Research Article

Presepsin as a Predictor of Positive Blood Culture in Suspected Neonatal Sepsis.

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Abstract
Introduction: Neonatal sepsis is the most common cause of morbidity and mortality during the neonatal period. Presepsin (P-SEP) is a truncated variant of soluble CD14. Pathogens stimulate P-SEP shedding from the surface of various immune cell types. **Aim of the work:** to evaluate the accuracy of presepsin as a novel biomarker for bacterial infection diagnosis and correlate its level with blood culture, CRP and procalcitonin (PCT) levels. **Methods**: This was a comparative prospective study included eighty neonates admitted to NICU. They were divided into two major groups: Group I: it included twenty full term neonates; infants who are born after 37 completed weeks. Group II: it included sixty preterm neonates; infants who are (<37 completed weeks of gestation), it was classified into three subgroups; *Group II A* 20 Low birth weight neonates: 1501- 2500 gm., *Group II B* 20Very low birth weight neonates: 1001-1500 gm., *Group II C* 20 Extremely low birth weight neonates: 500-1000 gm. **Results:** P-SEP 2 levels were higher in sepsis group than in non-sepsis group. No significant difference in levels of P-SEP 1 was found between the two groups. Presepsin showed more diagnostic accuracy than PCT in diagnosis of sepsis: the best cut-off value for Presepsin was 485pg/ml, with 97.8% sensitivity and 94.1% specificity. There were statistically significant positive correlations between P-SEP 2, PCT and CRP. **Conclusion:** Serum presepsin has superior accuracy than procalcitonin in diagnosis of neonatal sepsis. **Recommendation:** Presepsin can be used as a diagnostic and prognostic marker for neonatal sepsis.
Key Words: newborn, presepsin, sepsis.

Introduction
Neonatal sepsis is the most common cause of morbidity and mortality during the neonatal period. Neonatal sepsis is classified as either early-onset sepsis (EOS; ≤7 days after birth) or late-onset sepsis (LOS; >7 days after birth**).**[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 includes various systemic infections of the, newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infections, superficial infections like conjunctivitis and oral thrush are not usually included under neonatal sepsis**.**[2]

When blood and other sterile site cultures are negative, but the infant manifests signs consistent with infection they may be considered to have "clinical" sepsis. Interpretation of CRP in the diagnosis of EOS may be hindered by several non-infectious conditions that influence CRP during the first days after birth**.**[3,4] Presepsin (P-SEP), or soluble CD14 subtype, is a truncated variant of soluble CD14. Pathogens stimulate P-SEP shedding from the surface of various immune cell types; such as macrophages, monocytes, and neutrophils. Although its function is still unclear, P-SEP is believed to interact with B and T cells to modulate specific immune responses**.** P-SEP has recently been demonstrated to be a reliable diagnostic and prognostic marker of sepsis in adults. Preliminary reference values of P-SEP have mainly been evaluated in infants with late onset sepsis (LOS) [5,6]

Subjects and Methods

This study was a comparative prospective study conducted in neonatal intensive care unit (NICU), Minia Children University Hospital, in the period from July 2018 to June 2019. This study included eighty neonates admitted to NICU. They were divided into two major groups: **Group I**: it included twenty full term neonates; infants who are born after 37 completed weeks.

Group II: it included sixty preterm neonates; infants who are (<37 completed weeks of gestation), it was classified into three subgroups; *Group II A* 20 Low birth weight neonates, *Group II B* 20 Very low birth weight neonates, *Group II C* 20 Extremely low birth weight neonates. All neonates were subjected to the following:

1- Careful history taking &general and systemic examination
2- Laboratory investigations: **CBC** (using sysmex KX-2IN automated analyzer), **CRP** (using the AVITEX CRP kit), **Blood culture** (using oxoid system), **Serum presepsin** (first sample was collected from cord blood at birth & second sample was collected after the onset sepsis;both using ELISA system) and serum Procalcitonin (using ELISA system).

Results

Table (1): Comparison between sepsis group and Non sepsis group as regards Procalcitonin, P-SEP 1& P-SEP 2

	Sepsis (n=46)	**Non sepsis (n=34)**	**P value**
Procalcitonin *(microg/L)*	3.79±2.53	0.16±0.25	<0.001*
P-SEP 1(pg/ml) Median (IQR)	125 (80-170)	120 (100-150)	0.674
P-SEP 2 (pg/ml) Median (IQR)	650 (490-60)	120 (100-170)	<0.001*

Table (2): Diagnostic accuracy of serum P-SEP 2.

	AUC	**P value**	**Cutoff point**	**Sensitivity**	**Specificity**
P-SEP 2	0.97	**<0.001***	>485	97.8%	94.1%

The results showed statistically significant difference between the studied groups regarding gestational age, birth weight, onset of sepsis, outcome and risk factors. As regards the outcome, the heavier was the neonate the lower was the incidence of sepsis and the higher was the survival rate; Group I: 6 neonates (30%) developed sepsis, 15 neonates (75%) survived out of 20, Group II A: 8 neonates (40%) developped sepsis, 12 neonates (60%) survived out of 20,Group II B: 13 neonates (65%) developed sepsis, 8 neonates (40%) survived out of 20, Group II C: 19 neonates (95%) developed sepsis,6 neonates (30%) survived out of 20. Studied Lab. results revealed that, the lesser the weight of the neonate the more affected levels of Hb, TLC, PLT, CRP, procalcitonin and P-SEP 2; while there were no statistically significant differrence between presepsin in cord blood among all studied groups. Results revealed statistically significant increase of serum P-SEP 2 in sepsis group than in non-sepsis group. No significant difference in levels of

P-SEP 1 was found between the two groups.

