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Original Research Article

To Evaluate the Diagnostic Role of Procalcitonin and Presepsin in Bacterial and Fungal Sepsis in Neonates

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Abstract:

Aim: This study aimed to evaluate the diagnostic role of Presepsin in neonatal sepsis and compare it with Procalcitonin (PCT) for the diagnosis of fungal and bacterial sepsis.

Methods: This study was conducted in the Special Newborn Care Unit (SNCU) at S N Medical College, Agra, from September 2019 to March 2021. Neonates with 2 risk factors for sepsis or clinical features of sepsis were included. A total of 50 cases and 20 controls were taken. Blood samples for all the investigations were collected. A chi-square test was performed to find out the statistical significance.

Results: Amongst the cases, 52% (26) were found to be blood culture positive. At the chosen cut-off values, the sensitivity of PCT and presepsin was 86% and 92%, respectively, while specificity was 90% and 95.1%, respectively. The increase in the mean value of presepsin was more in cases of fungal sepsis (1228±50.27)than in bacterial sepsis (954±123.44).

Conclusion: Blood culture is the gold standard for confirming sepsis in neonates, but it has limitations like prolonged time-to-result and low yield. Presepsin, with better sensitivity and negative predictive value, can detect most cases of sepsis in neonates, reducing unnecessary treatment. It's more effective in fungal sepsis cases. Presepsin should be used alongside blood culture.

Keywords Procalcitonin, Presepsin, Neonate, Fungal Sepsis.

Introduction

Neonatal septicemia presents as a clinical syndrome manifesting signs and symptoms of infection with or without accompanying bacteremia in the first month of life. It includes various systemic infections of new-borns, such as pneumonia, septicemia, meningitis, arthritis, osteomyelitis, and urinary tract infections. Neonatal sepsis can be classified as EOS (early onset sepsis ≤ 3 days) and LOS (late onset sepsis > 3 days).

Neonatal sepsis is one of the most significant causes of neonatal morbidity and mortality. Most infection-related deaths in the neonatal period occur in low-income and middle-income countries due to poor hygiene and inefficient methods for infection control. The gold standard for diagnosis of sepsis is blood culture, but the result of the blood culture is awaited for 48–72hr. Procalcitonin (PCT) is a peptide precursor of the hormone named calcitonin. It comprises 116 amino acids and is produced by parafollicular cells (C cells) of the thyroid gland and by the neuroendocrine cells of the lung and the intestine. The PCT levels rise in response to a proinflammatory stimulus, especially bacterial origin. However, in neonates, a physiological postnatal increase of serum PCT occurs, with the peak at 24 h of life [1-3]. Presepsin (sCD14-subtype) produced as a byproduct during the inflammation process is a 13 KD truncated N- N-terminal fragment of 64 amino acid residues. CD14 is a member of Toll-like receptors (TLR) that can identify several groups of ligands of both Gram-positive and Gram-negative organisms, such as lipids, peptidoglycan, and other surface proteins. CD14 is expressed on the membrane surface of monocytes and macrophages (mCD14). It serves as a high-affinity receptor for complexes of lipopolysaccharides (LPSs), a compound of the outer cell wall of Gram-negative bacteria and LPS-binding proteins [4-5].

Antimicrobial resistance (AMR) is a global public health adversity that threatens the ability of modern medicine to combat infections [6]. The irrational usage of antimicrobials in humans is a major leading cause of the development of AMR [7]. Unreasonable use of antibiotics is present in all countries, but it is more commonly seen in developing countries due to the fragile or fragmented health system

[7]. Major reasons for the irrational use of antibiotics include lack of proper knowledge on behalf of the patients or prescriber, easy access to antimicrobials without prescriptions, pharmaceutical company promotions, parental pressure on the prescribers, lack of rapid microbial testing, and poor communication among health professionals in the health system. This may lead to antibiotic overuse, increasing antibiotic resistance and health costs [8]. The objectives of this study were to study the clinicopathological profile of neonates with sepsis and to evaluate the diagnostic role of presepsin compared to Procalcitonin (PCT**)** and its efficacy in diagnosing bacterial and fungal sepsis**.**

Material and Methods

This case-control study was conducted in the SNCU (Special Newborn Care Unit) of the Department of Pediatrics in collaboration with the Department of Microbiology and the Department of Pathology of S.N. Medical College Agra. Participant recruitment and sample collection were done for 19 months from September 2019 to March 2021. The sampling was done only after obtaining informed consent from parents/guardians. They were not charged for these tests. 70 newborns were enrolled in our study with ages less than ≤28 days. Neonates with ≥1 clinical feature of sepsis and/or two risk factors were included. The clinical features of sepsis included refusal to feed, feeding intolerance, lethargy, irritability, temperature instability, apnea, respiratory distress, poor perfusion, tachypnoea, bradycardia, high-pitched cry, seizures, hypotonia, abdominal distension, necrotizing enterocolitis, vomiting, sclerema, and mucosal bleeding.

