Original Article

Neonatal sepsis- Early detection comparing Procalcitonin and CRP as markers and newer tools

Bhat AA[1], Shamim A[2], Gul S[3], Akther R[4], Bhat I[5]

[1]Dr Altaf Ahmad Bhat
DNB Paediatrics
[2]Dr Anjum Shamim
MD Anesthesiology
[3]Dr Sabeeha Gul
MD Radiodiagnosis
[4]Dr Rukaya Akther
MBBS
[5]Dr Iqra Bhat
MBBS
[1,2,3]Senior Resident
[1,2,3,4,5]GMC Srinagar, India

Received: 24-11-2015
Revised: 30-11-2015
Accepted: 05-12-2015

Correspondence to:
Dr Altaf Ahmad Bhat
dr.altaf_bhat@rediffmail.com

ABSTRACT

Background: *Neonatal sepsis continues to be a major cause of morbidity and mortality in India, but is treatable if diagnosis is made in time.*

Objectives: *The present study was undertaken to evaluate and highlight the importance of procalcitonin v\s CRP in early detection of neonatal sepsis.*

Materials and Methods: *The prospective study enrolled 150 neonates who had maternal risk factors and clinically suspected of infection (study group). Abnormal total leukocyte count, abnormal total polymorphonuclear neutrophils (PMN) count, elevated immature PMN count, elevated immature: Total (I:T) PMN ratio, platelet count ≤150,000/mm^3, and pronounced degenerative or toxic changes in PMN were noted by the pathologist who were blind for the clinical status of the baby in NICU. Blood culture was taken as a gold standard for septicemia. The perinatal history, clinical profile and laboratory data were recorded and correlated in each case. Each hematological parameter was assessed for its individual performance and also with the culture-proven sepsis. Sensitivity, specificity, positive and negative predictive values (NPVs) were calculated for each parameter and for different gestational ages. P value was also calculated for different parameters.*

Results: *Among 150 babies evaluated for sepsis in NICU over a period of one year, Procalcitonin is observed as better early marker of neonatal sepsis over and CRP:- Procalcitonin in comparison with CRP: - Sensitivity was 97% Specificity was 59% PPV was 70% and NPV was 99.9%. With area under ROC curve being 0.915(p-value of 0.02) CRP in comparison with Procalcitonin: - Sensitivity was 75% Specificity was 75% PPV was 86% and NPV was 99%. With area under ROC curve being 0.769 (p- value 0.61)*

Conclusion: *The sensitivities of the screening test namely C-reactive protein and Procalcitonin were found to be satisfactory in identifying neonatal sepsis. Comparing to Other test procalcitonin appears to be simple and feasible diagnostic tool although costly.*

Keywords: *Neonatal sepsis, Procalcitonin, C- reactive protein, ROC*

Introduction

Neonatal sepsis continues to be a major cause of morbidity and mortality in India, but is treatable if diagnosis is made in time. [1] One to eight cases of neonatal septicaemia are reported in all live births [2] and it is one of the four leading causes of morbidity and mortality in India. Neonatal sepsis can be early or late in onset. In early onset, maximum cases are observed within 24 h of life, and smaller percentage thereafter up to 7 days. The infection can be transmitted from the mother via transplacental route, ascending infection, during passage through an infected birth canal, or exposure to infected blood at delivery. [3] The new born infants are more susceptible to bacterial invasion than the older children due to their weak immune system, premature are moresusceptible. [4] It is absolutely necessary to diagnose neonatal infection early, recognizing its risk

factors, its causes, using clinical signs and rapid diagnostic method so that no time gap is narrowed to start the appropriate treatment. If not recognized early, it can cause septicaemia 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.The major concern of the clinicians is its non-specific presentation and sometimes the rapid progression of sepsis. Blood culture is gold standard test but the procedure is time consuming (takes 48-72 h) [5,6] and the yield is low (8-73%)[5,6,7,8,9] and the facilities for the test might not be available in all the labs of resource poor countries. So, the significance of various screening tests, either singly or in combination is observed. Acute phase reactant are good indicators as sepsis marker but their cost is very, accurate slide study by pathologist can give us information about sepsis more accurately.

