Early diagnostic markers for neonatal sepsis – Haematological scoring system, C-Reactive protein and Procalcitonin

Dr Malvika Gaur, Dr Arathi C.A.

DOI: 10.29322/IJSRP.9.05.2019.p8975
http://dx.doi.org/10.29322/IJSRP.9.05.2019.p8975

***Abstract*- Background:** Neonatal sepsis is associated with high mortality and morbidity rate, as the clinical manifestations are nonspecific. Therefore, the need arises for early diagnostic markers of neonatal sepsis like Haematological scoring system (HSS), C-Reactive protein (CRP), Procalcitonin (PCT).

Aim : To evaluate the role of diagnostic parameters – HSS, CRP and PCT in the early detection of neonatal sepsis.

Methods: 50 cases of neonatal sepsis were studied, HSS was calculated as per the 7 point Rodwell et al scoring system. PCT was calculated by the semi-quantitative kit.

Statistical analysis : The results were compared with each other (comparative study design), with the gold standard (blood culture). Specificity, sensitivity, PPV & NPV were calculated.

Result: Blood culture was Positive - 46 % cases , negative - 54% cases, most common isolate obtained Coagulase negative staphylococcus aureus (CONS) 47.3% cases, Staphylococcus aureus (34.78% cases). HSS obtained Sepsis very likely - 56% cases, Sepsis possible - 40% cases, Sepsis unlikely - 4% cases.
CRP results obtained positive results - 60% cases, negative - 40% cases. PCT results were positive - 86% cases and negative - 14% cases.

Conclusion: Among the various screening tests, PCT has higher sensitivity of 91.3% as compared to CRP (73.9%), HSS (65.2%). Thus, PCT is a better marker for screening neonatal sepsis. However it is not very specific, can be raised in various other conditions.

***Index Terms*-** Blood culture, HSS, Neonatal sepsis, PCT

I. Introduction

Neonatal sepsis is associated with high mortality and morbidity rate, as the clinical manifestations are nonspecific.[1] therefore, it is very essential to diagnose the sepsis in early phase and also it is equally important to rule out neonatal sepsis.[2] Therefore, the need arises for early diagnostic markers of neonatal sepsis like Haematological scoring system (HSS), C-Reactive protein (CRP) and Procalcitonin (PCT). An early diagnosis using a sensitive marker can reduce the mortality and improve the outcome. According to the National Neonatal Perinatal Database (NNPD) report 2002-2003, the incidence of neonatal septicemia in tertiary care institutions has been reported to be 14.5 per 1000 live births (2.3%) and contributes to 16% of all mortalities among the hospital born neonates. (National Neonatal Perinatal Database. Report for the year 2002-03. National Neonatology Forum, India).[3]

Aim : To evaluate the role of diagnostic parameters – HSS, CRP and PCT in the early detection of neonatal sepsis.

Objective :

1. To evaluate the role of HSS, CRP and PCT in the early detection of neonatal sepsis.
2. To compare between HSS, CRP and PCT, as a better marker in the early detection of neonatal sepsis.
3. To derive the sensitivity and specificity of PCT as an early diagnostic marker.

II. MATERIALS AND METHODS

In the present study 50 cases of clinically suspicious cases of neonatal sepsis were studied.

Inclusion criteria : Clinically suspected cases of neonatal sepsis admitted in the neonatal intensive care (NICU) and neonates who developed signs and symptoms of sepsis while they were admitted in NICU.

Exclusion criteria : 1. Suspected cases of septicaemia, where antibiotics have already been administered, 2. Inborn errors of metabolism, 3. Congential anomalies.

An approval from the ethical committee was obtained and ethical practices were observed during the study. Written valid consent was taken from the parents. A detailed clinical history and findings were recorded. The blood samples were collected and processed for HSS, CRP and PCT. Blood culture – 1 ml of blood was drawn aseptically and inoculated into blood culture bottles containing 10 ml of brain heart infusion broth.