Risk factors that were considered included were – maternal fever within 2 weeks of delivery, premature rupture of amniotic membrane (PROM) (>18 h), foul-smelling and/or meconium-stained liquor, single unclean or > 3 sterile vaginal examinations during labor, prolonged labor (sum of stage 1 and 2 of labor ≥ 24 h), low birth weight babies, premature babies and history of faulty feeding in the neonate. [9]. Neonates with congenital anomalies or severe birth asphyxia were excluded from the study.

A total of 50 cases and 20 controls (with no clinical and laboratory evidence of sepsis) were included in our study. Both inborn and out born cases were included. Blood samples were obtained before initiation of antibiotics under strict aseptic conditions. The routine blood investigations CBC, sepsis screen, CRP, urine routine microscopy and culture, and blood culture were sent to the laboratory. Bact/Alert was used for blood culture, which uses fluorescence assay for measurement. PCT and presepsin levels were determined using specific Duo ELISA development kits (R&D Systems) with catalog number DY383-05(5 plates). This assay employs the quantitative sandwich enzyme immunoassay technique. We used a cut-off of 2000ng/ml for PCT and 860 ng/ml for presepsin. All values above these cut-offs were considered positive.

Result

Our study included 50 cases, with 32 males (64%) and 18 females (36%). In our study, a high proportion of cases were LBW babies, i.e., 68%.

Out of 50 cases of sepsis, 26 were blood culture positive (BCP), and 24 were suspected of having sepsis based on clinical and laboratory findings but were found to be culture negative (BCN). Among 26 BCP cases, 7 (26%) were Gram-positive sepsis cases, 12 (46%) were Gram-negative sepsis, and 7 (27%) were infected with candida. The most common organism isolated was Klebsiella pneumonia (46%), followed by Candida 7 (27%), Staphylococcus aureus 3 (13%), coagulase-negative Staphylococcus (7%), and Enterococcus fecalis 2 (7%) as shown Table 2 [15]. PCT was positive in 43(86%) cases and 2 out of 20 controls with a cut-off value of 2000 pg/ml used as depicted in Table 3, whereas presepsin was positive in 47(94%) cases and in none of the controls with a cut-off of 860pg/ml (Table 5).

Among the blood culture-positive cases, a rise in PCT levels was seen in 22 cases out of 26 (Table 4) compared to presepsin, which showed a rise in all 26 blood culture-positive cases (Table 6). PCT was also found to be positive in 4 blood culture-negative cases, which, when compared with presepsin, showed no positivity in blood culture-negative cases. The rise in levels of PCT was seen more among cases with bacterial sepsis (mean 4059±1445) than cases with fungal sepsis (mean 2122.40±40.5), as in Table 7. On the contrary, a rise in levels of presepsin was seen more among cases with fungal sepsis (mean 1228.40±50.27)than with cases of bacterial sepsis (954.47±123.44) Table 8. PCT showed a sensitivity of 86% and specificity of 90% among cases, whereas presepsin showed a sensitivity of 94% and specificity of 95% among cases.

Table 1: Blood culture distribution in the study

Blood CS	Case		Control		Total	
	No.	%	No.	%	No.	%
Positive	26	52.00	0	0.00	26	38.57
Negative	24	48.00	20	100.00	44	61.43
Total	50	100.00	20	100.00	70	100.00

Chi-square value=6.565, p-value=0.0103. As depicted in the table, among 50 cases, 26 (52%) were blood culture positive and 24 (48%) cases were blood culture negative. Among the controls, 20 (100%) were blood culture negative, and 0(0%) were positive. Blood culture showed a sensitivity of 52% and specificity of 95%, with a positive predictive value of 89.66% and a negative predictive value of 41.46%.

Table 2: Blood culture isolates in the study

Blood culture isolates	No. of Cases	Percentage
Candida	7	27%
Coag neg staph	2	7%
Enterococcus fecalis	2	7%
Klebsiella pneumonia	12	46%
Staph aureus	3	13%

As depicted in the table above, among 26 blood culture-positive cases, there were 7 (27%) gram-positive isolates, 12 (46%) gram-negative isolates, and 7 (27%) candida. The most common organism isolated was Klebsiella pneumonia, followed by staphylococcus and candida (Table-2, & Figure-1).

