of Pediatrics, Rajah Muthiah Medical College Hospital, Annamalai University over a period of one year from October 2014 to October 2015.

The blood samples from 100 babies meeting the inclusion and exclusion criteria constituted the material for study. Detail history and clinical findings were recorded in the proforma. Blood sample will be collected from the neonate and will be sent for: Procalcitonin levels, CRP levels, Blood culture and sensitivity, Total count, absolute neutrophil count and band cell ratio.

Results: This is a prospective study conducted over a period of one year from October 2014 to October 2015. 100 babies were included in the study. Males were 57 (57%) and females were 43 (43%). 28 cases were < 2.5 kgs and 72 babies are >2.5 kgs. Procalcitonin is positive in 34 (34%) and negative in 66 (66%). CRP was positive in 22 (22%) and negative in 78 (78%). 91 (91%) of cases had blood culture negative and in 9 (9%) cases blood culture was positive. Total count < 5000 was noted in 10 (10%) of patients and in the remaining 90 (90%) was > 5000. Absolute neutrophil count < 1000 was not observed in any of the cases and all the cases it was >1000. There was no sepsis observed in 67 (67%) of cases, probable sepsis was observed in 24 (24%) of cases and definite sepsis was observed in 9 (9%). Procalcitonin in comparison with CRP, sensitivity was 100%, specificity was 84.6%, PPV was 64.7%, and NPV was 100%

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INTRODUCTION

Neonatal sepsis is one of the commonest causes of morbidity and mortality in the neonates in India compared to the developed countries.[1] It is one of the four leading causes of morbidity and mortality in India among the neonates due to delivery and postnatal follow up in an unhealthy environment and low socio-economic state leading to maternal infection and premature delivery. It is absolutely 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. There are various diagnostic tests used for 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 significant impact on neonatal care. Early diagnostic test for infection would have 100% sensitivity and specificity. However, such a test is yet to be discovered. For infection, a neonate is more likely to suffer if infection

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is under diagnosed and not treated, than if 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 clearly differentiate the infected from non-infected neonates among the risk of infection by using various blood tests. To evaluate the levels of Procalcitonin and compare it with the normally used sepsis markers such as CRP, Absolute neutrophil count, band cell ratio and compare between these tests.

MATERIALS

The prospective study was conducted in Department of Pediatrics, Rajah Muthiah Medical College Hospital, Annamalai University over a period of one year from October 2014 to October 2015. The blood samples from 100 babies meeting the inclusion and exclusion criteria constituted the material for study. Detail history and clinical findings were recorded in the proforma. Inclusion Criteria: Neonates born to mothers with at least one of the following risk factors are included: Premature rupture of membranes (PROM) > 12 hours, More than 3 vaginal examinations after rupture of membranes, Intrapartum fever (>38⁰C).

Foul-smelling liquor, Meconium stained liquor, Maternal UTI within 2 weeks prior to delivery. Prolonged and difficult delivery with instrumentation. Neonates born in Rajah Muthiah Medical College Hospital, with clinical features suggestive of Sepsis. Exclusion Criteria: New born babies with gestational age < 28 weeks. Neonates with birth weight less than <1000gm. Babies older than 28 days. Babies already on antibiotics. Babies requiring mechanical ventilation on admission.

METHODS

All neonates born in Rajah Muthiah Medical College Hospital, Annamalai University over a period of one year from October 2014 to October 2015, meeting the inclusion and exclusion criteria were included in the study. The blood samples from neonates born to mothers with risk factors for neonatal sepsis was collected and sent for analysis. Detailed birth events, Apgar score, sex of the baby, weight of baby will be recorded on the precoded proforma made available. Gestational age was assessed by using modified Ballard scoring system.

Neonates were followed up for upto 72 hours from the time of birth for the development of any symptoms and signs suggestive of neonatal sepsis and if present were recorded. Blood sample will be collected from the neonate and will be sent for: Procalcitonin levels, CRP levels, Blood culture and sensitivity, Total count, absolute neutrophil count and band cell ratio. For the purpose of the study neonates will be divided in 3 groups: Definite sepsis: Neonate with signs and symptoms suggestive of sepsis with a positive blood culture. Probable sepsis: Will be based on any one of the following: Two or more signs suggestive of sepsis with at least one abnormal laboratory parameters. One or more signs suggestive of sepsis with two or more abnormal laboratory parameters. No Sepsis:

No signs of sepsis or abnormal lab parameters.[2]

Table 1 Shows distribution of cases according to sex (n=100)

Sex	Number of cases	Percentage
Male	57	57.0
Female	43	43.0
Total	100	100.0

Table 2 Shows distribution of cases according to Birth Weight (n=100)

Birth weight (kg)	No. of cases	Percentage
<2.5	28	28.0
>2.5	72	72.0
Total	100	100.0

Table 3 Shows distribution of cases according to Gestational age (n=100)

Gestational age(weeks)	No. of cases	Percentage
<37 weeks	23	23.0
>37 weeks	77	77.0
Total	100	100

Table 4 Shows distribution of cases according to risk factors (n=100)

