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Original Research Article

Diagnostic accuracy of procalcitonin as a marker of neonatal sepsis

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ABSTRACT

Background: Sepsis is defined as "life-threatening organ dysfunction, caused by a dysregulated host response to infection". Neonatal sepsis is the most common cause of morbidity and mortality in the neonatal period. Early diagnosis of neonatal sepsis is difficult. Therefore, this study was conducted with the objective to assess the diagnostic accuracy of procalcitonin as marker of neonatal sepsis and its comparison with C-reactive protein.
Methods: The present study was a hospital-based descriptive comparative study. A total of 59 neonates were enrolled. All suspected neonates for the sepsis admitted to NICU were enrolled in study on the basis of inclusion and exclusion criteria. A detailed clinical examination was done. Blood sample was collected for procalcitonin, C-reactive protein and blood culture. Statistical analysis was performed.
Results: In our study diagnostic accuracy of procalcitonin in diagnosis of neonatal sepsis was sensitivity (88.46%), specificity (87.88%), positive predictive value (85.19%), negative predictive value (90.63%) and diagnostic accuracy (88.14%). Diagnostic value of C-reactive protein in diagnosis of neonatal sepsis was sensitivity (88.46%), specificity (69.70%), positive predictive value (69.70%), negative predictive value (88.46%) and diagnostic accuracy (77.97%). Diagnostic accuracy of procalcitonin is maximum followed by C-reactive protein.
Conclusions: In our study all patient with gram negative organism were procalcitonin positive whereas 50% *Staphylococcus aureus* were procalcitonin positive and in candida positive cases out of 6 cases, 5 (83.3%) were procalcitonin positive.

Keywords: Neonatal sepsis, Serum procalcitonin, C-reactive protein, Blood culture, Positive predictive value, Negative predictive value

INTRODUCTION

Sepsis is defined as "life-threatening organ dysfunction which is caused by a dysregulated host response to infection". It is a spectrum of disease that ranges from minor signs and symptoms to organ dysfunction (severe sepsis) and shock.[1]

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. It circumscribe various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infection.[2] Neonatal Sepsis is classified into early-onset sepsis (<7 days of birth) and late-onset sepsis (>7 days).[3] Any delay in treatment may lead to neonatal death for that early diagnosis and treatment of sepsis are essential in neonates and infants.[4]

Rapid diagnosis of neonatal sepsis is problematic because the prompt signs of nosocomial infection may be minimal and are similar to those of various noninfectious conditions. As the immune system of neonates is not fully developed, it becomes difficult to differentiate sepsis from systemic inflammation clinically. Bacterial cultures are long drawn out and other laboratory tests are either not available for routine use or lack sensitivity or specificity.

The laboratory tests, which play an important role in its diagnosis, are: absolute neutrophil count (ANC), blood culture, procalcitonin, C-reactive protein (CRP), interleukin-6, interleukin-8 and lactate.[5,6] To prevent unnecessary treatment of non- infected neonates, an early sensitive and specific laboratory test would be helpful to guide clinician in neonatal units in deciding whether or not to start antibiotics.[7]

Blood culture takes at least three or five days to be determining and can be mistakenly negative because antibiotics are initiated empirically before collection and a well-developed microbiology laboratory is required. To overcome these problems, certain newer markers including procalcitonin are now being considered for the diagnosis of sepsis.[8] Procalcitonin is the precursor of calcitonin and does not demonstrate hormonal activity. It is a 116 amino acid peptide with a molecular weight of 14.5k Da.[2,8] Pre-procalcitonin is synthesized from thyroid C cells and this peptide is then transformed into procalcitonin by endopeptidase cleavage under normal homeostasis and its half-life is 20-24 hours.[9]

In sepsis, macrophages and monocytes of liver are responsible for its synthesis. Procalcitonin causes chemotaxis of monocytes, which leads to release of cytokines.[10] Its levels in healthy people are less than 0.046 ng/ml.[11] The level of procalcitonin in a healthy person is undetectable low. However, in severe bacterial, fungal, parasitic infections with systemic manifestations, a significant rise in procalcitonin levels is observed.[6] Procalcitonin levels increases in blood 2-4 hours after the onset of sepsis; achieve peak within 24 hours, and gradually decreases with proper treatment.[12]

Early diagnosis of neonatal sepsis is difficult, despite advanced bacteriologic techniques, so different investigative techniques were assessed for usefulness, either singly or in combination, for the forecast of neonatal sepsis. Assessment of procalcitonin level in serum may be helpful in rapid diagnosis of sepsis.[13] Therefore, this study was conducted with the aim to assess the diagnostic accuracy of procalcitonin as marker of neonatal sepsis and its comparison to C-reactive protein.