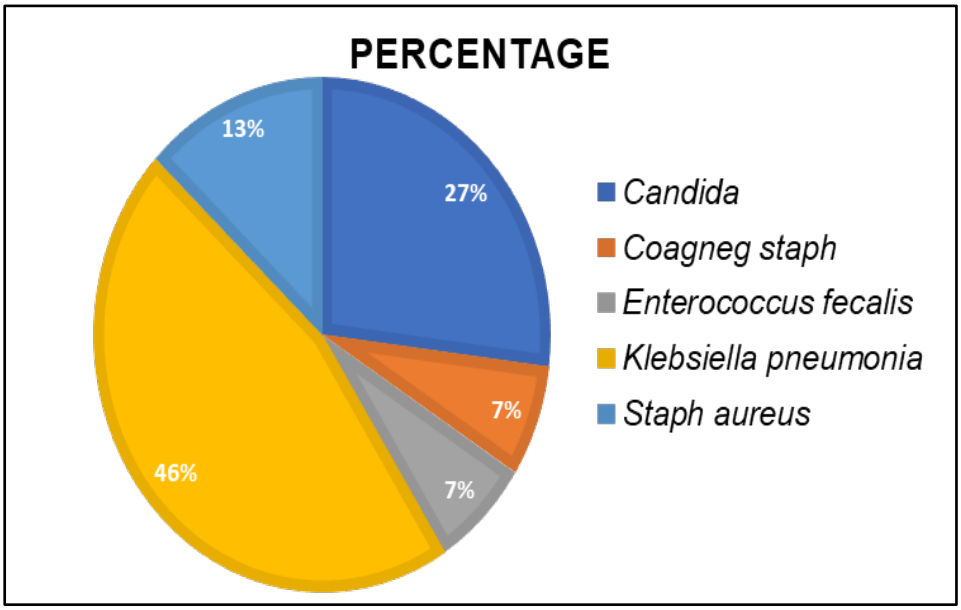

Figure 1: Percentage of blood culture isolates in the study

Table 3: PCT (Cutoff 2000Pg/ML)

PCT	Case		Control		Total	
	No.	%	No.	%	No.	%
Positive (≥2000)	43	86.00	2	10.00	45	64.29
Negative (<2000)	7	14.00	18	90.00	25	35.71
Total	50	100.00	20	100.00	70	100.00

Chi-square value=35.939, p-value=<0.0001. This test is statistically significant. As depicted in the table above 43(86%) cases were PCT positive, and 7(14%) cases were PCT negative. Among the controls, 2 (10%) cases were PCT-positive, and 18(90%) were negative. According to the ROC curve, the sensitivity of PCT was 86%, specificity 90%, the positive predictive value was 95.56%, and the negative predictive value was 72%.

Table 4: PCT among blood culture-positive and blood culture-negative cases

PCT	No. of blood culture-positive cases	No. of blood culture-negative cases
Positive	22	21
Negative	4	3
	26	24

As depicted above, PCT was found positive in 22 cases of blood culture-positive sepsis and 5 culture-negative sepsis, with a sensitivity of 84.6% in culture-positive sepsis and 87.07% sensitivity in culture-negative sepsis.

Table 5: Presepsin (pg/ml)

Presepsin (pg/ml)	Case		Control		Total	
	No.	%	No.	%	No.	%
≥860	46	92.00	1	5.00	47	67.14
<860	4	8.00	19	95.00	23	32.86
Total	50	100.00	20	100.00	70	100.00

Chi-square value=49.01, p-value=<0.0001, this test was significant. Among cases 46(92%) were Presepsin positive and 4(5%) were Presepsin negative. Among controls (5%) were Presepsin positive, and 19(95%) were presepsin negative. According to the ROC curve, sensitivity was 92%, specificity was 95%%, positive predictive value was 97.87%, and negative predictive value was 82.61%.

Table 6: Presepsin (pg/ml) among blood culture-positive and blood culture-negative cases

Presepsin (pg/ml)	No. of blood culture-positive cases	No. of blood culture-negative cases
≥860	26	21
<860	0	3
	26	24

As depicted above in the table, preseason has a sensitivity of 100% among blood culture-positive cases and a sensitivity of 87.5% among culture-negative sepsis.

Table 7: profile of PCT among bacterial and fungal sepsis

	No.	PCT		
		Mean ±SD	Min.	Max.
Candida	7	2122.40±40.5(1SD)	2021.70	2150
B. Sepsis	19	4059±1445(1SD)	2514	7754
Control	20	1206.85±726.57	508	3800

As depicted in the above table – Rise in PCT levels is less among fungal sepsis cases with an average mean of 2122.40±40.7 as compared to bacterial sepsis cases with a mean of 4059±1445.

