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Original Article

Procalcitonin as a diagnostic tool for bacterial neonatal sepsis

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Abstract

Background Bacterial sepsis is the main cause of morbidity and mortality in neonates. Early diagnosis and appropriate treatment can reduce the mortality rate. Blood culture is the gold standard for diagnosis of bacterial sepsis, but it requires 3-5 days for results. Since the disease may progress rapidly in neonates, a faster diagnostic test is needed. Measurement of procalcitonin levels may be a quick method to diagnose bacterial sepsis in neonates. Some studies found the sensitivity of procalcitonin to be between 92-100%.

Objective To assess the use of procalcitonin as an early diagnostic tool for bacterial neonatal sepsis.

Methods This diagnostic study was conducted from October 2011 to February 2012. Forty-three neonates in the Perinatology Unit at H. Adam Malik Hospital were suspected to have bacterial sepsis. They underwent routine blood counts, blood cultures, as well as C-reactive protein and procalcitonin measurements. Subjects were collected by consecutive sampling. The gold standard of sepsis was based on any microorganism found in blood culture.

Results Of 43 neonates, 36 neonates had bacterial sepsis. We found that procalcitonin sensitivity was 100%, specificity 85.71%, positive predictive value 97.29% and negative predictive value 100%. The ROC curve showed a cut-off point of 0.929 (95%CI 0.713 to 0.953).

Conclusion Procalcitonin is useful as an early diagnostic tool for bacterial neonatal sepsis. **[Paediatr Indones. 2015;55:268-72]**.

Keywords: *neonatal sepsis, procalcitonin, diagnostic tool*

Neonatal sepsis is an important cause of neonatal morbidity and mortality, particularly in developing countries.[1] Neonatal sepsis is classified into early or late, according to the age at onset of infection during the neonatal period.[2] The clinical relevance of this distinction is that early onset disease is often due to microbial pathogens acquired during delivery, while late onset disease is more frequently caused by microbial pathogens acquired from nosocomial or community sources.[3] The incidence of sepsis in developing countries remains high, 1.8 to 18 per 1000 of live births and with a mortality rate of 12-68%.[4] Septicemia in newborns manifests as several other signs. such as hyperthermia or hypothermia, tachycardia, and tachypnea.[5] Infection may be caused by bacteria, viruses, protozoa, or other microorganisms. Septicemia may lead to organ dysfunction, hypoperfusion, hypotension, hypoxemia, or lactic acidosis. The condition is often

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underdiagnosed, resulting in increased mortality.[3]

Diagnosing neonatal sepsis is difficult because the clinical signs of sepsis often overlap with other non-infectious causes of systemic inflammation.[6] Microbiological cultures can be used to distinguish sepsis from non-infectious conditions, however, the method lacks sensitivity and specificity, and often there is a substantial time delay.[7] Inflammatory markers including C-reactive protein (CRP), interleukins (IL-6 and IL-8), and procalcitonin have been evaluated as markers for neonatal sepsis with varying success. Although these markers may aid diagnosis, no single laboratory test has provided rapid and reliable identification of early infection. The best prediction is obtained using a combination of markers.[8]

Procalcitonin is an acute phase protein which has been reported to be a measureable laboratory marker in inflammatory response that increases during bacterial, fungal, and parasitic infections. In contrast to CRP, localized bacterial infections, severe viral infections and inflammatory reactions of non-infectious origin do not or only slightly change the procalcitonin level.[9] The diagnostic value of procalcitonin is not well-defined, but some studies reported procalcitonin to be more reliable than CRP for the diagnosis of neonatal sepsis.[10-12] The aim of our study was to assess the sensitivity and specificity of procalcitonin as a diagnostic tool for bacterial neonatal sepsis.

Methods

This diagnostic study was conducted to determine the sensitivity and specificity of procalcitonin as an early diagnostic tool for bacterial neonatal sepsis at the Perinatology Unit of Haji Adam Malik Hospital from October 2011 to February 2012. The subjects were suspected to have neonatal bacterial sepsis based on their clinical symptoms and risk factors. They were recruited by consecutive sampling. Blood specimens were taken either before or within 48 hours of antibiotic administration. We excluded neonates with multiple congenital anomalies, anemia or icterus within 24 hours of life. This study was approved by the Research Ethics Committee, North Sumatera University Medical School.