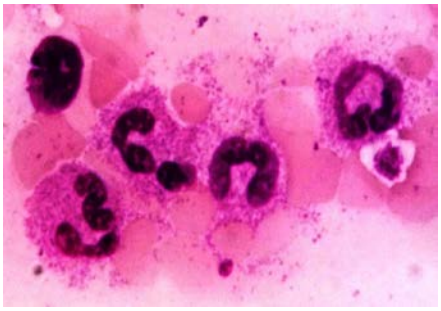
HSS was calculated as per the 7 point Rodwell et al scoring system in the present study.[4]

SN	Criteria	Abnormality	Score
1	Total WBC count	≤5,000/µl	1
		≥35,000/µl	
		≥30,000/µl	
		≥21,000/µl	
2	Total PMN count	≤1,800/µl & ≥5,400/µl (at birth)	1
		≥5,400/µl (12-24 hours)	
		≥5,400/µl (2 days onwards)	
		No mature PMN seen	2

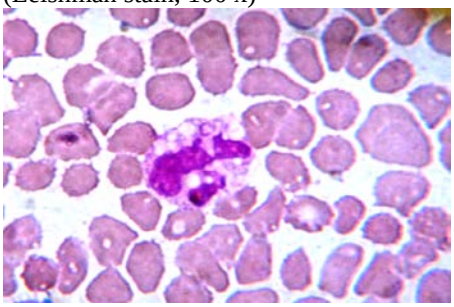
3	Immature PMN count (Picture 1	<600/µl	0
		≥600/µl	1
4	I:T PMN ratio	≤ 0.3	0
		≥ 0.3	1
5	I:M PMN ratio	≤ 0.3	0
		≥ 0.3	1
6	Degenerative changes in PMN (Picture 1,2)	Toxic granules(picture 1) /cytoplasmic vacuoles (picture 2)/dohle bodies	1
7	Platelet count	≤1.5 lakh/µl	1

Abnormal total PMN count is assigned score of 2, instead of 1, if no mature polymorphs are seen on peripheral smear examination to compensate for low immature to mature ratio. Thus a score of 0 to 8 was obtained and interpreted as – score ≤2 - Sepsis unlikely, 3-4 - Sepsis possible, ≥5 - Sepsis very likely.[4]

Picture 1 – Peripheral smear showing band forms and toxic granules (Leishman stain, 100 x)

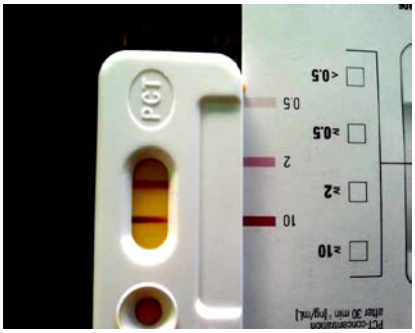


Picture 2 – Peripheral smear showing cytoplasmic vacuolations (Leishman stain, 100 x)



CRP was assessed using the rapid slide latex agglutination qualitative method (LAB-CARE DIAGNOSTICS (INDIA) PVT LTD). PCT was assessed using B.R.A.H.M.S PCT-Q KIT (Picture 3) manufactured by Thermo SCIENTIFIC, an immunochromatographic test for the semi-quantitative detection of PCT concentrations in serum/plasma. PCT level of <0.5 ng/ml - Sepsis not likely, ≥0.5 ng/ml to <2ng/ml - Sepsis possible, ≥2 ng/ml to 10 ng/ml - Sepsis likely and ≥10 ng/ml - Sepsis very likely (Picture 3).

Picture 3 – Commercially available PCT – Q Kit : positive PCT (≥10 ng/ml)

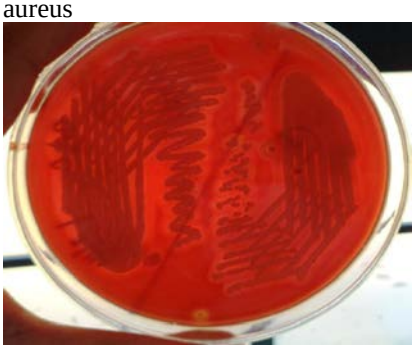


Statistical analysis : The results were compared with each other and with the gold standard (blood culture). Specificity, sensitivity, PPV & NPV were then calculated.

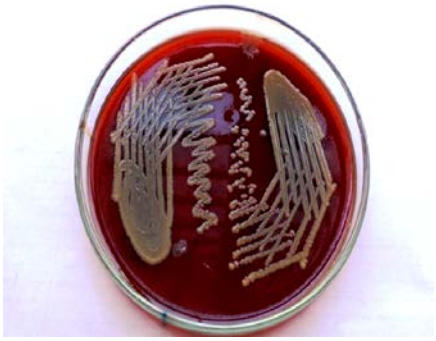
III. RESULT

Blood culture was Positive in 46 % cases and negative in 54% cases. Blood culture most common isolate obtained Coagulase negative staphylococcus aureus (CONS) 47.3% cases and Staphylococcus aureus (34.78% cases) (Picture 4,5).