Material and Methods

The prospective study was conducted in Neonatal Division of Department of Pediatrics in a tertiary care hospital, from August 2012 to August 2013, the blood samples from 150 babies meeting the inclusion and exclusion criteria constituted the material for study. Detail history and clinical findings were recorded in the proforma.

Inclusion Criteria

1) Neonates born to mothers with at least one of the following risk factors are included:

a) Premature rupture of membranes (PROM) > 12 hours.
b) More than 3 vaginal examinations after rupture of membranes.
c) Intrapartum fever (>38^{0}C).
d) Foul-smelling liquor.
e) Meconium stained liquor.
f) Maternal UTI within 2 weeks prior to delivery.
g) Prolonged and difficult delivery with instrumentation.
h) Babies Brought from outside to NICU.

Exclusion Criteria

a) New born babies with gestational age < 28 weeks.
b) Neonates with birth weight less than <1000gm.
c) Neonates with lethal congenital anomalies.
d) Still born and fetal deaths.
e) Post-dated neonates

The following are considered as signs and symptoms suggestive of sepsis:
General: Hypothermia, Poor feeding, Sclerema, Mottling, Lethargy
Cardiovascular system: Bradycardia, Tachycaidia, CFT>2 second
Respiratory system: Apnea, RDS, Chest retractions, Cyanosis, Grunting
Central nervous system: Hypotonia, Irritability, Seizures, High pitched cry
Gastrointestinal system: Vomiting, Abdominal distension, Hepatomegaly

The following are considered as abnormal laboratory parameters:

- Total leukocyte 5000/cmm.
- Absolute Neutrophil count <1000/cmm.
- Band cell count >20%.

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: Based on any one of the following:

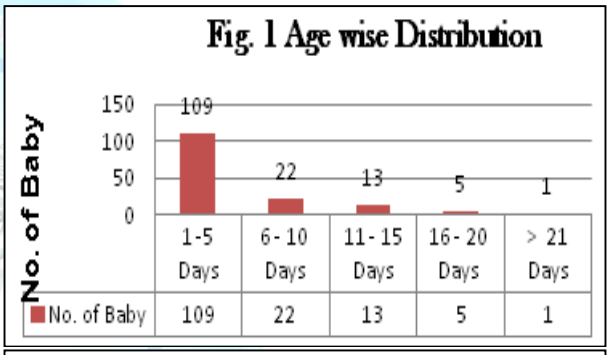
- Two or more signs suggestive of sepsis with at least one abnormal laboratory parameters.
- One or more signs suggestive of sepsis with two or more abnormal laboratory parameters.

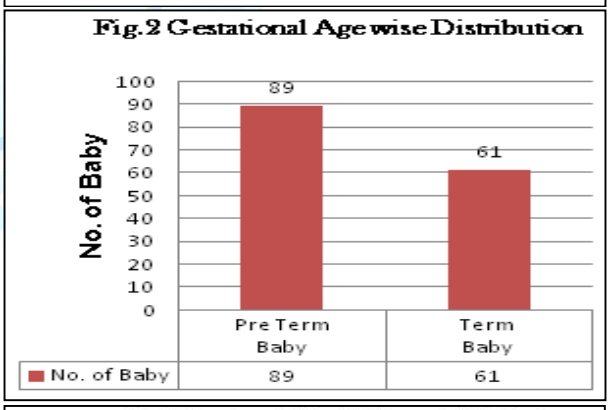
No Sepsis: No signs of sepsis or abnormal lab parameters

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 present were recorded, Infants with <37 weeks gestational age were regarded as preterm and >37 weeks term. [10] Under complete aseptic conditions, 0.5-1 ml of blood sample was obtained by peripheral venepuncture. Sepsis work-up involved complete blood counts, C-reactive protein, procalcitonin and blood culture. Reduced platelet count as a part of observational data was recorded, but not included as sepsis marker in the study, though in various studies it has been correlated with sepsis, [11] reduced platelet count can be due to other causes as well was Peripheral blood smears were prepared immediately, stained with Leishman stain and examined under oil-immersion lens of light microscope at a magnification of ×1000. Differential counts were performed on these smears by counting at least 200 cells. All the peripheral blood smears were analysed by pathologists blinded to the infection status of these infants and observed manually:

- White blood cell (WBC) count and its differential count.
- Nucleated red blood cell count (to correct total WBCs count)
- Abnormal total leukocyte count, abnormal total PMN count, elevated immature PMN count, elevated immature to total (I:T) PMN ratio,

Sensitivity, specificity, positive and negative predictive values (NPVs) were calculated for each parameter. *P* value was also calculated for different parameters. Data was compiled and statistically analyzed by using SPSS software.





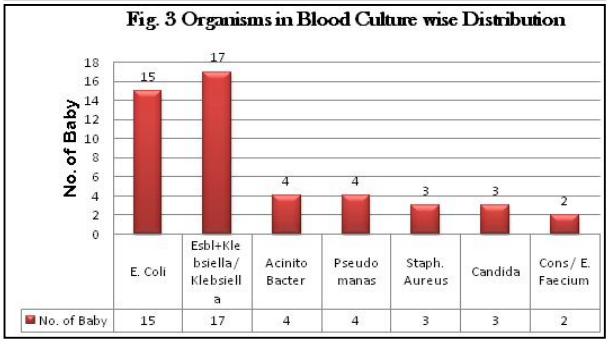


Table: 1(a) Distribution of Symptoms in relation to sepsis

Sl. No.	Type of Symptoms	No. of Baby	% of Baby	No. of Sepsis Baby	% of Sepsis Baby with Symptoms
1	**General**	62	41.33%	28	58.33%
2	**CVS**	21	14.00%	10	20.83%
3	**RS**	82	54.67%	25	52.08%
4	**CNS**	16	10.67%	11	22.92%
5	**GIT**	54	36.00%	23	47.92%
6	**Renal**	7	4.67%	1	2.08%
7	**Hematology**	12	8.00%	6	12.50%

Table:1(b) Number of different types clinical symptoms in baby in relation to sepsis

Sl. No.	No. of Symptoms	No. of Baby	% of Baby	No. of Sepsis Baby	% of Sepsis Baby with Symptoms
1	0	11	7.33%	2	18.18%
2	1	64	42.67%	10	15.63%
3	2	60	40.00%	26	43.33%
4	>3	15	10.00%	10	66.67%
	Total	**150**		**48**	

Table: 1(c) Growth of babies v/s number of babies (cases)

Sl. No.	Growth	No. of Baby
1	No Growth	102
2	Growth	48
	Total Cases	150

Among 150 babies included in the study on the basis of maternal risk factors and clinical signs following were the observational points:-

Males were 85(56%) and females were 65(43%). 99 (66%) cases were less than 2.5 kg and 51(34%) babies were more than 2.5 kg. 89 (59.9%) cases are less than 37 weeks and 61 (40.6%) cases were more 37 weeks of gestation. With risk factor 6% had meconium stained liquor, 27% had PROM, 2% had prolonged or instrumental delivery, 2% had maternal UTI, 9.3%had foul smelling liquor 20% had intrapartum fever 4% having more than 3 vaginal examinations. Regard to signs of sepsis, 82(54%) had developed respiratory problems out which 25 babies (52.08%) developed sepsis, 62 babies (41.33%) had developed general signs. Out of which 28 (58.33%) developed sepsis, 54 babies (36%) developed gastrointestinal tract related problems out of which 23(47.92%) developed sepsis, 16(10.6%) babies had CNS related problems out of which 11(22.9%) developed sepsis, 21(14%) babies had cardiovascular problems out of which 10(20%) developed sepsis, 7(4.67%) babies had renal problems out of which 1(2.08%) developed sepsis and 12(8%) babies had haematological problems out of which 6(12.5%) developed sepsis. Procalcitonin is positive in 88 cases and negative in 62 babies. CRP was positive 61 cases and negative in 89 cases. 102 cases had blood culture negative and in 48 cases blood culture was positive. Total count Positive Test Report (TLC ≤ 5,000 &> 20,000) was noted in 39 of patients and in the remaining 111 was Negative Test Report (TLC <= 20,000 &> 5,000). Absolute neutrophil count < 1500 was observed in one baby rest of the babies (149) ANC > 1500. Band cell ratio >20% was noted in 20 cases and 1130 of cases had ratio of <20%. There was no sepsis observed in 58 of cases, probable sepsis was observed in 44 of cases and definite sepsis was observed in 48 cases.

