CHILD HEALTH

The Evaluation of Procalcitonin Accuracy in Early and Late Onset Neonatal Sepsis

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ABSTRACT

Procalcitonin is a useful test for sepsis diagnosis in newborns. However, fluctuations normally occur within 48 hours. Hence the need to assess the diagnosis accuracy and cut-off points for both early onset (EOS) or late onset (LOS) neonatal sepsis.

Objective: **To evaluate the accuracy of procalcitonin in neonatal sepsis diagnosis.**

Methods: **A cross-sectional analytical study was conducted in perinatology unit Haji Adam Malik Hospital Medan, involving 65 neonates suspected sepsis. Procalcitonin and blood culture values were evaluated for EOS and LOS diagnosis.**

Results: **There were 35 and 30 EOS and LOS cases respectively. The proportion of positive cultures was 41.5%. Procalcitonin in EOS with 0.5 ng/mL cut-off of had sensitivity 77.8%, specificity 9.5% PPV 26.9%, NPV 50%, PLR 0.85 and NLR 2.3. While at 2.5 ng/mL cut-off, sensitivity was 77.8%, specificity 61.9%, PPV 46.7%, NPV 86.7%, PLR 3.5, NLR 0.35 and AUC 0.683. Finally, procalcitonin in LOS with 0.5 ng/mL cut-off had sensitivity 92.9%, specificity 81%, PPV 76.5%, NPV 94.4%, PLR 4.9, NLR 0.08 and AUC 0.889.**

Conclusion: **Procalcitonin is a reliable marker for LOS to administer antibiotic therapy. However, it is less useful for EOS screening due to the fluctuation in the value.**

KEY WORDS

neonatal sepsis, procalcitonin, blood culture, diagnostic value

INTRODUCTION

Neonatal sepsis is a systemic disease with the presence of bacteria in the first month of life[1]. It can be categorized, based on neonatal period, into early-onset sepsis (EOS) when the occurrence is in the first 72 hours of birth and late-onset sepsis (LOS) for the occurrence after that period[2]. Early diagnosis and prompt treatment are crucial factors to morbidity and mortality rates due to sepsis in newborns[3]. Blood culture is the gold standard for the diagnosis, but it has high false negative rate. Moreover, the diagnosis is complicated by many factors, especially in low-resource settings, such as non-specific clinical symptomatology and the absence of specific biomarkers[4].

Procalcitonin (PCT) is a pro-peptide of calcitonin that increases markedly with sepsis[1]. It is useful as an early diagnostic tool for bacterial neonatal sepsis. Study conducted by Nelly *et al*., (2015) found that PCT sensitivity was 100%, specificity 85.71%, positive predictive value (PPV) 97.29% and negative predictive value (NPV) 100%. The ROC curve showed a cut-off point of 0.929[5]. Procalcitonin level is useful for sepsis diagnosis in neonates, however, the reliability is inconsistent because of various conditions encountered in neonatal intensive care units (NICUs) like small for gestational age and respiratory distress. Other factors, such as very low birth weight, low APGAR score at 5 minutes, prenatal antibiotic and surfactant administrations, also increase PCT levels[6]. Bloomendahl *et al*., (2002) and Chiesa *et al*., (2003) suggested that PCT have advantages for EOS diagnosis, such as the rapid increase when compared to other infection markers[7,8]. On the contrary, Koskenvuo *et al*., (2007) observed the lack of accuracy in PCT as a marker for sepsis mainly due to other factors, besides infections, which can affect the level of PCT[9]. The use of PCT for neonatal sepsis diagnosis is still debatable, nevertheless the serum has become commercially available recently. It is useful for the detection of sepsis with vertical transmission, however its cut-off values for each evaluation point for EOS and LOS cases need to be determined[10]. Vijayan *et al*., (2017) in their systematic review suggested to conduct more studies with high methodological quality, particularly in neonates, to assess EOS and LOS separately to improve specificity[11]. This study evaluates procalcitonin accuracy and reliability in diagnosing early and late onset neonatal sepsis.

METHODS

This research was a cross-sectional study conducted to neonates suspected with early and late onset sepsis in perinatology unit Haji Adam Malik Hospital Medan from May ─ October 2019. Research subjects were patients with chronological age below 28 days admitted to perinatology ward and they were not suspected or proven with immunodeficiency, hematological disorder or receiving immunomodulator drugs. Informed consent was obtained from the guardians of the participants. History taking, physical examination and anthropometric measurements were carried out.