Picture 4 – MacConkey agar showing growth for Staphylococcus aureus



Picture 5 – Blood agar showing growth for Coagulase negative Staphylococcus aureus.



HSS obtained Sepsis very likely (56% cases), Sepsis possible (40% cases) and Sepsis unlikely (4% cases). CRP results obtained positive results in 60% cases and negative in 40% cases. PCT results were positive in 86% cases and negative in 14% cases.

Table 1 : Correlation of HSS with gold standard (blood culture)

HSS	Blood culture		Total
	Positive	Negative	
Positive	15	13	28
Negative	8	14	22
Total	23	27	50

Table 2 : Correlation of CRP with gold standard (blood culture)

CRP	Blood culture		Total
	Positive	Negative	
Positive	17	13	30
Negative	6	14	20
Total	23	27	50

Table 3 : Correlation of PCT with gold standard (blood culture)

PCT	Blood culture		Total
	Positive	Negative	
Positive	21	22	43
Negative	2	5	7
Total	23	27	50

Table 4 : Sensitivity, specificity, NPV and PPV of PCT, CRP and HSS.

Parameter	Sensitivity	Specificity	PPV	NPV
PCT	91.3%	18.5%	48.8%	71.4%
CRP	73.9%	51.9%	56.7%	70.0%
HSS	65.2%	51.9%	53.6%	63.3%

Among the various screening tests, PCT has a higher sensitivity of 91.3% as compared to CRP (73.9%) and HSS (65.2%). Thus, PCT is a better marker for screening neonatal sepsis. However it is not very specific and can be raised in various other conditions. 94% cases were healthy when discharged, 2% were discharged against medical advice and 4% died.

It was noted that neonatal risk factors associated with sepsis were low birth weight (<2.5 kg) (78% cases), preterm (<37 weeks of gestational age) (80% cases), lower socioeconomic status (82% cases) and born to multigravida mothers (72% cases). Early onset neonatal sepsis (presented within 7 days of birth) was seen in (78% cases). Respiratory distress syndrome was seen in 51.28% cases and Meconium aspiration syndrome in 20.51% cases. Maternal risk factors associated with neonatal sepsis were Anaemia during pregnancy (32.69% cases), Pregnancy induced hypertension (30.77% cases) and Premature rupture of membranes (26.92% cases).

IV. DISCUSSION

Blood culture is gold standard for definitive diagnosis of neonatal sepsis, but it has its own limitations.[5] The yield of a positive blood culture ranges from 8-73%.[6] A negative blood culture does not exclude sepsis[7] and about 26% of all neonatal sepsis could be due to anaerobes.[8] Maternal antibiotics given in preterm deliveries may suppress the growth of bacteria in culture.[1]

HSS is a simple cost, quick and effective tool in the early diagnosis of neonatal sepsis, but its sensitivity is unsatisfactory. Therefore it cannot provide a guideline to decisions regarding antibiotic therapy.[9,10] It can be applied to even those neonates who have received antibiotic therapy. WBC varied widely across studies, with sensitivity & specificity ranging from 17% to 90% and 31% to 100%.[11] WBC maybe helpful in diagnosing sepsis, however normal WBC counts maybe observed in as many as 50% of culture proven sepsis cases, and neonates who are not affected may also have abnormally high WBC counts as a result of the stress of delivery.[12] 39 of 50 neonates presented with neutrophilia. Total neutrophil count was of limited value for the diagnosis of sepsis since the elevation is often late and inconsistent. Neonates with proven bacterial sepsis had normal neutrophil count, but the bands increased beyond the normal range.[8,13] The associated band count and a leftward shift of the myeloid immaturity measurements may improve the diagnostic yield, but their subjective measurement is problematic.[14] Neutrophilia itself is not a reliable or sensitive indicator of infection.[8] Thrombocytopenia was frequently associated with sepsis and indicated poor prognosis.[4,13] It is an important parameter in supporting the diagnosis of sepsis, although it appears to be a late finding and nonspecific.[15] 21 cases of low platelet count were seen in the present study.