Blood specimens were obtained from 43 newborns (20 females and 23 males) suspected to have septicemia. Blood smears were obtained from the venous blood in tubes without anticoagulant and blood cultures were performed to confirm diagnoses of septicemia. Three mLs of venous blood were taken using a 3 mL syringe, put into transport medium for the *Bactec* culture method in the Clinical Pathology Department of our hospital. Two mLs of venous blood were taken using a 3 mL syringe, centrifuged for 15 minutes, and the serum examined by *Cobas 6000*. The procalcitonin level of ≥ 0.5 ng/mL was considered as abnormal.

All statistical analyses were conducted with *SPSS version 15.0 for Windows*. Sensitivity, specificity, positive predictive value, and negative predictive value of procalcitonin were determined using a 2x2 table with 95% confidence intervals. The cut-off point of the diagnostic test was determined by ROC curve analysis.

Results

Forty-three neonates who were admitted to the Perinatology Unit with suspected neonatal sepsis underwent routine blood examinations, blood cultures, and procalcitonin measurements.

Table 1 shows the subjects' characteristics, such as gestational age, gender, birth weight, and comorbidities. We found 36 infants with sepsis (positive blood cultures), an incidence of 83.72%. More subjects had a gestational age of <37 weeks than ≥37 weeks and more were males (52.7%). The most common concurrent comorbidities in our subjects was respiratory tract infection. No growth was found in 7 out of 43 blood cultures.

Table 2 shows the microorganisms found in blood cultures of the presumed septic newborns. Most microbes were Gram-negative bacteria and *Pseudomonas* (27.9%) was most commonly found.

The sensitivity of procalcitonin was 100%, specificity was 85.71 %, positive predictive value was 97.29 %, and negative predictive value was 100%. The positive likelihood ratio was 6.933 and negative likelihood ratio was 0. The area under the curve in this study was 0.929 (95%CI 0.713 to 0.953; P<0.05). This result shows that procalcitonin had good accuracy as a diagnostic test.

Table 1. Demographic data of subjects

Characteristics	Blood culture results	
	Positive (n=36)	Negative (n=7)
Gestational age, n		
Preterm (< 37 weeks)	22	5
Full term (≥ 37 weeks)	14	2
Gender, n		
Male	19	4
Female	17	3
Birth weight, n		
< 1,000 g	1	0
1,000-1,499 g	5	2
1,500-2,499 g	1	0
≥ 2,500 g	29	5
Comorbidities, n		
Respiratory tract infection	13	0
Neonatal asphyxia	5	0
Very low birth weight (VLBW)	4	2
Transient tachypnea of the newborn (TTN)	4	2
Hypoxic ischemic encephalopathy (HIE)	4	0
Hirschsprung's disease	1	1
Anal atresia	2	0
Abscess	1	0
Meningocele	0	1
ASD secundum	0	1
Hydrocephalus	1	0
Extremely very low birth weight (EVLBW)	1	0

Table 2. Microorganisms found in subjects' blood cultures

Microorganisms	n (%)
Pseudomonas sp	12 (27.9)
Staphylococcus epidermidis	5 (11.6)
Staphylococcus saprophyticus	4 (9.3)
Enterobacter aerogenes	3 (7.0)
Serratia odorifera	2 (4.7)
Streptococcus viridans	2 (4.7)
Klebsiella sp	2 (4.7)
Staphylococcus aureus	2 (4.7)
Streptococcus fecalis	2 (4.7)
Entamoeba coli	1 (2.3)
Providencia reugeri	1 (2.3)
No bacterial growth	7 (16.3)

Table 3. Sensitivity and specificity of procalcitonin

Blood culture results Procalcitonin	Positive	Negative	Total
Positive (≥ 0.5 ng/mL)	36	1	37
Negative (< 0.5 ng/mL)	0	6	6
Total	36	7	43

