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Original Article

Paediatrics Section

Diagnostic Accuracy of Presepsin versus Procalcitonin in Early-Onset Neonatal Septicaemia: A Prospective Cohort Study

PRASIDUTT SHARMA[1], KHURSHED ALAM CHOUDHURY[2], SHUBHI AGARWAL[3]

ABSTRACT

Introduction: As a systemic inflammatory condition, neonatal sepsis causes serious morbidity and mortality. Septic shock and multiple organ dysfunction are swift, life-threatening consequences. For survival, early diagnosis and treatment are cardinal necessities. There is a need to evaluate biomarkers that can fulfill these requirements to increase survival.

Aim: To compare the emerging diagnostic roles of Presepsin (P-SEP) and Procalcitonin (PCT) at 48 to 72 hours of life in Early-onset Neonatal Sepsis (EONS) patients.

Materials and Methods: This prospective cohort study was conducted in the Neonatal Intensive Care Unit (NICU) of Mayo Medical College Barabanki, Uttar Pradesh, India from November 2019 to March 2021. A total of 58 cases at 48 to 72 hours of life, presenting with clinical features or risk factors of EONS, and 58 controls were included for blood culture, P-SEP, and PCT estimation. Comparison of quantitative variables between the study groups was conducted using the Mann-Whitney U test. The Chi-square (χ^2) test and Fisher's-exact test were used when the expected frequency was <5 for comparing categorical data. Receiver Operating Characteristic (ROC) curve analysis was performed, and the criterion value was estimated based on specificity and sensitivity.

Results: A total of 58 cases and 58 healthy controls were included. Out of the 58 cases, 36 (62.06%) were male, and 22 (37.94%) were female, with a mean age of 35 weeks±1.12 SD. A total of 28 were Blood Culture Positive (BCP). In ROC curve analysis, at a specific cut-off value, the sensitivity of P-SEP and PCT was 82.76% and 62.07%, respectively, while the specificity was 89.66% and 96.55%, respectively.

Conclusion: The P-SEP stands out as a superior biochemical marker compared to PCT. It has a promising future as an efficient sepsis detector and a positive indicator to avoid unnecessary NICU admissions and limit antibiotic therapy due to its high Negative Predictive Value (NPV).

Keywords: Biochemical marker, Blood culture, Life-threatening consequences, Septic shock

INTRODUCTION

Neonatal sepsis is the paramount cause of morbidity and mortality in both preterm and term newborn babies [1]. In developing countries, it is a serious concern, as maintaining asepsis in the NICU is still a major obstacle.

An unbridled host response to various infectious agents, such as viruses, bacteria, and fungi, occurs during the neonatal period of life. This systemic condition is life-threatening, as it ranks among the top three causes of neonatal mortality [1]. Septic encounters occurring before 72 hours of life are considered Early-Onset Neonatal Sepsis (EONS). Vertical transmission of pathogens, mostly bacteria, which occurs before or during delivery, is the major route [2]. Escalating drug resistance, unhygienic conditions, lack of breastfeeding, failure to detect early signs and constantly changing epidemiology are crucial factors that contribute to sepsis remaining a leading cause of neonatal mortality, even in the modern antibiotic era [1]. Although blood culture is the gold standard, sepsis screening and other blood parameters can also be useful and lifesaving at times. A major limitation of blood culture is that it takes time to yield results.

In recent years, several novel septic markers have emerged to assist in early diagnosis and treatment guidance. P-SEP is formed by the cleavage of the N-terminal of soluble CD14. It is a promising early biomarker with higher prognostic potential for neonatal sepsis [3]. Physiologically, it is present on the surface of monocytes and macrophages. Whenever there is stimulation by exogenous antigens, its level increases in systemic circulation [4]. Procalcitonin (PCT) is almost undetectable in healthy subjects, but during inflammation, Lipopolysaccharide (LPS) secreted by exogenous organisms is a powerful inducer. It promotes the release of PCT into the systemic circulation. PCT is also produced through indirect pathways induced by various inflammatory mediators, like Interleukin-6 (IL-6) and Tumour Necrosis Factor-α (TNF-α) [5]. In most neonates, PCT increases after birth, peaks at around 24 hours of life, and gradually decreases to below 0.5 ng/mL by 48 to 72 hours of life [6].