CRP is commonly used for detection of sepsis in neonates, but it is not useful as an early phase infection marker and it lacks specificity.[16] Long duration between invasion by infectious agent and the rise in serum CRP concentrations.[12] CRP can be considered as a specific but late marker of neonatal infections.[11]

PCT rapidly increases in 6 to 8 hours, and then a plateau in 12 to 48 hours. Plasma elimination is approx 25 to 30 hours.[17] Therefore it has value in early detection of neonatal sepsis, and shows quick reduction in its level post antibiotic therapy.[14,1,19] PCT is more sensitive than CRP, in the diagnosis of septicaemia, meningitis and UTI29. PCT used together with CRP, a negative PCT test may help in “ruling out” while a raised CRP result helps in “ruling in”, the possibility of sepsis, particularly of the late onset type.[14] The early response to appropriate antibiotic therapy can be evaluated by PCT in the septic neonates, but not by CRP. Late response to treatment can be evaluated by both CRP and PCT.[20] It is not the sole marker of neonatal sepsis, and is relatively expensive.

This study correlated with a study by Sucilathangam G in 2012 studied PCT and CRP in neonates admitted to NICU. They concluded that PCT was more sensitive than CRP in the detection of neonatal sepsis. A negative PCT test result may help to “rule out”, while a raised CRP result helps to “rule in”, the possibility of sepsis.[20] Monsef A and Eghbalian F in 2012 concluded that PCT has a high sensitivity, specificity, PPV and NPV for the diagnosis of neonatal sepsis.[21] Mamdouh M. Esmat in 2012 concluded that the serum levels of PCT is more reliable marker than the serum levels of CRP in the early diagnosis of neonatal sepsis and in the evaluation of the response of the disease to the antibiotic therapy.[1] H Altunhun in 2011 studied PCT, CRP and blood cultures of neonates admitted to NICU for neonatal sepsis and concluded that PCT measurement at birth may initially be

normal, a serial PCT measurement at 24 hours of age may be more helpful for an early diagnosis. During the first 24 hours of life PCT is a more sensitive marker of infection that CRP.[22] Ibeh Isaiah Nnanna in 2011 concluded that PCT monitoring could be helpful in the early diagnosis of neonatal septicemic infection in the intensive care unit. Both absolute values and variations should be considered and evaluated in further studies.[23]

A combination of 3 or all of 4 tests was highly specific 95%-100%.[24]

Limitations in this study were -small sample size, lack of follow up repeat PCT levels and blood culture negative results, even in clinically proven sepsis, this reduced the sensitivity and specificity of CRP and PCT.

V. CONCLUSION

HSS and CRP are simple, quick and cost effective tool in the early diagnosis of neonatal sepsis, but its sensitivity in detection of neonatal sepsis is unsatisfactory.PCT had a higher sensitivity (91.3%) as compared to CRP & HSS.PCT is a better marker for screening neonatal sepsis. However is not very specific and can be raised in various other conditions.

ACKNOWLEDGEMENTS

1. Dr Arathi CA – my guide for her constant support and guidance. She is MD Pathology, working in Sri Siddhartha medical college, Tumkur during the study.

2. Dr Shardadevi MY, Department of microbiology, Shri Siddhartha medical college, Tumkur, Karnataka for carrying out the blood cultures and providing reports and photography, and cooperation.

FUNDING: author 1 – Dr Malvika Gaur

COMPETING INTERESTS:
NA

REFERENCES

[1] Esmat MM, Hassan A, Moghazy HM, Sadek AA. Procalcitonin or C-reactive protein or both for diagnosis of neonatal sepsis. Journal of Applied Sciences Research 2012;8(8):4615-23.

[2] Buch AC, Srivastava V, Kumar H, Jadhav PS. Evaluation of haematological profile in early diagnosis of clinically suspected cases of neonatal sepsis. International Journal of Basic and Applied Medical Sciences 2011;1(1):1-6.

[3] NNPD Network. National Neonatal-Perinatal Database. Report 2002-03. New Delhi:NNPD Nodal Center;2005.

[4] Rodwell RL et al. Hematological scoring system in early diagnosis of sepsis in neutropenic newborn. The Pediatric infectious disease journal 1993;12(5):372-76.

[5] Tripathi S , Malik GK. Neonatal Sepsis: past, present and future; a review article. Internet Journal of Medical Update 2010 July;5(2):45-54.