The sample size in this research was calculated based on the sample size formula for diagnostic value testing in a population with the AUC (area under curve) value as the outcome. The calculation was done using 95% confidence level with minimal sample size of 30 patients. There were 65 neonates involved in this study as the research samples. They were divided into 2 groups, such as group EOS and LOS. Routine blood test, procalcitonin and blood culture tests were performed during admission. All data obtained was recorded and tabulated. Research approval was obtained from the health research ethical committee,

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Data Processing and Data Analysis

Univariate analysis was performed to obtain demographic characteristics and clinical samples distribution. Numerical data with normal distribution was presented in mean ± standard deviation (SD); whereas median (maximum and minimum) data was used if the data was not distributed normally. Categorical data was in frequency and percentage. Procalcitonin diagnostic value in neonatal sepsis was analyzed by using ROC curve, tabulated in Microsoft Excel and plotted in graph. The cut point was obtained between sensitivity and specificity lines which lead to procalcitonin cut-off point. Cut-off point was used to analyzed the sensitivity, specificity, PPV, NPV, PLR, and NLR values for procalcitonin. Data processing was performed by using Statistical Package for Social Sciences for Windows (SPSS) version 24.0, 2016 with significance level of $p < 0.05$ and 95% confidence interval

RESULT

There were 65 neonates suspected sepsis and met the inclusion and exclusion criteria. Research samples were divided into 2 groups, 35 and 30 newborns in EOS and LOS groups respectively. In EOS group, 54.3% neonates were female and there were 63.3% of preterm birth. In LOS group, there were more male (56.7%) than female. The preterm birth rate was lower at 36.7% in LOS group compared to EOS group. The median procalcitonin level of both groups was 0.4 ng/dL (range 0.01 — 100). All characteristic data of the research samples was shown in Table 1.

Table 1: Subject characteristics

Characteristics	EOS Group N = 35	LOS Group N = 30
Gender, n(%)		
Male	16 (45.7)	17 (56.7)
Female	19 (54.3)	13 (43.3)
Age, n(%)		
0-12 hours	7 (23.3)	-
12 — 24 hours	9 (30.0)	-
1-3 days	14 (46.7)	-
Age (days), median (range)	-	10.0 (4-28)
Weight (gram), mean (SD)	2369.14 (728.14)	2089.67 (999.971)
Body length (cm), mean (SD)	43.94 (4.621)	41.52 (6.001)
Gestational age, n(%)		
Term	11 (36.7)	19 (63.3)
Premature	19 (63.3)	11 (36.7)
Procalcitonin (ng/mL), median (range)	0.4 (0.01 — 100)	0.4 (0.01 — 100)
Blood culture, n(%)		
Acinetobacter Baumannii	1 (2.9)	2 (6.7)
Klebsiella pneumoniae	3 (8.6)	4 (13.3)
K. Pneumoniae (EBSL +)	1 (3.5)	-
Pseudomonas aeruginosa	-	2 (6.7)
Enterobacter asburiae	2 (5.7)	1 (3.3)
Micrococcus luteus	1 (2.9)	1 (2.9)
Enterobacter cloacae	3 (8.6)	1 (3.3)
MRSA	1 (2.9)	-
Dermacoccus nishinomiyaensis	1 (2.9)	-
Staphylococcus aureus	1 (2.9)	-
Staphylococcus hominis	-	1 (3.3)
Klebsiella oxytoca	1 (2.9)	-

The accuracy of PCT in EOS and LOS was presented in Table 2.

Table 2: Procalcitonin accuracy in EOS and LOS groups

Variables	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
Procalcitonin (EOS) *cut-off* 0.5 ng/mL	77.8	9.5	26.9	50.0	0.85	2.3
Procalcitonin (EOS) *cut-off* 2.5 ng/mL	77.8	61.9	46.7	86.7	3.5	0.35
Procalcitonin (LOS) *cut-off* 0.5 ng/mL	92.9	81.0	76.5	94.4	4.9	0.08

Procalcitonin level in EOS with 0.5 ng/mL was poor at sensitivity 77.8%, specificity 9.5%, PPV 26.9%, NPV 50%, PLR 0.85 and NLR 2.3. However, a better diagnostic accuracy was obtained with 2.5 ng/mL cut-off point where sensitivity 77.8%, specificity 61.9%, PPV 46.7%, NPV 86.7%, PLR 3.5 and NLR 0.35 with AUC 0.683 (Figure 1).