Recently, both P-SEP and PCT have proven to be valuable blood markers in addressing the detrimental outcomes of lethal neonatal sepsis. Previous studies targeted both early and late-onset septicaemia [7,8], but very few were based on the role of P-SEP in EONS [4,9]. In the present study, the authors not only aimed to evaluate their role in EONS patients but also specifically targeted the 24-hour time period between 48 and 72 hours of life. This narrow time window posed a challenging limitation, but authors conducted the study to explore this gap in the literature.

With this background, the present study was conducted to assess and compare the emerging diagnostic roles of P-SEP and PCT at 48 to 72 hours of life in EONS patients.

MATERIALS AND METHODS

The present prospective cohort study was conducted at Mayo Medical College, Barabanki, Uttar Pradesh, India from November 2019 to March 2021. The study commenced after obtaining ethical

clearance from the Institutional Ethical Committee (Ref. No. MIMS/EX/2020/357) and written informed consent from the parents.

Inclusion criteria: Neonates with any risk factors or clinical features of sepsis were considered as suspected cases for EONS and included in the study. Neonates of similar age with no risk factors or clinical features of EONS were enrolled as controls. Controls were included to calculate the defined cut-off values of P-SEP and PCT.

Exclusion criteria: Newborns who were already on antibiotics, those delivered with congenital anomalies, or those who experienced severe birth asphyxia were excluded from the study.

Features such as Premature Rupture of Amniotic Membrane (PROM), liquor stained with meconium, foul-smelling vaginal discharge, maternal fever, multiple pervaginal examinations (single unclean or more than three clean), prematurity, low birth weight, and prolonged labour are considered risk factors for EONS. Refusal to feed, respiratory distress, seizures, hypoglycaemia, apnoea, shock, feeding intolerance or necrotising enterocolitis, unexplained hypothermia and bleeding are considered clinical features of EONS [10,11].

Sample size calculation: The reference study used for the calculation of sample size was conducted by Fleischmann-Struzek C et al., [12], in which the authors reported that a proportion of 17% of the subjects had neonatal sepsis in India (an incidence of 17,000 per 100,000 live births).

Cochran formula used for calculation of Sample size is as follows:

$n= (Z^2\alpha \times P \times (1-P))/d^2$

Where,

Z, α is the level of significance at 5% i.e. 95% confidence interval = 1.96

P= Proportion of neonatal sepsis is 17%= 0.17 as reported in the reference study used.

d= Desired error of margin= 10%= 0.10

Hence, 54 patients are needed for the study. This number has been increased to 58 per group (a total of 116) to allow for a predicted dropout from treatment. A total of 58 cases and 58 healthy controls were included.

Study Procedure

After considering the inclusion and exclusion criteria, neonates were recruited for the study. Blood samples for P-SEP, PCT, and blood culture were taken with all aseptic precautions at 48-72 hours of age. P-SEP level estimation was done using a human presepsin Enzyme-linked Immunosorbent Assay (ELISA) kit manufactured by Wuhan Fine Biotech Co., Ltd. (Fine Test). The authors followed the protocol provided by the manufacturer of the Human Presepsin ELISA kit.