Table: 2 Product Moment Correlation Coefficients - r

R	ProCalcitonin	CRP	Total Leucocyte Count (TLC)	Absolute Neutophil Count	Band Cell Count
ProCalcitonin					
CRP	0.166				
Total Leucocyte Count (TLC)	-0.123	0.255			
Absolute Neutophil Count	0.003	0.245	0.459		
Band Cell Count	0.128	0.625	0.691	0.404	
I/T Ratio	0.399	0.676	0.146	0.194	0.657
Outcome of Sepsis (Growth in Blood Culture)	0.471	0.401	0.086	0.099	0.480

Table: 3 Testing of Correlation Coefficients

Pair	r	95% CI		p-value
Procalcitonin & Band Cell Count	0.128	-0.033	to 0.282	0.1198
Procalcitonin & I/T Ratio	0.399	0.255	to 0.525	<0.0001
Procalcitonin & Outcome of Sepsis	0.471	0.336	to 0.587	<0.0001
CRP & Band Cell Count	0.625	0.517	to 0.714	<0.0001
CRP & I/T Ratio	0.676	0.578	to 0.754	<0.0001
CRP & Outcome of Sepsis	0.401	0.257	to 0.527	<0.0001

H0:ρ= 0

The correlation coefficient ρ of the bivariable population is equal to 0.

H1: ρ ≠ 0

The correlation coefficient ρ of the bivariable population is not equal to 0. Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level. Do not reject the null hypothesis at the 5% significance level.

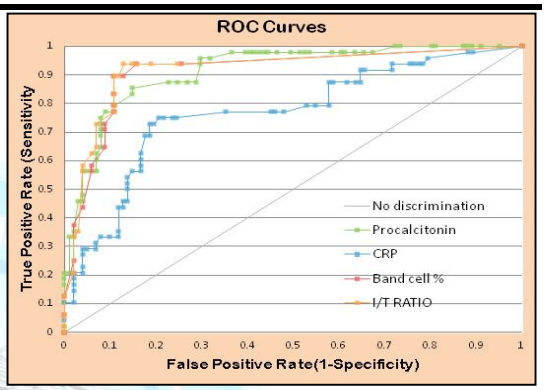


Table: 4 Area under ROC Curve

Test	AUC	95% Confidence Interval		S. E.
		LCL	UCL	
Logistic Regression	0.963	0.937	0.990	0.0134
I/T RATIO	0.917	0.867	0.968	0.0259
Procalcitonin	0.915	0.868	0.962	0.0238
Band cell %	0.912	0.861	0.964	0.0263
CRP	0.769	0.684	0.854	0.0434

Discussion

Neonatal sepsis with its high mortality rate, still remains a diagnostic and treatment challenge for neonatal health care providers, developing countries have the highest incidence and mortality rates. This may be due to problems in utero by anatomical defects, infections and infected birth passage etc. Early diagnosis of neonatal septicemia helps the clinician in instituting antibiotics therapy at the earliest thereby reducing mortality in neonates. Early identification of an infected neonate also helps in avoiding unnecessary treatment of a non-infected neonate.