[6] Adib M, Bakhshiani Z, Navaei F, Fosoul FS, Fouladi S, Kazemzadeh H. Procalcitonin: A Reliable Marker for the Diagnosis of Neonatal Sepsis. Iranian Journal of Basic Medical Sciences 2012;15(2):777-82.

[7] Misra RN, Jadhav SV, Ghosh P, Gandham N, Angadi K, Vyawahare C. Role of sepsis screen in the diagnosis of neonatal sepsis. Medical Journal of Dr. D.Y. Patil University 2013;6(3):254-57.

[8] Mayuga WAB, Isleta PFD. Clinical correlations of neonatal and maternal hematological parameters as predictors of neonatal sepsis. PIDSP Journal 2005;9(2):36-43.

[9] Shirazi H, Riaz S, Tahir R. Role of the Hematological Profile in Early Diagnosis of Neonatal Sepsis. Ann. Pak. Inst. Med. Sci. 2010;6(3):152-56.

[10] Khalada Binte Khair KB et al. Role of Hematologic Scoring System in Early Diagnosis of Neonatal Septicemia. BSMMU J 2010;3(2):62-67.

[11] Ng PC. Diagnostic markers of infection in neonates. Arch Dis Child Fetal Neonatal Ed 2004;89:229-35.

[12] Aboud MI, Waise MMA, Shakerdi LA. Procalcitonin as a Marker of Neonatal Sepsis in Intensive Care Units. IJMS 2010;35(3):1-6.

[13] Makkar M, Gupta C, Pathak R, Garg S, Mahajan NC. Performance Evaluation of Hematologic Scoring System in Early Diagnosis of Neonatal Sepsis. Journal of Clinical Neonatology 2013;2(1):25-29.

[14] Sucilathangam G, Amuthavalli K, Velvizhi G, Ashihabegum MA, Jeyamurugan T, Palaniappan N. Early Diagnostic Markers for Neonatal Sepsis: Comparing Procalcitonin (PCT) and C-Reactive Protein (CRP). Journal of Clinical and Diagnostic Research. 2012;6(4):627-31.

[15] R Bhat Y, Rao A. The performance of haematological screening parameters and CRP in early onset neonatal infections. Journal of Clinical and Diagnostic Research 2010;4:3331-36.

[16] Satar M, Ozlu F. Neonatal sepsis: a continuing disease burden. The Turkish Journal of Pediatrics 2012;54:449-57.

[17] Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 2013; 13:426–35.

[18] Zahedpasha Y, Kacho MA, Hajiahmadi M , Haghshenas M. Procalcitonin as a Marker of Neonatal Sepsis. Iran J Pediatr Jun 2009;19(2):117-22.

[19] Koksal N, Harmanci R, Cetinkaya M, Hacimustafaoglu M. Role of procalcitonin and CRP in diagnosis and follow-up of neonatal sepsis. The Turkish Journal of Pediatrics 2007;49:21-29.

[20] Sucilathangam G, Velvizhi G, Jeyamurugan T, Ashihabegum MA, Palaniappan N. Utility of Pro-calcitonin (PCT) as an early diagnostic marker of sepsis in the neonatal intensive care unit. Tirunelveli e Journal of Medical Sciences 2012:3:67-70.

[21] Altunhan H, Annagur A, Ors R, Mehmetoglu I. Procalcitonin measurement at 24 hours of age may be helpful in the prompt diagnosis of early onset neonatal sepsis. International journal of infectious diseases 2011;15:854-58.

[22] Monsef A , Eghbalian F. Evaluation of Diagnostic Value of Procalcitonin as a Marker of Neonatal Bacterial Infections. Iran J Pediatr Sep 2012;22(3):314-18.

[23] Nnanna II, Ehis OJ, Sidiquo II, Nnanna IG, Adekunle O. Serum procalcitonin: Early detection of neonatal bacteremia and septicemia in a tertiary healthcare facility. North American Journal of Medical Sciences 2011;3(3):157-60.

[24] Mondal SK, Nag DR, Bandyopadhyay R, Chakraborty D, Sinha SK. Neonatal sepsis: Role of a battery of immunohematological tests in early diagnosis. International Journal of Applied and Basic Medical Research 2012;2(1):43-47.

AUTHORS

First Author – Dr Malvika Gaur
Second Author – Dr Arathi C.A.