Results of blood culture were positive in 100% of septic neonates, the causative organisms included: MRSA (28%), GBS (18%), E.Coli (15%), Pseudomonus (11%), Streptococcus agalactiae (9%), Klebsiella Pn (7%), Klebsiella oxytoca (4%) and Enterococus Fecalis (4%).
Presepsin showed more diagnostic accuracy than PCT in diagnosis of sepsis, the AUC for P-SEP 2 was 0.97, at best cut-off value on ROC curve (485pg/ml), with 97.8% sensitivity and 94.1% specificity, while the AUC for PCT was 0.95, at best cut-off value (<0.7microg/L), with 85.16% specificity and 60.4 % sensitivity.

The results revealed statistically significant positive correlation between P-SEP 2, PCT and CRP, while both P-SEP2 and PCT correlates negatively to PLT.

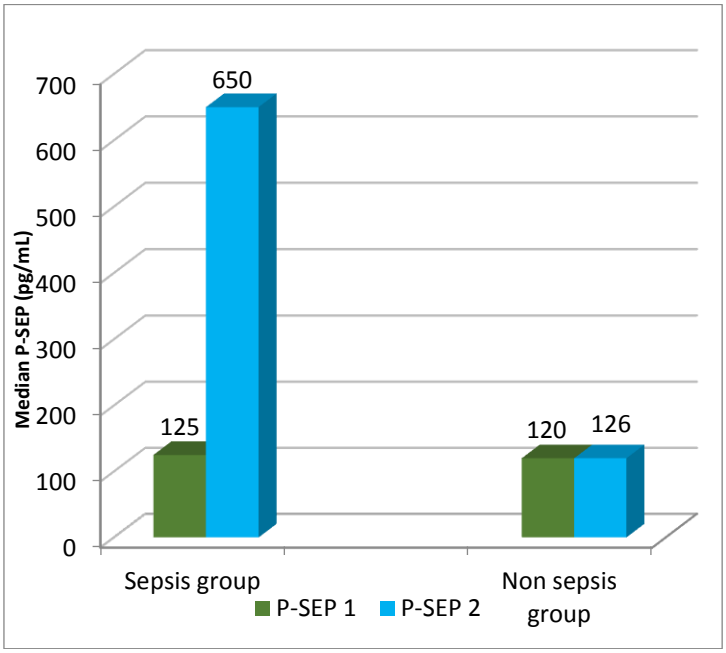

Fig. (1): Levels of presepsin in both cord blood (P-SEP 1) and after onset of sepsis (P-SEP 2) among sepsis and Non sepsis groups

Discussion

This study included 80 neonates (42 male and 38 female) 46(54.3%) of these neonates developed sepsis, with mean gestational age (33.87±1.3 weeks) and birth weight (1,747.5±267.5gm). 36 neonates (78.3%) of the sepsis group developed EOS, while10 neonates (21.7%) developed LOS. In accordance to our results, Miyosawa et al., study revealed that there were statistically insignificant differences between study group and control group regarding gender, gestational age and birth weight.[7]

In our study, CRP levels were higher in septic group than in non-sepsis group, this is in agreement with Miyosawa et al., 2018 & Adu, 2017.[8,9]

Our study revealed that Hb levels were lower in sepsis group, while TLC levels were higher in sepsis group, this agrees wiht Adu, 2017; but Bhat et al., 2010 found that leukopenia was a better predictor for neonatal sepsis compared to leukocytosis and is more common in gram negative infections.[10,11] TLC increases in severe

neonatal infections secondary to the release of growth factors and cytokine that stimulate the bone marrow production [12]

our study revealed that PLT levels were lower in sepsis group than in non-sepsis group. Similarly, Singh et al., 2018 study showed that thrombocytopenia was present in 100 neonates (95.2%) out of 105 culture positive neonate [13]

In our study there was significant increase of serum P-SEP 2 in preterm groups; being lowest in full-term group and highest in ELBW group so the less the weight of the neonate the more elevated levels of P-SEP 2.this agrees with Pugni et al., 2015, But disagrees with Mussap et al., 2012 who found no statistically significant correlation between gestational age and P-SEP levels. [14,15]

In our study, there were no differences between sepsis group and non-sepsis group regarding P-SEP 1 levels. On contrast P-SEP2 levels were higher in sepsis group than in non-sepsis group, this is in agreement with Miyosawa et al., 2018 & Adu, 2017.[16,17]

Our study revealed that serum P-SEP 2 had high diagnostic accuracy to detect sepsis. Similarly, Topcuoglu et al., 2016 reported that cut-off value for P-SEP was 800.5 pg/mL, with 67% sensitivity and 100% specificity. Also, in 2017, Montaldo et al. found that cut-off value was 788 pg/mL, with 93% sensitivity and 100% specificity. Recently, in 2018, Miyosawa et al, found that 795 pg/mL was established as the cut-off for P-SEP, with 85% sensitivity and 89% specificity.[18,19,20]

In our study, a positive correlation was observed between serum P-SEP 2, PCT and CRP levels, this comes in agreement with Miyosawa et al., 2018 who found the same results.[21]

In our study, presepsin showed more diagnostic accuracy than PCT in diagnosis of sepsis. This comes in agreement with studies done by Topucuoglu et al., 2016 and Montaldo et al., 2017.[22,23]

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