Maternal risk factors	No. of cases (n=100)	%
Meconium stained liquor	60	60.0
PROM	25	25.0
Prolonged or Inst Del	12	12.0
Maternal UTI	5	5.0
> 3 Vaginal examination	5	5.0
Foul smelling liquor	2	2.0
Intrapartum fever(>38*C)	2	2.0
Maternal infections	0	0.0

Table 5 Shows distribution of cases according to signs of sepsis

Signs of sepsis	No. of cases (n=100)	%
General	27	27.0
RS	53	53.0
GIT	25	25.0
CNS	13	13.0
Circulatory	7	7.0
Hematology	4	4.0

Table 6 Association of Gestational age and Procalcitonin positive

Gestational age in weeks	No. of cases (n=100)	No. Of Procalcitonin positive	Percentage	P value
<37 weeks	23	10	43.5	0.336
>37 weeks	77	24	31.2	0.604

Table 7 Association of Maternal characteristics and Procalcitonin positive

Risk factors	No. of cases (n=100)	No. Of Procalcitonin positive	Percentage	p value
Foul smelling liquor	2	2	100.0	0.049*
> 3 Vaginal examination	5	3	60.0	0.219
PROM	25	9	36.0	0.832
Prolonged OR Inst Del	12	4	33.3	0.957
Meconium stained liquor	60	20	33.3	0.908
Maternal UTI	5	1	20.0	0.509
Intrapartum fever	2	0	0.0	0.544

RESULTS

This prospective study was conducted in Department of Pediatrics, Rajah Muthiah Medical College Hospital, Annamalai University over a period of one year from October 2014 to October 2015. The blood samples from 100 babies meeting the inclusion and exclusion criteria constituted the material for study.

Table 8 Association of Gestational Age and CRP positive

Gestational age in weeks	No. of cases (n=100)	Number of CRP positive	Percentage	p value
<37 weeks	23	8	34.8	0.138
>37 weeks	77	14	18.2	0.421

Table 9 Association of Maternal characteristics and CRP positive

Risk factors	No. of cases (n=100)	Number of CRP positive	Percentage	p value
Foul smelling liquor > 3 Vaginal examination	2	2	100.0	0.008**
Meconium stained liquor	5	2	40.0	0.331
PROM	60	13	21.7	0.955
Prolonged or Inst Del	25	5	20.0	0.809
Maternal UTI	12	2	16.7	0.657
Intrapartum fever	5	0	0.0	-
	2	0	0	-

Table 10 Frequency Distribution of Procalcitonin

Procalcitonin (ng/ml)	Number (n=100)	%
Negative (<0.50)	66	66.0
Positive (>0.50)	34	34.0
Total	100	100%

Table 11 Frequency Distribution of CRP

CRP (mg/l)	No of cases	Percentage
Negative (<5.0)	78	78.0
Positive (>5.0)	22	22.0
Total	100	100%

Table 12 Frequency distribution of Blood culture

Blood culture	Number (n=100)	%
Negative	91	91.0
Positive	9	9.0
Total	100	100%

Table 13 Distribution of Blood culture Species

Blood culture findings	Number (n=100)	%
No growth	91	91.0
MRSA	1	1.0
E. coli	2	2.0
Klebsiella	4	4.0
Pseudomonas	2	2.0

Table 14 Shows the distribution of cases according to Total Count, ANC, Band cell ratio

Total count	No. of cases (n=100)	Percentage
>5000	90	90.0
<5000	10	10.0
Absolute neutrophil count		
>1000	100	100.0
<1000	0	0.0
Band cell ratio		
<20%	96	96.0
>20%	4	4.0

Table 15 Distribution of cases according to final diagnosis

Category	No. of cases (n=100)	Percentage
No sepsis	67	67.0
Probable sepsis	24	24.0
Definite sepsis	9	9.0
Total	100	100%

Table 16 Correlation of Procalcitonin, CRP in relation to blood culture- An observation

	True positive	False Positive	False Negative	True negative	Total
Procalcitonin (>0.5 ng/ml)	5	29	4	62	100
CRP (>5 mg/l)	5	17	4	74	100

Table 17 Evaluation of Procalcitonin in relation to CRP

	Procalcitonin in relation to CRP positivity	CRP in relation to Procalcitonin positivity
True positive; No	22	22
False positive; No	12	0
False negative; No	0	12
True negative; No	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

Table 18 Evaluation of Procalcitonin in relation to Total count

	Procalcitonin in relation to Total count positivity	Total count in relation to Procalcitonin positivity
True positive ; No	25	25
False positive ; No	11	0
False negative ; No	0	11
True negative ; No	64	64
Sensitivity (%)	100.0	65.9
Specificity (%)	83.4	100.0
PPV (%)	65.9	100.0
NPV (%)	100.0	83.4
Accuracy (%)	91.0	91.00

Table 19 Evaluation of Procalcitonin in relation to Absolute neutro count

	Procalcitonin in relation to Absolute neutro count positivity	Absolute neutro count in relation to Procalcitonin positivity
True positive ; No	27	27
False positive ; No	14	0
False negative ; No	0	14
True negative ; No	59	59
Sensitivity (%)	100.0	66.6
Specificity (%)	82.9	100.0
PPV (%)	66.6	100.0
NPV (%)	100.0	82.9
Accuracy (%)	87.0	87.00

