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Presepsin: A New Marker of Neonatal Sepsis-Experience of a Tertiary Level NICU in Delhi

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Abstract

Neonatal sepsis is a significant problem in any level of NICU with non-specific clinical features. Sepsis screen and blood culture are considered classical tools for diagnosis of neonatal sepsis. However sepsis screen components are non-specific for neonatal sepsis and blood culture positivity rate is low. Empirical use of routine and broad spectrum antibiotic for one or two positive markers of sepsis and probability of sepsis in any clinically sick baby is a common practice especially in developing countries. We studied level of presepsin as a new marker of neonatal sepsis in our unit and results are very promising. When faced with clinical and biochemical dilemma of neonatal sepsis, use of prespsin level as a marker of sepsis can decrease overuse of expensive and irrational antibiotics and also decrease financial burden of family.

Keywords

Neonatal; Complete blood count; Sepsis; Lipopolysaccharides

Abbreviations: EOS: Early Onset Sepsis; LOS: Late Onset Sepsis; INAP: India Newborn Action Plan; NICU: Neonatal Intensive Care Unit; DOL: Day Of Life; CRP: C Reactive Protein; TLC: Total Leukocyte Count; IUGR: Intra Uterine Growth Retardation; CAT: Category; CRT: Capillary Refill Time; CBC: Complete Blood Count; PCT: Procalcitonin

Introduction

According to the India newborn action plan (INAP) 2014, sepsis accounts for 33% of total neonatal deaths [1]. Babies under advance neonatal care in Level 3 and level 2 are not only at high risk for neonatal sepsis but stable babies under level 1 care also developing sepsis in significant number. Despite all advances in neonatal care, diagnostic modalities for neonatal sepsis remain dependent on different markers of sepsis screen and blood culture. In neonatal care, different markers for diagnosis of sepsis are available like CRP, TLC, band cells, Platelet count and procalcitonin (PCT). Clinical features of sepsis are nonspecific [2] and sepsis screen markers can be positive in many noninfectious inflammatory conditions like asphyxia and in post-operative period. Blood culture positivity is also affected in cases of early onset sepsis by use of antibiotics in mother in peripartum period. Blood culture remains gold standard for diagnosis but rate of positivity is between 20-30% in sepsis. Also, it takes around 48-72 hours for growth and identification of organism and antibiotic sensitivity testing. For neonatal population this window period is very critical in view of risk of mortality and irrational use of antibiotics. In a septic neonate, rapid diagnosis and early treatment is lifesaving. For every hour of delay in the administration of appropriate antibiotic therapy, there is a 7% rise in associated mortality [3]. Delay in diagnosis and treatment is directly related to financial burden to the family. Recent US data suggest the annual cost of hospital care for patients with septicemia is USD 14 billion [4].

None of the markers including hematologic indices, acute phase reactants, cytokines, and cell surface markers have shown sensitivity, specificity, positive and negative predictive value that are sufficiently powerful to guide the clinical management of neonatal sepsis [5,6]. Thus, there is an urgent need for finding a marker which is able to detect infection at an early stage with high sensitivity, specificity as well as positive and negative predictive value. Also, processing time in laboratory should be low.

Recently in Poland, Stojewska et al. studied diagnostic value of presepsin for neonates sepsis in 124 babies. Presepsin concentration in septic newborns, independently of their gender, fetal maturity, birth asphyxia was significantly ($p<0.001$) higher than in others newborns. The clinical specyfity and sensivity were found 89.2% and 63.4%, respectively in this study. In India till date, no study was done to evaluate the level of presepsin for diagnosis of sepsis.

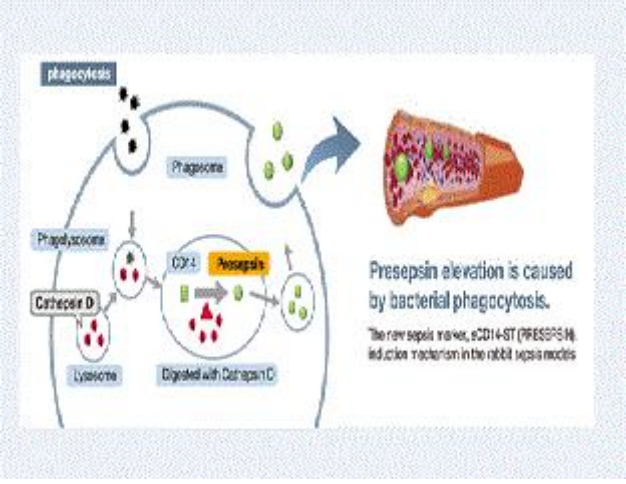

Figure 1: Mechanism of presepsin production in infection [9].