The whole blood sample was placed at room temperature for two hours or at 2-8°C overnight. It was then centrifuged for 20 minutes at 1000 x g, and the supernatant was collected for immediate detection. This procedure was based on sandwich Enzyme-Linked Immunosorbent Assay (ELISA) technology. Anti-P-SEP antibody was precoated onto the 96-well plate. For the detection of the antibody, a biotin-conjugated anti-P-SEP antibody was used. The standards and pilot samples were subsequently added to the wells. After incubation, unbound conjugates were removed with wash buffer. Then, the biotinylated detection antibody was added to bind with P-SEP conjugated to the coated antibody. After washing off the unbound conjugates, Horseradish Peroxidase (HRP) -Streptavidin (the protein streptavidin and the enzyme horseradish peroxidase) was added. After a third wash, 3, 3′, 5, 5′-tetramethylbenzidine (TMB) substrates were added to visualise the HRP enzymatic reaction. TMB was catalysed by HRP to produce a blue-coloured product that turned yellow after the addition of a stop solution. The Optical Density (OD) was read at 450 nm absorbance in a microplate reader. A standard curve was drawn to calculate the concentration of P-SEP in the sample. The concentration of the target substance is proportional to the OD450 value. In the present study, the cut-off value for P-SEP was found to be 636 ng/L.

The Chemiluminescent Microparticle Immunoassay (CMIA) was used to determine the PCT level. Samples and anti-PCT-coated paramagnetic microparticles were incubated together. If PCT is present in the sample, it binds to the anti-PCT-coated microparticles. The mixture was then washed. The reaction mixture was created by adding the anti-PCT acridinium-labelled conjugate, which was subsequently incubated. Following a wash cycle, pre-trigger and trigger solutions were added. The resulting chemiluminescent reaction was measured in Relative Light Units (RLUs). The amount of PCT in the sample and the RLUs detected by the system optics are directly correlated [13]. The cut-off value for PCT in the present study was found to be 0.5 ng/mL.

STATISTICAL ANALYSIS

The data were described in terms of range, mean±Standard Deviation (±SD), frequencies (number of cases), and relative frequencies (percentages) as appropriate. The comparison of quantitative variables between the study groups was performed using the Mann-Whitney U test. The Chi-square (χ^2) test and Fisher's-exact test were used when the expected frequency was less than 5 for comparing categorical data. ROC curve analysis was conducted, and the criterion value was estimated based on specificity and sensitivity. The Area Under the Curve (AUC) was measured. A probability value (p-value) of less than 0.05 was considered statistically significant. All calculations were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA) statistical programme for Microsoft Windows.

RESULTS

Out of a total of 58 neonates, the male-to-female ratio in the study was 1.63, with a minimum gestational age of 31 weeks and a maximum of 42 weeks. The newborn with a birth weight of 1300 grams was the lowest among all 58, while the newborn with a birth weight of 3860 grams was the highest. The statistical outcomes in terms of p-values for gender, birth weight, and gestational age were found to be non-significant. The detailed baseline clinical profile of cases and controls is shown in [Table/Fig-1].

Upon evaluating the mean values of P-SEP and PCT, the mean value of P-SEP was 821.6±387.478 for cases and 216.55±146.318 ng/L for controls, respectively. In the case of PCT, the values were found to be 0.83±0.645 ng/mL for cases and 0.35±0.347 ng/mL for controls, respectively [Table/Fig-2].

Among the 58 suspected cases, 28 (48.27%) were found to be Blood Culture Positive (BCP), and 30 (51.72%) were found to be Blood Culture Negative (BCN). A total of 16 (57.14%) of the BCP cases were gram-positive, while 11 (39.2%) were due to gram negative organisms. Group B *Streptococcus* and *Escherichia coli* were the most common gram positive and gram negative bacteria grown, respectively. The remainder were due to other organisms, including fungi, as shown in [Table/Fig-3].

Characteristic	Category	Cases (n=58) n (%)	Controls (n=58) n (%)	p-value
Gender	Male	36 (62.06)	40 (68.96)	0.437
	Female	22 (37.94)	18 (31.04)	
Birth weight	<2.5 kg	37 (63.79)	39 (67.24)	0.697
	>2.5 kg	21 (36.21)	19 (32.76)	
Gestational age	Preterm (<37 week)	30 (51.72)	32 (55.17)	0.711
	Term (>37 week)	28 (48.28)	26 (44.83)	
Blood sample taken at	Between 48-72 hours of life			
Risk factors present	PROM (> 18 h)	18 (31.03)		
	Multiple PV examination	10 (17.24)		
	Foul-smelling liquor	7 (12.06)		
	Prolonged labour	9 (15.51)		
	Maternal fever	3 (5.17)		
	Meconium-stained liquor	11 (18.96)		
Clinical profile	Refusal to feed	10 (17.24)		
	Respiratory distress	18 (31.03)		
	Seizures	3 (5.17)		
	Hypoglycaemia	7 (12.06)		
	Apnoea	4 (6.89)		
	Shock	5 (8.62)		
	Feeding intolerance	6 (10.34)		
	Unexplained hypothermia	5 (8.62)		