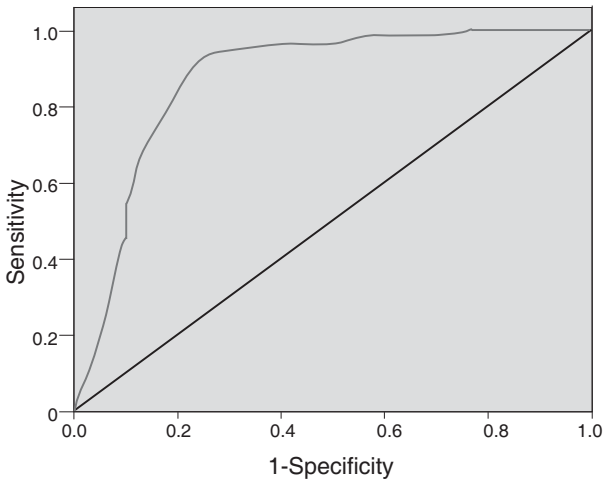

Figure 1. ROC curve of procalcitonin

Discussion

Neonatal sepsis remains a major health problem in developing countries, including Indonesia, and is the major cause of mortality in neonates.[13] Previous studies have shown high procalcitonin levels in neonates with proven or clinically diagnosed neonatal sepsis of various types.[14,15] A Turkish study found that serum procalcitonin levels were superior to serum CRP levels, in terms of early diagnosis of neonatal sepsis, both in detecting the severity of illness and in evaluating the response to antibiotic treatment.[14] In our study, serum procalcitonin levels were high in most patients before the initiation of therapy, but there was not a significant correlation between the serum procalcitonin level and the type of sepsis. We found 36 of 43 neonatal subjects (83.7%) to have bacterial sepsis based on positive blood cultures. Most subjects with bacterial sepsis had gestational ages of < 37 weeks (57%). This observation was consistent with the theory that a risk factor of bacterial sepsis is prematurity, because premature babies have increased predisposition to health problems due to their underdeveloped organs.[16] Such problems may include respiratory distress, intake, risk of bleeding, and infection, making premature infants at higher risk for neonatal sepsis than full term infants.[17]

Other risk factors for sepsis in neonates are low birth weight, respiratory distress syndrome, and a history of aggressive resuscitation. Severe asphyxia predisposes to infection due to cellular hypoxia and inflammation.[16] We found that low birth weight neonates were more likely to have sepsis than those with normal birth weight. More males (52.7%) had sepsis than females in our study. These findings were consistent with a German study.[18]

Respiratory distress was the most common concurrent comorbid in our subjects (36.1%), similar to that of a US study with the most common causes of sepsis reported to be respiratory tract infection (38%), gastrointestinal infection (18%), post-operative infection (9%), meningitis (6%), and urinary tract infection (5%).[19]

Neonatal sepsis is more common in male infants than females because metabolic activity is higher in males than in females. Hence, male infants have a higher oxygen demand.[4] In this study, we found 19 septic male infants compared to 17 female infants. An Italian study reported that the types of bacteria in neonates with sepsis were *Pseudomonas* (33.2%), *Klebsiella* (31.4%), *Acinetobacter* (14.4%), and *S. aureus* (9.2%). We also found that the most common bacteria cultured was *Pseudomonas* (27.9%).[20]

We found that the procalcitonin sensitivity for bacterial sepsis was 100%, specificity 85.71%, positive predictive value 97.29%, and negative predictive value 100%. A US study reported procalcitonin sensitivity of 97% and specificity 80%, using a cut-off value of 0.5 ng/mL.[21] A Spanish study reported that the procalcitonin sensitivity was 92% and specificity 76%, using a cut-off value of 1.1 ng/mL.[22]

To generalize the results for a large population, studies involving neonates in general are needed. Procalcitonin measurements are considered to be sufficiently accurate as a diagnostic test for sepsis in neonates. Parallel tests increase sensitivity, with a negative result revealing an absence of sepsis. Serial testing may be used to increase specificity. There is high probability of having sepsis, if the result was positive.

In conclusion, procalcitonin level is a good measurement to diagnose bacterial sepsis in neonates with sensitivity of 100% and specificity of 85.71%, for a cut-off value of 0.5 ng/ml.

Conflict of interest

None declared.

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