We studied presepsin level as a marker of sepsis in 25 clinically septic babies and compared this level with previously established markers of sepsis and blood culture. Biological properties of presepsin are very unique because its level increases only after bacterial phagocytosis rather than in any inflammatory condition. Presepsin is a specific 13 kDa fragment derived from CD14, a55 kDa membrane glycoprotein of monocytes, macrophages and neutrophils. CD14 serves as a receptor for complexes of bacterial lipopolysaccharides (LPS) in both Gram-positive and Gram–negative bacteria (Figure 1) [7]. The fragment soluble CD14 (sCD14) is shed from the cell membrane into the circulation where it is further fragmented by proteases such as cathepsins or during phagocytosis to sCD14 subtype (sCD14-ST) or Presepsin. Presepsin levels were elevated even earlier than IL-6, and much earlier than procalcitonin (PCT), with a peak at about 3 hour after onset of the infection. The cutoff of Presepsin level for diagnosis of sepsis in newborns is 643 pg/ml and a median value of 578 pg/ml [8]. Results become available within 30-60minutes.

Material and Methods

This study was conducted in a tertiary level NICU of Delhi from May 2015 to October 2015. We studied total 25 babies during neonatal period/early infancy in which we suspected sepsis clinically [9,10] or there was a discrepancy between clinical condition and laboratory parameters [11]. Babies with clinically suspected early as well as late onset sepsis were enrolled. TLC, band cell count, platelet count, procalcitonin (PCT), CRP, blood culture along with presepsin level was sent simultaneously (Table 1).

Baseline characters recorded for all babies included antenatal risk factors for sepsis (leaking PV, IUGR, chorioamnionitis), type of delivery, gestation, birth weight, APGAR score at 5 min, DOL at admission in NICU, DOL when clinical sepsis suspected, early (<72 hours of age) or LOS(>72 hours of age)sepsis. Presepsin level was measured using 2 ml EDTA blood sample with the compact PATHFASTTM analyzer in the laboratory by immunoassay based on chemiluminescence.

Markers Cat		N	Mean	Std. Deviation	Std. Error Mean	P value
Band cells	1	14	30	3	0.3975	0.0001
	2	11	12	2	0.7673	
Platelet count	1	14	3.1036	1.56161	0.41736	0.750
	2	11	3.7455	1.53060	0.46149	
CRP	1	14	10.218	10.5376	3.1772	0.001
	2	11	2.243	3.3931	0.9069	
TLC	1	14	13239.29	7342.452	1962.353	0.070
	2	11	12663.64	3357.759	1012.402	
Procalcitonin	1	14	7.7257	14.01185	3.74482	0.052
	2	11	4.8545	4.47892	1.35045	
Presepsin	1	14	1590.21	564.109	150.765	0.000
	2	11	122.27	83.766	25.257	

Table 1: Sepsis parameters

Signs of clinical sepsis were used according to Okascharoen in term and Rosenberg in preterm babies [10,11]. These signs included hypotonia, tachycardia, bradycardia, fever or hypothermia, residual feed volume, abdominal distention, tachypnea, retraction, grunting, hypotension, prolonged CRT, increased ventilator requirement etc. Cut off diagnostic values of different sepsis screen parameters were taken as band cell >20% of TLC, TLC <5000, CRP>1 mg/dl as per Phillp and Gerdes [12]. PCT value >2 ng/ml ((BRHAMS PCT, Roche Diagnostic, Italy) and presepsin value >643 pg/ml (PATHFAST (Mitsubishi Chemical Medience Corporation, Japan) Diagnostics, Italy) were taken as positive for sepsis. Blood culture was sent in all study subjects. CSF analysis and urine culture was sent only in babies with positive blood culture.

After getting final blood culture report babies were divided in two categories. CAT I included babies with definite sepsis proven by a positive blood culture and CAT II included babies with probable sepsis as blood culture was negative.

Analysis and Results

We analysed data of all 25 babies. Presence of clinical sepsis was the main parameter for sending presepsin and other sepsis indicators like TLC, band cells, CRP, procalcitonin and others (Figure 2).