The higher proportions of cases were found, with gestational age less than 37 weeks, Preterm are more susceptible to infections than are the term babies, which is due to their poor immune system, low levels of immunoglobulins and low weight at birth. [12]

The I/T ratio evaluation is significant in many other ways also, regarding its easy availability, accessibility, low cost, less time consuming and practically possible in all the laboratories, which makes it convenient for any common man to get a high risk infant tested and diagnosed on time. Most of babies presented in our study in first few days of life and were managed as early onset sepsis. [13, 14]

In our study, we correlated the sensitivity, specificity, PPV, and NPV of the various test and compared also with the each other. Elevated I:T ratio was found to be the most reliable indicator of sepsis in our study, and also in various other studies like those done by Ghosh et al [4] and Narasimha et al. [15, 16] Immature PMN count and I:T PMN ratio was also a very sensitive indicator of neonatal sepsis. Also, in our study, the total PMN count had a limited role in sepsis screening. These finding were similar to the study done by Akenzua. [17]

In our study procalcitonin was found to be highly sensitive rapid and simple method of identification of neonatal sepsis in comparison to C-reactive protein.

References

1. Manucha V, Rusia U, Sikka M, Faridi MM, Madan N. Utility of haematological parameters and C-reactive protein in the detection of neonatal sepsis. J Paediatr Child Health 2002;38:459–64.
2. Baley J, Goldfarb J. MH, Klaus MH, Fanaroff AA. Neonatal infections. Care of the high risk neonate. 4th ed. Philadelphia: WB Saunders Company; 1993.
3. Mayuga WA, Isleta PF. Clinical correlation of neonatal and maternal hematological parameters as predictors of neonatal sepsis. PIDSP 2005;9:36–42.
4. Ghosh S, Mittal M, Jaganathan G. Early diagnosis of neonatal sepsis using a hematological scoring system. Indian J Med Sci 2001;55:495–500.
5. Sharma A, Kutty CV, Sabharwal U, Rathee S, Mohan H. Evaluation of sepsis screen for diagnosis of neonatal septicemia. Indian J Pediatr 1993;60:559–63.
6. Misra PK, Kumar R, Malik GK, Mehra P, Awasthi S. Simple hematological tests for diagnosis of neonatal sepsis. Indian Pediatr 1989;26:156–60.
7. Baltimore RS, Huie SM, Meek JI, Schuchat A, O Brien KL. Early-onset neonatal sepsis in the era of group B streptococcal prevention. Pediatrics 2001;108:1094–8.
8. Gladstone IM, Ehrenkranz RA, Edberg SC, Baltimore RS. A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience. Pediatr Infect Dis J 1990;9:819–25.
9. Varsha, Rusia U, Sikka M, Faridi MM, Madan N. Validity of hematologic parameters in identification of early and late onset neonatal infection. Indian J Pathol Microbiol 2003;46:565–8.
10. Arias F, Daftary SN, Bhide AG. Practical Guide to High Risk Pregnancy and Delivery. A South Asian Perspective. 3rd ed. New Delhi: Elsevier; 2008.p.193–216.
11. Rodwell RL, Leslie AL, Tudehope DI. Early diagnosis of neonatal sepsis using a hematologic scoring system. J Pediatr 1988;112:761–7.
12. Bhat YR, Rao A. Sepsis screen in early neonatal sepsis. J Clin Diagn Res 2010;4:3331–6.
13. Anwer SK, Mustafa S. Rapid identification of neonatal sepsis. J Pak Med Assoc 2000;50:94–8.

14. Bellig L, Ohning B. Neonatal Sepsis. E Medicine Journal Pediatrics /Neonatology 2003;4(1):6.
15. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. J Pediatr 1979;95:89–98.
16. Narasimha A, Harendra Kumar ML. Significance of Hematological Scoring System (HSS) in early diagnosis of neonatal sepsis. Indian J Hematol Blood Transfus 2011;27:14–7.
17. Akenzua GI, Hui YT, Milner R, Zipursky A. Neutrophil and band counts in the diagnosis of neonatal infections. Pediatrics 1974;54:38–42.

Cite this article as: Bhat AA, Shamim A, Gul S, Akther R, Bhat I. Neonatal sepsis - Early detection comparing Procalcitonin and CRP as markers and newer tools. Int J Med and Dent Sci 2016; 5(1):1048-1055.

Source of Support: Nil

Conflict of Interest: No