METHODS

Study design

The present study was a hospital-based descriptive comparative study, done at NICU, Geetanjali Medical College and Hospital, Udaipur, during the term February 2021-July 2022.

Inclusion criteria

Neonate with any one of following were included: any neonate with suspected sepsis includes any of following signs; temperature instability, apnea, need for supplemental oxygen, need for ventilation, bradycardia, tachycardia, hypotension/hypoperfusion, feeding intolerance, poor feeding, high pitched cry, bulging fontanelle, necrotizing enterocolitis and specific features related to other systems; any neonate with maternal risk factor for neonatal sepsis; prolonged labor, premature rupture of membrane or prolonged premature rupture of membrane(>18 hours), maternal intrapartum fever, urinary tract infection, and chorioamnionitis.

Written informed consent form by parents/legal guardian.

Exclusion criteria

Administration of antibiotic therapy prior to admission. Birth asphyxia, aspiration syndromes, laboratory finding suggestive of inborn errors of metabolism, congenital anomalies and gestational diabetes.

Procedure

59 eligible neonates as per inclusion criteria were consecutively enrolled in the study after taking prior informed consent from the parents. Demographic profile, baseline characteristics of both mother and neonate, presenting complaints will be collected using well-structured proforma by interviewing the parents/attendant. At the time of enrollment, detailed history and physical examination of each neonate were done. All the neonates suspected of sepsis were under went relevant investigations including serum procalcitonin before initiation of antibiotic therapy. Blood samples were drawn and the samples for complete blood count, blood culture, and procalcitonin and C-reactive protein measurements were taken, in biochemistry laboratory, thermostasis of sample done on procalcitonin slides and put on COBAS6000 machine in Rochekit. After 20-30 minutes' results were out.

Statistical analysis

Data was entered into Microsoft excel software. Statistical analysis was performed using the statistical packages for social sciences (SPSS) version 21 IBM Corporation. Statistical analysis of categorical variables was compared between patients using the chi-squared test. Fisher's exact test (two-tailed) were used where appropriate. Quantitative data were analyzed using student t test. A p value<0.05 was considered to be significant. Additionally, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of both procalcitonin and C-reactive protein were calculated.

RESULTS

In our study 42 (71.19%) newborn were male and rest were female. 44 (74.58%) cases had birth weights of 1.5 kilograms or more and 15 (25.42%) were birth weight less than 1.5 kg. 30 (50.85%) were term and rest were preterm (Table 1). Out of total 59 cases enrolled in the study,26 were blood culture positive. In our study, all cases with

gram negative organism were procalcitonin positive. Out of 4 neonates with *Staphylococcus aureus* positive, 2 (50%) were procalcitonin positive. Out of 6 neonates with *Candida* positive, 5 (83.33%) were procalcitonin positive (Table 2).

Diagnostic accuracy of different investigations were compared (Table 3). Among different blood investigation, I/T ratio has minimum sensitivity (38.46%) followed by absolute neutrophil count (42.31%), peripheral blood film toxic granules (50%), platelet count (61.54%) and in C-reactive protein and procalcitonin has similar and maximum sensitivity (88.46%). In specificity I/T ratio have minimum specificity (42.42%), followed by peripheral blood film toxic granule and C-reactive protein has similar specificity (69.70%), platelet count has 78.79%, absolute neutrophil count has (81.82%) and maximum specificity in procalcitonin are (87.88%). Among different blood investigation, procalcitonin have maximum, positive predictive (90.63%) value and negative predictive value (88.14%) followed by C-reactive protein, platelet count, peripheral blood film toxic granule and absolute neutrophil count respectively. Procalcitonin have maximum sensitivity (88.46%), specificity (87.88%) followed by C-reactive protein. Diagnostic accuracy was maximum for procalcitonin (88.14%) in our study.

Table 1: Distribution of cases according sex and birth weight.

Sex (number)	Birth weight (number)
Female (17)	≥1.5 kg (44)
Male (42)	<1.5 kg (15)
Total (59)	Total (59)

Table 2: Procalcitonin positivity according to organism growth in blood culture.

Blood culture organism	Total, number (%)	Procalcitonin positive, number (%)
Burkholderia	1 (100)	1 (100)
Candida	6 (100)	5 (83.33)
E. coli	6 (100)	6 (100)
Enterobacter faecalis	1 (100)	1 (100)
Klebsiella	5 (100)	5 (100)
Pseudomonas	2 (100)	2 (100)
Serratia marcescenc	1 (100)	1 (100)
Staphylococcus aureus	4 (100)	2 (50)
Total	26	23

Table 3: Comparison of diagnostic accuracy of different screening test for diagnosis of neonatal sepsis.