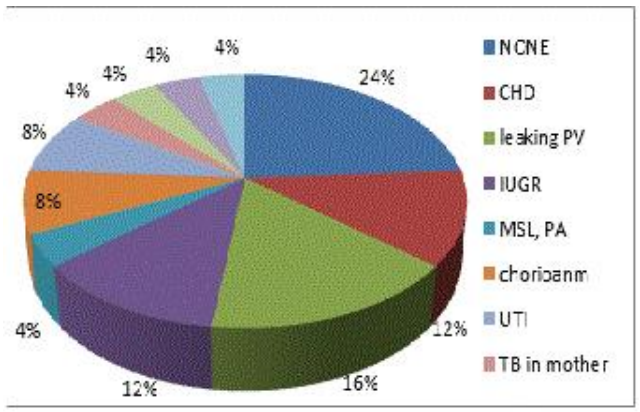

Figure 2: Antenatal risk factors in study population

Antenatal risk factors for sepsis were also evaluated as baseline risk factor for sepsis. Among clinically septic babies no antenatal risk factor was found in 24%, PROM more than 18 hours in 16% mothers, 8% mothers had chorioamnionitis and UTI each. Out of 25 cases, 40% of babies were preterm and 60% were term.

Mean gestation in our study was 35.08 weeks (SD 3.25), mean birth weight 2425 gm (SD 775gms), mean day of life at which we suspected clinical sepsis was 4.6 day of life (SD 3.5). Blood culture was positive in 14/25 (56%) of clinically septic babies. CSF was analysed in all 14 blood culture positive cases and meningitis was diagnosed in 3 cases. Further, 25 cases were categorized according to blood culture positive results in 2 categories. CAT I were definitive sepsis babies with positive blood culture and CAT II was probable sepsis. All traditional sepsis marker along with procalcitonin and presepsin were evaluated in both categories. Results showed that only band cells, CRP and presepsin were significantly associated with definitive sepsis. Mean value of band cells, CRP and presepsin in cat 1 were 30% (SD 3), 10.2 mg/dl (SD10.5) and 1590.2 pg/ml (SD 150) with P value (0.0001), (0.00) and (0.00001)

respectively. Other markers like TLC and procalcitonin did not show significant correlation with positive blood culture. Value of presepsin in our babies ranged from 20 to 2600 pg/ml.

Discussion

Neonatal sepsis remains one of the leading causes of morbidity and mortality both among term and preterm infants [13]. Isolation of bacteria from blood is considered the gold standard for the diagnosis of sepsis. However, it takes 24–48 hr for culture results to identify the organism. Sepsis cannot always be excluded even when blood cultures are found to be negative [14]. The CBC has a poor predictive value for diagnosis of neonatal sepsis [15]. Low WBC and absolute neutrophil counts, as well as high immature-to-total neutrophil ratio (band cells) are associated with an increased risk of infection. But I: T ratio can be affected by various noninfectious processes like labor, prolonged induction with oxytocin and even prolonged crying. Evidence suggested that WBC, ANC, and I/T ratio have significant limitations in the diagnosis of neonatal sepsis [16]. CRP is one of the most extensively studied, easily available and most frequently used laboratory tests for the diagnosis of neonatal sepsis [17]. It takes 10–12 h for CRP to change significantly after onset of infection. Serial determination of CRP 24–48 hr after the onset of symptoms increases its sensitivity. The specificity and positive predictive value of CRP ranges from 93–100% [18]. Thus, CRP can be considered as a "specific" but "late" marker of neonatal infection.

Serum concentrations of PCT begin to rise 4 hr after exposure to bacterial endotoxin, peak at 6 to 8 hr, and remain elevated for at least 24 hr [19-21]. The PCT response is quicker and has higher sensitivity and specificity as compared to elevation of CRP. But PCT has its own limitations as it may increase in healthy neonates. It has been shown that PCT concentrations are affected by maternal GBS colonization and prolonged rupture of membranes ≥ 18 hr [22]. I:T ratio (band cells) and CRP level were found significantly positive in blood culture positive babies in our study. Procalcitonin (PCT) level was not found significantly high in these babies.