Table 8: To study profile of presepsin among bacterial and fungal sepsis

	No.	Presepsin(pg/ml)		
		Mean ±SD	Min.	Max.
Candida	7	1228.40±50.27(1SD)	1078	1378
B. Sepsis	19	954.47±123.44(1SD)	578	1194
Control	20	531.90±119.07(1SD)	308	904

As depicted above, a rise in presepsin levels is seen more with fungal sepsis, with an average mean of 1228±50.27 as compared to bacterial sepsis, whose mean value is 954±123.44, thereby concluding that Presepsin values rise more in fungal sepsis as compared to PCT.

Discussion

This study aimed to compare Presepsin and PCT as a better marker for fungal sepsis in neonates and improvise a more sensitive and specific test for sepsis analysis at an affordable cost. According to our knowledge, this study is among a few studies that compare PCT and presepsin as a better marker for fungal sepsis in neonates. In our study, males outnumbered females, comparable to other studies. Khinchi et al in 2010 studied the clinical presentation, investigation profile and outcomes of neonatal sepsis. In this study, among 411 newborns enrolled, 65% were males [10]. Assudani et al in 2015 studied the bacteriological profile of septicemia in neonates. Out of 116 clinically suspected cases of neonatal sepsis, 76.2% were found to be males [11]. The male preponderance in neonatal septicemia may be linked to X liked immunoregulatory gene resulting in host susceptibility to infection in males. This is also probably due to the attitude of parents who seek more medical services for their male babies than females. Our study had a higher proportion of cases that were LBW babies (68%) and preterm (≤37wk). Mohammad D et al also studied bacterial nosocomial infections in NICU in 2014 and found these infections to be more common in preterm (54.7%) [12]. Most of the cases in our study were of late-onset sepsis (80%), the most common cause of NICU admissions. PROM was found to be the most important maternal risk factor associated with EOS, observed in (14%) of cases followed by more than 3 vaginal examinations after rupturing of the membrane (10% cases) and prolonged labor. The clinical presentation of newborns with sepsis in our study included symptoms like lethargy (24% cases) followed by abnormal body movement (14%), difficulty in breathing (10%), delayed capillary filling time (10%), hypothermia (10%), hyperthermia (6%) case. This correlates with a study by Noor et al, where the majority had

presented with lethargy (37.8%) and respiratory distress (31.1 %) [13].

In our study, as shown in Table 2, blood culture was positive amongst 26 (52%) cases. The most common isolates were Klebsiella pneumonia (46%), candida (14%), and staphylococcus (13%). In a study done by Kumhar et al. to determine the profile of bacteriological isolates from blood cultures of neonates in a tertiary care hospital in New Delhi, Staphylococcus and Klebsiella were found to be the commonest organisms [14].

We used PCT cut levels >2000 pg/ml among sepsis cases in our study. PCT showed a sensitivity of 86%, specificity-90%, PPV- of 95.56%, and NPV - of 72%. Similar results were found in a study conducted by Emad, at a cut-off of 1.1ng/ml with PCT as a marker for neonatal sepsis. PCT value among blood culture-positive cases showed a sensitivity of 91.2% and 80.07% among culture-negative cases. [15,16]

We used a cut-off of 860 pg/ml for Presepsin, which showed sensitivity, specificity, PPV, and NPV of 92%, 95%, 97.87%, and 82.61%, respectively. These results correlate well with the study done at Bharati Vidyapeeth in 2018. In our study, the sensitivity of presepsin was 84.6% among blood culture-positive cases and 87.07% in blood culture-negative cases [17].

In our study, we realized that the rise in levels of PCT was seen as more pronounced in cases with bacterial sepsis (mean 4059±1445) compared to those with fungal sepsis (mean 2122.40±40.5).On the contrary, an increase in levels of presepsin was seen more among cases with fungal sepsis (mean 1228.40±50.27) than in cases of bacterial sepsis (954.47±123.44), which correlates with the study of Chengzi fang and Lille Xie done in June 2020(100) and Giuseppe Lippi, Gianfranco leveling. Similar results were also seen in studies done by Pieralli F and Bamba Y in 2018. [18-22]

Conclusions

Blood culture remains the gold standard for confirmation of sepsis in neonates but has various limitations, such as prolonged time-to-result and low yield. Presepsin, compared to PCT, has better sensitivity and, hence, can detect most cases of sepsis in neonates with a better negative predictive value, leading to a decrease in the number of patients treated unnecessarily. The rise in values of Presepsin was more significant in cases with fungal sepsis compared to PCT levels. Hence, the levels of Presepsin can reflect the likelihood of sepsis due to fungal infections, thereby making it a better marker for fungal sepsis in neonates. Presepsin and blood culture should be used to diagnose sepsis in neonates. Presepsin, if introduced in the lab as a routine investigation, will fall in the same price range as Procalcitonin. However, further studies from multiple centers would be needed before conclusions are drawn.

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