[Table/Fig-1]: The detailed baseline clinical profile of cases and controls.
Statistical test applied- Chi-square test

Variables	Cases			Control			p-value
	Mean	SD	Median	Mean	SD	Median	
P-SEP	821.60	387.478	863.00	216.55	146.318	184.50	0.001
PCT	0.83	0.645	0.80	0.35	0.347	0.30	0.001

[Table/Fig-2]: Mean value and Standard Deviation (SD) for P-SEP and PCT.
Statistical test applied- Mann-Whitney test

Name of the organism	Number of cases positive for blood culture (n=28)	Gram positive group	Gram negative group
Group-B *Streptococcus*	12	12	
Escherichia coli	9	-	9
Klebsiella	2	-	2
Staphylococcus aureus	4	4	-
Candida sp.	1	-	-

[Table/Fig-3]: Isolated organisms from culture-positive EONS cases.

Out of the 58 cases, a total of 13 neonates did not survive. Neonates with P-SEP values above 636 ng/L and PCT values above 0.5 ng/mL are considered positive. [Table/Fig-4,5] show the trends and statistical data of the survivor and non survivor groups. In the survivor group, P-SEP was positive in 29 (64.44%) cases, with a mean value of 677.96 ng/L, while in the non survivor group, it was positive for all 13 (100%) non survivors, with a mean value of 1276.08 ng/L. The results for both groups were statistically significant. The mean value for PCT was 0.73 ng/mL for survivors and 1.15 ng/mL for non survivors, respectively. PCT was in the positive range in 23 (51.11%) survivors and 9 (69.23%) non survivors, respectively [Table/Fig-6].

Variables		Blood culture		Total	p-value
		Negative	Positive		
P-SEP	Negative	16	0	16	0.001
	Positive	14	28	42	
Total		30	28	58	
PCT	Negative	22	0	22	0.001
	Positive	08	28	36	
Total		30	28	58	

[Table/Fig-4]: Depicting the comparative outcomes of P-SEP and PCT with blood culture.
Statistical test applied- Chi-square test

In the case of BCP, P-SEP was positive in 28 cases, while in the BCN group, it was positive for 14 subjects [Table/Fig-4]. A ROC analysis was performed for both P-SEP and PCT, and their diagnostic performance for EONS was compared. Blood culture was considered the gold standard in the present study to assess diagnostic accuracy. In the ROC analysis, the AUC for PCT was 0.7, with sensitivity and specificity of 62.07% and 89.66%, respectively, at a cut-off value of 0.5 ng/mL. Meanwhile, the AUC for P-SEP was 0.9, with sensitivity and specificity of 82.76% and 96.55%, respectively, at a cut-off value of 636 ng/L, as shown in [Table/Fig-5,7,8].

The Negative Predictive Value (NPV) for P-SEP and PCT was 84.85% and 70.27%, respectively. When comparing the results of P-SEP and PCT with blood culture results (considered the gold standard), every BCP case was positive for both P-SEP and PCT, with a statistically significant p-value.

DISCUSSION

Millions of new neonatal sepsis cases occur each year, resulting in the deaths of thousands of tiny, helpless neonates worldwide. Sepsis is responsible for approximately 8% of global neonatal mortality, and the constantly changing epidemiological challenges are alarming. In this scenario, prevention and early prompt diagnosis are fundamental keys to countering it [1]. Fleischmann C et al., conducted a recent meta-analysis and concluded that the incidence of EONS is approximately 2.6 times greater than that of late-onset sepsis in live births [14].