A recent study in neonates to evaluate presepsin as a marker of sepsis showed sensitivity 63.4% with high specificity of 89.2%. Our study is small but the first in India to the best our knowledge that investigates the possible role of Presepsisn in the diagnosis of sepsis in neonates. We found that presepsin levels were significantly higher in neonates with definitive sepsis as compared to those with probable sepsis, thereby suggesting its potential utility in the early diagnosis of sepsis. Unfortunately because of unavailability of kit in India right now we could not continue this study further. But our experience with this novel marker as an early indicator of neonatal sepsis has been quite encouraging.

Conclusion

This is the first study in India to our knowledge which evaluated presepsin as an early biomarker of sepsis with promising results. Along with presepsin, CRP and band cells level also showed significant positive relation with sepsis in our study. We plan to resume this study with a bigger sample as soon as presepsin kit becomes available our laboratory.

References

1. Liu I (2012) Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 379: 2151-2161.
2. Gerdes JS (2004) Diagnosis and management of bacterial infections in the neonate. Pediatr ClinNorth Am 51: 939-959.
3. Kumar A, Roberts D, Wood KE (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34: 1589-1596.
4. HCUP (2008) Statistics on Hospital-Based Carein the United States. Rockville.
5. Bhandari V, Wang C, Rinder C, Rinder H (2008) Hematologic profile of sepsis in neonates: neutrophil CD64 as a diagnostic marker. Pediatrics 121: 129-134.
6. Wright SD, Ramos RA, Tobias PS, Ulevitch RJ, Mathison JC (1990) CD14,a receptor for complexes of lipopolysaccharide (LPS) and LPSbinding protein. Science 249: 1431-1433.
7. Mussap M, Puxeddu E, Burrai P, Noto A, Cibecchini F, et al. (2012) Soluble CD14 subtype (sCD14-ST) presepsin in critically ill preterm newborns: preliminary reference ranges. J Matern Fetal Neonatal Med 25: 51-53.
8. Nakamura M, Takeuchi T, Naito K, Shirakawa K, Hosaka Y, et al. (2008) Early elevation of plasma soluble CD14 subtype, a novel biomarker for sepsis, in a rabbit cecal ligation and puncture model. Critical Care 12: P194.
9. okascharoen C, Sirinavin S, Thakkistian A (2005) A bedside prediction scoring model for late onset neonatal sepsis. J Perinatol 25: 778-783.
10. Rosenberg RE, Ahmed AN, Saha SK (2009) Nosocomial sepsis risk score for preterm infant. J Trop Pediatr 56: 82-89.
11. Okamura Y, Yokoi H (2011) Development of a point-of-care assay systemfor measurement of presepsin (sCD14-ST). Clin Chim Acta 412: 2157-2161.
12. Camacho-Gonzalez A, Spearman PW, Stoll BJ (2013) Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am 60: 367-389.
13. Goldstein B, Giroir B, Randolph A (2005) International Consensus Conference on Pediatric Sepsis.International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 6: 2-8.
14. Rozycki HJ, Stahl GE, Baumgart S (1987) Impaired sensitivity of a single early leukocyte count inscreening for neonatal sepsis. Pediatr Infect Dis J 6: 440-442.
15. Murphy K, Weiner J (2012) Use of leukocyte counts in evaluation of early-onset neonatal sepsis. Pediatr Infect Dis J 31: 16-19.
16. Hofer N, Zacharias E, Müller W, Resch B (2012) An update on the use of C-reactive protein in earlyonset neonatal sepsis: current insights and new tasks. Neonatology 102: 25-36.
17. Pourcyrous M, Bada HS, Korones SB, Baselski V, Wong SP (1993) Significance of serial C-reactive protein responses in neonatal infection and other disorders. Pediatrics 92: 431-435.
18. Dandona P, Nix D, Wilson MF, Aljada A, Love J, et al. (1994) Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 79: 1605-1608.
19. Chiesa C, Panero A, Rossi N, Stegagno M, De Giusti M, et al. (1998) Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. Clin Infect Dis 26: 664-672.
20. Whicher J, Bienvenu J, Monneret G (2001) Procalcitonin as an acute phase marker. Ann Clin Biochem 38: 483-493.
21. Assumma M, Signore F, Pacifico L, Rossi N, Osborn JF, et al. (2000) Serum procalcitonin concentrations in term delivering mothers and their healthy offspring: a longitudinal study. Clin Chem 46: 1583-1587.
22. Stojewska M, Behrendt J, Szymańska Am (2015) Diagnostic Value of Presepsin (Scd14-St Subtype) Evaluation in the Detection of Severe Neonatal Infections. IJRSB 3:6.