Diagnostic value	I/T ratio (%)	Peripheral blood film toxic granules (%)	Absolute neutrophil count (%)	Platelet count (%)	C-reactive protein (%)	Procalcitonin (%)
Sensitivity	38.46	50.00	42.31	61.54	88.46	88.46
Specificity	42.42	69.70	81.82	78.79	69.70	87.88
Positive predictive value	34.48	56.52	64.71	69.57	69.70	85.19
Negative predictive value	46.67	63.89	64.29	72.22	88.46	90.63
Diagnostic accuracy	40.68	61.02	64.41	71.19	77.97	88.14

DISCUSSION

The present study showed that out of 59 clinically suspected neonatal sepsis cases 42 (71.19%) were males and rest 17 (28.81%) were female. Male predominance may be due to X-linked immunoregulatory gene factor contributing to increased host's susceptibility to infections in male neonates.[14] In the present study among female neonates out of 17 cases, 47.05% were procalcitonin positive and 52.94% were blood culture positive. In males, out of 42, 44.18% were procalcitonin positive and 40.48% were blood culture positive.

In our study according to birth weight, out of total 59 cases enrolled in the study, 44 (74.58%) were birth weight (kg) ≥1.5 kg and rest 15 (25.42%) were weight <1.5 kg group. In our study among the birth weight (kg) ≥1.5 out of 44 cases, 15 (34.09%) were procalcitonin positive and 14 (31.82%) were blood culture positive. In birth weight <1.5 out of 15 cases, 12 (80%) were procalcitonin positive and 12 (80%) were blood culture positive.

In our study according to blood culture 26 (44.07%) were culture positive and rest 33 (55.93%) were culture negative. Similar positivity report of blood culture found in the study done by Vishwanathan et al in Kolkata which revealed 46.3% of blood culture positivity in 216 samples.[15] In contrast low positivity of blood culture had been reported in studies by Kar et al in Bhubaneshwar which revealed 16.2% of blood culture positivity in 120 samples.[16]

In our study all cases with gram negative were procalcitonin positive and in gram negative, 50% cases found procalcitonin positive and rest 50% procalcitonin negative.

Koizumi et al found procalcitonin was lower responsiveness to gram positive bacteremia. They did comparison of biomarkers between patients with gram-negative versus gram-positive bacteremia and found that the procalcitonin (PCT) level higher in patients with gram-negative bacteremia, and C-reactive protein (CRP) level

was higher in patient with gram-negative bacteremia than in those with gram-positive bacteremia.[17,18] They also found that procalcitonin responsiveness is lower for Candida. Cortegiani et al also found lower procalcitonin values in patients with candidemia compared to bacteremia.[19]

In our study, association of procalcitonin against blood culture was studied. Out of 27 procalcitonin positive, 85.19% were culture positive and 14.81% were culture negative. Sucilathangam et al observed that most (64.3%) of the infants with sepsis had procalcitonin positive. Out of 50 cases, elevated procalcitonin was detected in 22, whereas C-reactive protein was noticed only in 18 cases.[20] Among the 14 culture positive cases, elevated serum procalcitonin level was noticed in 13 (92.85%) cases whereas C-reactive protein level was noticed in 7 (50%) cases. Jeergal et al observed procalcitonin concentration in his study was elevated in culture positive neonates.[21] These findings were similar to our study, support the usefulness of the procalcitonin to establish an early diagnosis of neonatal sepsis.

Diagnostic accuracy of procalcitonin in diagnosis of neonatal sepsis was studied. Sensitivity was observed 88.46%, specificity was 87.88%, positive predictive value was 85.19%, negative predictive value was 90.63% and diagnostic accuracy was 88.14%. Sucilathangam et al in his study observing the sensitivity of the procalcitonin in detecting sepsis was 92.8%, its specificity 75.0%, its positive positive predictive value was 59.0% and negative predictive value was 96.0%.[20] This study had lower specificity and positive predictive value than our study. Pontrelli et al calculated a sensitivity of 85% and specificity of 54%.[22]

CONCLUSION

Neonates with sepsis have high levels of procalcitonin as compared to C-reactive protein. Sensitivity and specificity was maximum for procalcitonin followed by C-reactive protein, Platelet count, peripheral blood film toxic granule and absolute neutrophil count respectively. Diagnostic accuracy was maximum for procalcitonin (88.14%) in our study.