DISCUSSION

Among the 100 babies, there were 55 (55%) males and 45 (45%) females. Among the 100 babies, there were 28 (28%) with birth weight <2.5 kg and 72 (72%) with birth weight of >2.5 kg. Among the babies, there were 23 (23%) with gestational age < 37 weeks and 77 (77%) with gestational age of > 37 weeks. Among 100 babies with maternal risk factors 60 (60%) had meconium stained

liquor, 25 (25%) had PROM, 12 (12%) had prolonged or instrumental delivery, 5 (5%) had maternal UTI, 5 (5%) had more than 3 vaginal examinations, 2 (2%) had foul smelling liquor, 2 (2%) had intrapartum fever and none of the babies had maternal infections as a risk factor.[3]

Among 100 babies who developed signs of sepsis, 53 (53%) had developed respiratory problems, 27 (27%) had developed general signs, 25 (25%) developed gastrointestinal tract related problems, 13 (13%) babies had CNS related problems with, 7 (7%) babies had cardiovascular problems and 4 babies had hematological problems. Among the cases with procalcitonin positive, compared with gestational age 10 (43.5%) cases were positive with gestation of <37 weeks and 24 (31.2%) cases positive of cases >37 weeks and there was no statistical significance in relation to gestational age. With relation to risk factors, 2 (100%) cases with foul smelling liquor were positive, 3 (60%) cases with > 3 vaginal examinations were positive, 9 (36%) of cases with PROM were positive, 4 (33.3%) cases with prolonged or instrumental delivery were positive, 20 (33.3%) cases with meconium stained liquor were positive, 1 (20%) with maternal UTI were positive and none positive in cases with intrapartum fever as risk factor. Statistical significance was observed only in cases with foul smelling liquor (p value=0.049).

Among the cases with CRP positive, compared with gestational age 8 (34.8%) cases were positive with gestation of <37 weeks and 14 (18.2%) cases positive of cases >37 weeks and there was no statistical significance in relation to gestational age. With relation to risk factors, 2 (100%) cases with foul smelling liquor were positive, 2 (40%) cases with > 3 vaginal examinations were positive, 13 (21.7%) of cases with meconium stained liquor were positive, 5 (20%) cases with PROM were positive, 2 (16.7%) cases with prolonged or instrumental delivery were positive, none positive in cases with maternal UTI, intrapartum fever as risk factor.

Statistical significance was observed only in cases with foul smelling liquor (p value=0.008). [4] Among 100 babies, Procalcitonin is positive in 34 (34%) and negative in 66 (66%) Among 100 cases CRP was positive in 22 (22%) and negative in 78 (78%) Among 100 cases blood culture was positive in 9 (9%) of babies and negative in 91 (91%) of babies Among the 100 cases, There was no sepsis observed in 67 (67%) of cases, probable sepsis was observed in 24 (24%) of cases and definite sepsis was observed in 9 (9%). Among the 100 cases, compared with blood culture, Procalcitonin was true positive in 5 cases, false positive in 29, false negative in 4 and true negative in 62. CRP was true positive in 5, false positive in 17, false negative in 4 and true negative in 74 cases.

Among the 100 cases, Procalcitonin in comparison with CRP, sensitivity was 100%, specificity was 84.6%, PPV was 64.7%, and NPV was 100%. CRP in comparison with Procalcitonin, sensitivity was 64.7%, specificity was 100%, PPV was 100%, and NPV was 84.6%.

Procalcitonin in comparison with CRP shows better sensitivity and negative predictive value.

Among the 100 cases, Procalcitonin in comparison with Total count, sensitivity was 100%, specificity was 83.4%, PPV was 65.9% and NPV was 100%. Total count in comparison with Procalcitonin, sensitivity was 65.9%, specificity was 100%, PPV was 100% and NPV was 83.4%. Procalcitonin in comparison with total count shows better sensitivity and negative predictive values Among the 100 cases, Procalcitonin in comparison with Absolute neutro count, sensitivity was 100%, specificity was 82.9%, PPV was 66.6% and NPV was 100%. Absolute neutro count in comparison with Procalcitonin, sensitivity was 66.6%, specificity was 100%, PPV was 100% and NPV was 82.9%. Procalcitonin in comparison with Absolute neutro count shows better sensitivity and negative predictive values.

SUMMARY

This is a prospective study conducted over a period of one year from October 2014 to October 2015. Neonatal septicaemia is a leading cause of mortality and mortality of neonates in our country. Early diagnosis with a reasonable degree of accuracy will help the clinician to decide on the usage of proper antibiotic which will help in reducing the morbidity and mortality. A positive blood culture is the only definitive and fool proof method of confirming a case of septicemia. The culture and sensitivity test requires a minimum period of 48 hours which is a precious time in making a decision in the treatment of sepsis in the newborn. Rapid diagnosis by using Procalcitonin and CRP gives reasonable degree of accuracy in diagnosing neonatal sepsis and will also guide antibiotic therapy. [5] 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 decrease in the number of patients treated unnecessarily.

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