Out of 58 cases, 28 (48.27%) were BCPs. This result aligns with yields obtained by many studies [7,9,15]. Group B *Streptococcus, E. coli*, and *Staphylococcus aureus* were found in 42.6%, 32.14%, and 14.28% of the total BCP cases, respectively. The present study findings are supported by [16,17], but they contradict studies that concluded gram negative organisms were the most commonly grown in cultures [9,18]. Maternal Group B *Streptococcus* antibiotic prophylaxis practices are a major factor behind the varying culture yields.

Regarding the biomarkers of this study, P-SEP showed higher blood levels in cases compared to healthy controls, as concluded by other studies [19-22]. The authors found the AUC of P-SEP in the ROC analysis to be 0.9. This result is in concordance with that of Kamel MM et al., who compared P-SEP and CRP [23]. They found that the higher AUC of P-SEP (0.97) led them to conclude that P-SEP is a more sensitive and specific sepsis marker.

Kumar N et al., also found P-SEP to be superior to PCT in EONS patients, showing sensitivities and specificities of 79.2% and 100% for PCT, and 80.49% and 95.12% for P-SEP, respectively. This finding aligns with the present results [7]. Motalib TA et al., also found P-SEP to be more sensitive and specific than other biomarkers [9].

Variables		Mean	Std. deviation	Std. error	95% Confidence interval for mean		Z	p-value
					Lower bound	Upper bound		
P-SEP	Survivors	677.96	316.47	46.66	583.98	771.94	-4.920	0.001
	Non survivors	1276.08	274.80	76.21	1110.02	1442.13		
PCT	Survivors	0.73	0.65	0.10	0.53	0.92	-2.847	0.004
	Non survivors	1.15	0.50	0.14	0.85	1.46		

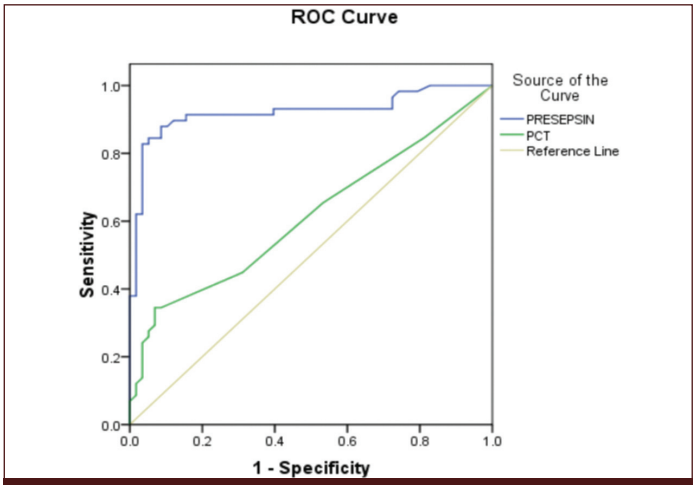
[Table/Fig-5]: Depicting statistical outcomes of P-SEP and PCT in survivors and non survivors groups.
Statistical test applied- Mann-Whitney test

Vari-ables		Outcome				Total	Chi-square value	p-value
		Survivors		Non-survivors				
P-SEP	Negative	16	35.56%	0	0.00%	16	6.383	0.012
	Positive	29	64.44%	13	100.00%	42		
Total		45	100.00%	13	100.00%	58		
PCT	Negative	22	48.89%	4	30.77%	22	10.240	0.001
	Positive	23	51.11%	9	69.23%	36		
Total		45	100.00%	13	100.00%	58		

[Table/Fig-6]: Depicting P-SEP and PCT trends in survivors and non-survivors groups.
Statistical test applied- Chi-square test

Statistical parameters	P-SEP	PCT
Sensitivity	82.76%	62.07%
Specificity	96.55%	89.66%
PPV	95.45%	85.71%
NPV	84.85%	70.27%
AUC	0.9	0.7
Cut-off value	636 ng/L	0.5 ng/mL

[Table/Fig-7]: Statistical comparison of P-SEP and PCT.