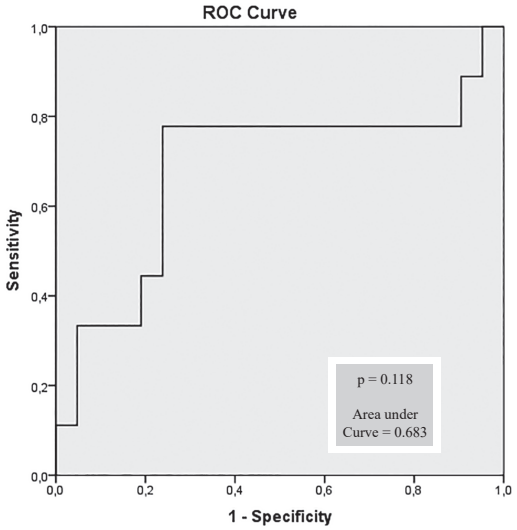

Figure 1: ROC curve for procalcitonin in EOS

Procalcitonin level assessment in LOS showed good accuracy at cut-off 0.5 ng/mL with sensitivity 92.9%, specificity 81%, PPV 76.5%, NPV 94.4%, PLR 4.9 and NLR 0.08 with AUC 0.889 (Figure 2).

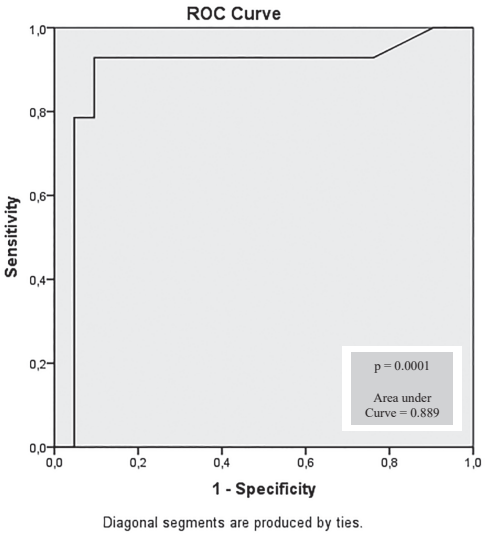

Figure 2: ROC curve for procalcitonin in LOS

DISCUSSIONS

Neonatal sepsis, as an invasive infection, occurs within the first 28 days of life, usually can be classified into early-onset (< 48-72 hours) and late-onset (> 48-72 hours) sepsis, depending on the chronological age of the sepsis episode[12]. Bacterial neonatal sepsis is a low-incidence with high-risk disease. Accurate diagnosis is difficult as it does not have definitive diagnostic tests; when even blood culture test as the gold standard, has a low sensitivity[13].

The increase in procalcitonin level in relation to bacterial infection was first discovered by Assicot and friends[14]. The actual mechanism of PCT production in infection is not yet known. It is suspected that bacterial lipopolysaccharide stimulates the release of cytokines and mononuclear cell to produce PCT. Microbial infection induces the expression of CALC-1 gene followed by the secretion of PCT which correlates with disease severity and mortality[11].

There were total 65 neonates involved in this research, in which 35 of them were early-onset and 30 late-onset neonatal sepsis. The proportion of positive culture in this study was 41.5%. Blood culture results in EOS were dominated by *Acinetobacter Baumannii*, *Klebsiella pneumoniae*, *Staphylococcus hominis*, *Pseudomonas aeruginosa* while the results in LOS were dominated by *Enterobacter asburiae*, *Dermacoccus nishinomiyaensis*, *Enterobacter cloacae*, *Klebsiella pneumoniae*. These culture results on EOS were different from the general pattern of EOS bacteria, such as Group B *Streptococcus* (GBS), *Escherichia coli*, other *Streptococci and Staphylococcus aureus*. The difference may be caused by nosocomial infections[15]. The study done by Mohammed and El (2014) reported 38.5% cases of nosocomial infections in babies admitted to NICU in Egypt, where the most found pathogens were *Klebsiella sp* and *Staphylococcus aureus*. The most frequent nosocomial infections were bloodstream infections and pneumonia mainly due to low birthweight and prematurity as the main risk factors[16].