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REFERENCES

1. Kőszegi T. Advances in the diagnosis of sepsis. eJIFCC. 2017;28(2):99-103.
2. Whicher J, Bienvenu J, Monneret G. Procalcitonin as an acute phase marker. Ann Clin Biochem. 2001;38(5):483-93.
3. Behrman Re, Kliegman R, Jensen HB Barbara S. Infections of the neonatal infant. In: editors. Behrman: Nelson Textbook of Pediatrics. Philadelphia: WB Saunders CO. 2008;42(5):794-811.
4. Vasantha AR, Kutty SN, Theodore RB. Neonatal sepsis: Aetiological agents and risk factors. J Acad Clin Microbiol. 2017;19(1):36-41.
5. Iroh Tam P, Bendel C. Diagnostics for neonatal sepsis: Current approaches and future directions. Pediatric Res. 2017;82(4):574-83.
6. Rashwan N, Hassan M, Mohey El-Deen Z, Ahmed A. Validity of biomarkers in screening for neonatal sepsis (single centerhospital based study). Pediatric Neonatol. 2019;60(2):149-55.
7. Pérez Solís D, López Sastre JB, Coto Cotallo GD, Diéguez Junquera MA, Deschamps Mosquera EM, Crespo Hernández M. Procalcitonin for the diagnosis of nosocomial neonatal sepsis. An Pediatr (Barc). 2006;64(4):349-53.
8. Levy M, Evans L, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive Care Med. 2018;44(6):925-8.
9. Naher BS, Mannan MA, Noor K, Shahidullah M. Role of serum Procalcitonin and C-reactive protein in the diagnosis of neonatal sepsis. Bangladesh Med Res Council Bulletin. 2011;37(2):40-6.
10. Vijayan A, Vanimaya, Ravindran S, Saikant R, Lakshmi S, Kartik R, et al. Procalcitonin: A promising diagnostic marker for sepsis and antibiotic therapy. J Intensive Care. 2017;5:51.
11. Rogic D, Juros GF, Petrik J, Vrancic AL. Advances and pitfalls in using laboratory biomarkers for the diagnosis and management of sepsis. eJIFCC. 2017;28(2):114-21.
12. Trasy D, Molnar Z. Procalcitonin–assisted antibiotic strategy in sepsis. eJIFCC. 2017;28(2):104-13.
13. Hasan F, Khan SA, Maharoof MK, Muhammed N. Role of Procalcitonin in early diagnosis of neonatal sepsis. Int J Contemp Pediatrics. 2017;4(2):383-9.
14. Shrestha RK, Rai SK, Mandhal PK. Bacteriological study of neo natal sepsis and antibiotic susceptibility pattern of isolates in Kathmandu, Nepal. Nepal Med Coll J. 2013;15(1):71-3.
15. Viswanathan R, Singh AK, Ghosh C, Dasgupta S, Mukherje S, Basu S. Profile of Neonatal Septicaemia at a District-level Sick Newborn Care Unit. J Health Popul Nutr. 2012;30(1):41-8.
16. Kar SS, Dube R, Mahapatro S, Kar SS. The role of clinical signs in the diagnosis of late onset neonatal sepsis and formation of clinical score. Indian J Clin Prac. 2003;23(23):654-60.
17. Koizumi Y, Sakanashi D, Ohno T, Nakamura A, Yamada A, Shibata Y, et al. Plasma procalcitonin levels remain low at the onset of gram-positive bacteremia regardless of severity or the presence of shock: A retrospective analysis of patients with detailed clinical characteristics. J Microbiol Immunol Infect. 2021;54(6):1028-37.
18. Wang H, Yin F, Shen DX, Zhang YJ, Luo YP, Liu CJ, et al. Predictive value of procalcitonin for excluding bloodstream infection: results of a

retrospective study and utility of a rapid, quantitative test for Procalcitonin. J Int Med Res. 2013;41(5):1671-81.
19. Cortegiani A, Misseri G, Ippolito M, Bassetti M, Giarratano A, Martin-Loeches I, et al. Procalcitonin levels in candidemia versus bacteremia: a systematic review. Crit Care. 2019;23(1):190.
20. World Health Organization. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2nd edition. World Health Organization. 2013. Available at: https://apps.who.int/iris/handle/10665/81170. Accessed on 24 March 2023.
21. Jeergal NA, Rizwan-u-zama NA, Malagi N, Farooqui F, Ukkali SB, Naganoor R, Thobbi AN. Procalcitonin as a marker of neonatal sepsis. Al Ameen J Med Sci. 2016;9(1):70-3.
22. Pontrelli G, De Crescenzo F, Buzzetti R, Jenkner A, Balduzzi S, Calò Carducci F, et al. Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: a meta-analysis. BMC Infect Dis. 2017;17(1):302.

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