[Table/Fig-8]: ROC curve showing the AUCs of P-SEP and PCT. At 636 ng/l, with an AUC of 0.9, the sensitivity and specificity of P-SEP are 82.76% and 96.55%, respectively. At 0.5 ng/mL, with an AUC of 0.7, the senstivity and specificity of PCT are 62.0% and 89.66%, respectively.
(Sample size 116; p-value <0.001)

At a cut-off value of 672 pg/mL, they reported sensitivities and specificities of 97% and 98%, respectively.

Another study by Zou Q et al., reported that P-SEP is a better biomarker that is not only promising for prompt diagnosis but also for assessing prognosis [24]. A study dedicated to EONS agreed with the present results, finding a significant difference between P-SEP and other biomarkers like PCT, CRP, and IL-6. In the present study, P-SEP ranked among the top, while PCT was at the bottom [4].

The statistical analysis showed an 84.85% NPV for P-SEP, which is still relatively high but is contradicted by studies reporting 97.3% [3] and 97.8% [5]. Sampling at a specific 24-hour age duration and a smaller sample size are certain limitations of the present study that may have affected the results. A comparison of the findings in the present study with contrasting studies is shown in [Table/Fig-9] [4,7,9,23].

Higher NPV values are beneficial as they help rule out EONS and protect a large number of patients from unnecessary exposure to empirical antibiotic therapy. By monitoring the serial values of P-SEP, clinicians can gain a clearer picture to help make decisions regarding the cessation of antibiotic therapy [5].

Limitation(s)

The failure to detect certain nonspecific clinical features, the limited availability of ELISA kits, and the questionable implementation of P-SEP as a single biomarker for EONS are some of the limitations of the study.

CONCLUSION(S)

A supererogatory and indecorous use of antibiotics, along with an unnecessarily extended stay in the NICU, leading to exposure to more risk factors, are the two major adverse effects of not having a reliable early diagnosis protocol for neonatal sepsis. Sometimes, this also compromises the final outcome, such as death. The present study analysis proposes that P-SEP is a more auspicious biomarker than PCT at 48-72 hours of age in EONS cases. The authors found it to be more accurate and rapid. Despite certain limitations, based on the results, authors recommend conducting larger-scale, specific studies and trials to gain additional certainty, safety, and proper reference ranges for using P-SEP as an early

Name of the study	Place/year of the study	Sample size (n)	Sensitivity of P-SEP (%)	Specificity of P-SEP (%)	Sensitivity of PCT (%)	Specificity of PCT (%)
Motalib TA et al., [9]	Menoufia University Hospital and Ahmed Maher Teaching Hospital, Egypt /2015	62	97	98	NA	NA
Kumar N et al., [7]	SNMC, Agra/2019	41	100	95.12	79.2	80.49
Kamel MM et al., [23]	Minia University, Egypt/2021	80	97.8	94.1	93.5	79.4
Pospisilova I et al., [4]	Thomayer University Hospital in Prague, Czech Republic/2023	184	90	71.6	NA	NA
Present study (2024)	MIMS Barabanki/2024	58	82.76	96.55	62.07	89.66

[Table/Fig-9]: Comparison of statistical results of various recent studies [4,7,9,23].

biomarker for EONS. This approach is also beneficial for identifying a combination test, such as blood culture or other biomarkers alongside P-SEP, to achieve enhanced negative predictive power. However, when considering India in the current scenario, the use of P-SEP as a principal biomarker will be questionable due to its limited availability in specific centres and its high cost compared to other popular sepsis biomarkers.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Paediatrics, UIMS, Prayagraj, Uttar Pradesh, India.
2. Assistant Professor, Department of Paediatrics, UIMS, Prayagraj, Uttar Pradesh, India.
3. Senior Resident, Department of Paediatrics, UIMS, Prayagraj, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Prasidutt Sharma,
54/32, Chhota Baghara, Prayagraj, Uttar Pradesh-211003, India.
E-mail: prashidutt24@gmail.com

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