Procalcitonin test has better diagnostic and prognostic value when compared to other tests like C-reactive protein. Adib *et al*., (2012) in their research showed higher sensitivity in procalcitonin (70%) than in c-reactive protein (45%) for the diagnosis of neonatal sepsis. PCT appeared to be a more useful marker to indicate the severity of infections[17]. Moreover, it clearly distinguishes between viral and bacterial meningitis[18]. PCT levels start to rise at the first 2 hours after the start of septic insult and reaches the peak within 12 hours[19]. In this study, the use of procalcitonin in EOS with a cut-off of 0.5 ng/mL had sensitivity 77.8%, specificity 9.5%, PPV 26.9%, NPV 50%, PLR 0.85 and NLR 2.3. Whereas, at 2.5 ng/mL cut-off point, sensitivity 77.8%, specificity 61.9%, PPV 46.7%, NPV 86.7%, PLR 3.5 and NLR 0.35 with AUC 0.683. The use of procalcitonin in LOS with a cut-off of 0.5 ng / mL gave sensitivity 92.9%, specificity 81%, PPV 76.5%, NPV 94.4%, PLR 4.9 and NLR 0.08 with AUC 0.889. The diagnostic value for EOS in this study was similar to the systematic review done by Pontrelli *et al*., (2017), in which PCT values from EOS and LOS cases of different studies were combined, resulted in sensitivity of 0.85 (CI = 0.76; 0.90) and specificity 0.54 (CI = 0.38; 0.70) at PCT 2.0-2.5 ng/ml cut-off[20]. The study done by Hasan *et al*., (2017) showed that PCT with > 2 ng/mL cut-off for both EOS and LOS had sensitivity 100%, specificity 50%, PPV 48.5% and NPV 100%. When the level of PCT was moderately elevated from 2 ─ 10 ng/mL had sensitivity 100%, specificity 84.5%, PPV 62.5% and NPV 100%, whereas highly elevated PCT level (> 10 ng/mL) had 100% sensitivity, 80% specificity, 75% PPV and 100% NPV[21]. Adib *et al*., (2012) showed PCT level was significantly higher in suspected infants and septic cases than in normal infants ($P < 0.05$). The sensitivity of PCT level for neonatal sepsis early diagnosis was 70%, specificity 80%, PPV 80% and NPV 75%[17]. Lee *et al*., (2017) reported that PCT level provided better diagnosis after 12 hours postpartum (LOS)[6].

Procalcitonin is useful as an early diagnostic tool for bacterial neonatal sepsis. Auriti *et al*., (2017) suggested procalcitonin serum as a useful diagnostic marker for neonatal sepsis on day-to-day clinical practice in NICUs. The overall probability of nosocomial sepsis was doubled or more if PCT was > 0.5 ng/ml. In very-low-birth-weight (VLBW) infants, > 2.4 ng/ml cut-off of gave neonatal sepsis PPV at approximately 50% with a probability of false-positive diagnosis at ~10% in patients. The study suggested that PCT value < 2.4 ng/ml may help to exclude neonatal sepsis, irrespective of birth weight[22].

Vijayan *et al*., (2017) reported that procalcitonin alone may not be effective to distinguish between bacterial and viral infections. However, it is an ideal biomarker for bacterial infection due to its rapid elevation in the concentration during an infection and correlation with the severity of illness. Moreover, PCT level can be used to monitor antimicrobial therapy response, diagnose secondary inflammation and renal involvement in pediatric urinary tract infections[11]. However, the interpretation of PCT values is challenging due to its strong physiological rise and fall during the first 72 hours of life. Neonatal procalcitonin levels were higher and the normal range was based on the chronological age[23]. Lee *at al*., (2017) reported fluctuating levels in neonates at different chronological ages, where PCT level was 0.55 ng/mL at birth (sensitivity 75.4%, specificity 72.3%), 4.7 ng/mL at 12 ─ 24 hours of life (sensitivity 73.8%, specificity 79.2%)[6]. These levels were also influenced by the presence and absence of the accompanying syndrome and antibiotics prescribed to the mothers[23]. Perinatal factors, such as chorioamnionitis,

hypoxemia, perinatal asphyxia, and maternal preeclampsia can also cause PCT to increase[8]. This study, however, did not exclude babies whose mothers had received antibiotics and there was no polymerase chain reaction test carried out to identify viruses as etiology of neonatal sepsis.

This study has assessed the PCT cut-off points separately for EOS at 0.5 ng/mL and 2.5 ng/mL and LOS at 0.5 ng/mL as references for initial antibiotic therapy administration to neonatal sepsis while waiting for the results from more accurate tests like blood culture. Procalcitonin test was observed as a reliable marker for LOS, however, it is less accurate for EOS diagnosis due to the fluctuation in PCT values despite the improvement in diagnostic level at elevated cut-off point to 2.5 ng/mL.

CONCLUSION

Procalcitonin is a reliable marker for LOS to administer antibiotic therapy before blood culture results are available. However, it is less useful for EOS screening due to the fluctuation in the value which often only occurs as early as 48 hours after birth.

REFERENCES

1. Christakis Gomella TL, Cunningham MD, Eyal GE. Sepsis. In: Jaszczak M, Kharidehal N, Ohyama M, Pas AT, Ramji S, Seshia M *et al*, editor. Neonatology: Management, procedures, on-call problems, disease, and drugs. 7th Edition. United States: The McGraw-Hill Companies Inc; 2013. p865-73.
2. Plunkett A, Tong J. Sepsis in children. BMJ. 2015; 350: 3017.
3. Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. Virulence. 2014; 5: 170-8.
4. Brown DR, Kutler D, Rai B, Chan T, Cohen M. Bacterial concentration and blood volume required for a positive blood culture. J Perinatol. 1995; 15: 157-9.
5. Nelly, Tjipta GD, Hakimi, Lubis BM. Procalcitonin as a diagnostic tool for bacterial neonatal sepsis. Pediatr Indones. 2015; 55: 1-5.
6. Lee J, Bang YH, Lee EH, Choi BM, Hong YS. The influencing factors on procalcitonin values in newborns with noninfectious conditions during the first week of life. Korea J Pediatr. 2017; 50: 10-8.
7. Blommendahl J, Janas M, Laine S, Miettinen A, Ashorn P: Comparison of procalcitonin with CRP and differential white blood cell count for diagnosis of culture-proven neonatal sepsis. Scand J Infect Dis. 2002; 34: 620-2.
8. Chiesa C, Pellegrini G, Panero A, Osborn JF, Signore F, Assumma M, Pacifico L: C-reactive protein, interleukin-6, and procalcitonin in the immediate postnatal period: influence of illness severity, risk status, antenatal and perinatal complications, and infection. Clin Chem. 2003; 49: 60-8.
9. Koskenvuo MM, Irjala K, Kinnala A, Ruuskanen O, Kero P: Value of monitoring serum procalcitonin in neonates at risk of infection. Eur J Clin Microbiol Infect Dis. 2003; 22: 377-8.
10. Sastre JB, Solis DP, Serradilla VR, Colomer BF, Cotallo GD, Castrillo GH. Evaluation of procalcitonin for diagnosis of neonatal sepsis of vertical transmission. BMC Pediatr. 2007; 7: 1-9.
11. Vijayan AL, Ravindran S, Saikant R, Lakshmi S, Kartik R, Manoj G. Procacitonin: a promising diagnostic marker for sepsis and antibiotic therapy. J Int Care. 2017; 5: 1-7.
12. Labib AZ, Mahmoud AB, Eissa NAA, Gendy FME, Soliman MA, Aly AA. Early Diagnosis of Neonatal Sepsis: A Molecular Approach and Detection of Diagnostic Markers Versus Conventional Blood Culture. Int J Microbiol Res. 2013; 4: 77-85.
13. Shane AL, Sanchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017; 390: 1770-80.
14. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C *et al*. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993; 27: 515-8.
15. Russel ARB. Neonatal sepsis. Paediatr Child Health. 2015; 25: 271-5.
16. Mohammed D, El Seifi OS. Bacterial nosocomial infections in neonatal intensive care unit, Zagazig University Hospital, Egypt. Egypt Pediatr Assoc. 2014; 62: 72-9.
17. Adib M, Bakhshiani Z, Navaei F, Fosoul FS, Fouladi S, Kazemzadeh H. Procalcitonin: A reliable marker for the diagnosis of neonatal sepsis. Iranian J Basic Med Sci. 2012; 15: 777-82.
18. Chan DK. Usefulness of C-reactive protein in diagnosis of neonatal sepsis. Singapore Med J. 1997; 38: 252-5.
19. Usama M, Nermin A, Ayman A, Sultan MH. Serum procalcitonin in viral and bacterial meningitis. J Glob Infect Dis. 2011; 3: 14-8.
20. Pontrelli G, Crescenzo FD, Buzzetti R, Jenkner A, Balduzzi S, Carducci FC, dkk. Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: a meta-analysis. BMC Infectious Dis. 2017; 17: 302-14.
21. Hasan F, Khan SA, Maharoof MK, Muhammed N. Role of procalcitonin in early diagnosis of neonatal sepsis. Int J Contemp Pediatr. 2017; 4: 383-9.
22. Auriti C, Fiscarelli E, Ronchetti MP, Argentieri M, Marrocco G, Quondamcarlo A *et al*. Procalcitonin in detecting neonatal nosocomial sepsis. Arch Dis Child Fetal Neonatal. 2017; 97; 366-70.
23. Memar MY, Varshochi M, Shokouhi B, Asgharzadeh M, Kafil HS. Procalcitonin: the marker of pediatric bacterial infection. Biomedicine and pharmacotherapy. 2017; 11: 149-52.