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Original Research Paper

Neonatology

THE ROLE OF D-DIMER LEVELS AS A MARKER OF NEONATAL SEPSIS

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ABSTRACT Sepsis is a major cause of neonatal morbidity and mortality. One complication of sepsis is coagulation dysfunction. Coagulation dysfunction is a complication of neonatal sepsis that can manifest clinically or subclinically in intravascular coagulation. D-dimer, a crosslinked fibrin degradation product, is increased in neonates with sepsis. A diagnostic study with cross-sectional design was conducted in October until December 2018 among 34 neonates with sepsis in the neonatology unit of General Hospital Center Haji Adam Malik Medan. In this study, D-dimer and blood culture were examined. A diagnostic test is to define value of D-dimer sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio. There are 24 subjects with D-dimer levels <0.3 mg%. The sensitivity was 28%, specificity 70%, positive predictive value 40%, negative predictive value 58%, positive likelihood ratio 0.95 and negative likelihood ratio 1.02. D-dimer level is not a useful marker for neonatal sepsis.

KEYWORDS : D-dimer; sepsis; neonatal.

INTRODUCTION

Over the past decade, mortality rate of neonatal sepsis decreased from 87% in 1928 to 3% in 2003. However, sepsis remains a major cause of neonatal morbidity and mortality.[1] There has no the exact data of epidemiology sepsis in Indonesia yet, however the incidence of neonatal sepsis in Cipto Mangunkusumo Hospital (RSCM) in 2009 was 98 per 1000 live births.[2] The incidence of neonatal sepsis at Haji Adam Malik Hospital, Medan in 2015 was 24.6%.[3]

Neonatal sepsis is a result of bacteremia causing some nonspecific systemic signs and symptoms, including temperature instability, respiratory distress, cyanosis, apnea, bradycardia or tachycardia, feeding difficulties, hypotonia, lethargy, irritability, seizures, bulging fontanel, long capillary refill time, paleness, mottled skin, abdominal distention, and jaundice.[4,5] Isolate the pathogen is the gold standard for the diagnosis of sepsis, but it requires a long time to get results.[4]

Coagulation dysfunction is one of the complications of neonatal sepsis that can manifest clinically or subclinically in disseminated intravascular coagulation. In sepsis, bacterial products and cytokines activate coagulation by increasing tissue factors followed by impaired functioning of the anticoagulation mechanism and preventing fibrinolysis. D-dimer one of degradation of crosslinked fibrin is increased in disseminated intravascular coagulation.[6] This process causes an increased intravascular fibrin and the formation of microvascular thrombosis resulting in multiple ischemic organ dysfunction causing necrosis.[7] D-dimer test use monoclonal antibodies (specific antibodies) which is the gold standard to detect fibrin degradation products in plasma or whole blood.[8]

Study in Italy reported an increased D-dimer in neonatal sepsis compared with mild infections.[9] Study in India in 2010 reported that D-dimer had a sensitivity of 90% in patients with positive culture.[7] In preliminary study conducted in intensive care unit and critical unit emergency with the sample of adult patients reporting D-dimer can be used to exclude organ dysfunction.[10]

In Indonesia there have been no studies of D-dimer level as a marker of neonatal sepsis. Therefore, the main objective of this study is to determine the role of D-dimer level as a marker for neonatal sepsis.

METHODS

Study Design

A diagnostic study with cross-sectional design was conducted in October until December 2018 among 34 neonates with sepsis in the neonatology unit of General Hospital Center Haji Adam Malik Medan. The inclusion criteria was neonates with sepsis clinically. Exclusion criteria was neonates with overt bleeding. In this study, D-dimer and blood culture were examined.

All neonates with sepsis clinically were investigated as per the protocol at admission and simultaneously the D-dimer levels were measured. D-dimer levels were evaluated for predicting neonatal sepsis and were compared with blood culture as the gold standard of neonatal sepsis. D-dimer was measured using Coatron kit. Values <0.3 mg% were considered to be normal.

A diagnostic test is to define value of D-dimer sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio. Data analysis were performed using Statistical Package for Social Sciences (SPSS) software version 24. This study was approved by the Health Research Ethical Committee, Medical School, Universitas Sumatera Utara.

RESULTS

This study was conducted in the neonatology unit of General Hospital Haji Adam Malik Medan. Thirty four neonates with sepsis clinically were included in this study. A total of 26 subjects were born at a gestational age of less than 37 weeks. A total of 20 subjects in this study were boys. The average age of the subject is 11.5 days. The average body weight and body length are 2341.1 grams and 45.2 cm. The average head circumference is 33.0 cm. The mean hemoglobin and hematocrit is 13.9 g/dL and 40.7%. The mean leukocyte and platelet was 15210.0/mm^3 and 195994.1/mm^3. A total of 20 subjects were negative blood cultures. D-dimer levels <0.3mg% were 24 subjects (Table 1).

Table 2 showed diagnostic value of D-dimer levels. Based on the table D-dimer levels >0.3mg% were found 4 subjects in the sepsis group with positive blood culture result and 6 subjects in the sepsis group with negative blood culture result. D-dimer has a sensitivity value of 28%, specificity 70%, positive predictive value 40%, negative predictive value 58%, positive likelihood ratio 0.95 and negative likelihood ratio 1.02.

Table 1 Demographic characteristics of subjects

Characteristics	n=34
Gender, n	
Boy	20
Girl	14
Gestational age, n	
≤37 weeks	26
≥37 weeks	8
Age, days, mean, (SD)	11.5 (9.29)
Body weight, gram, mean (SD)	2341.1 (841.18)
Body length, cm, mean (SD)	45.2 (6.01)
Head circumference, cm, mean (SD)	33.0 (2.00)
Hemoglobin, g/dL, mean (SD)	13.9 (2.49)
Hematocrit, %, mean (SD)	40.7 (7.46)
Leucocytes, /mm3 , mean (SD)	15210.0 (7560.17)
Platelets, /mm3 (SD)	195994.1 (131943.00)
Blood culture result, n	
Positive	14
Negative	20
D-dimer, n	
<0.3mg%	24
>0.3mg%	10

Table 2 Diagnostic Value of D-dimer Levels

D-dimer level	Sepsis		Sn (%)	Sp (%)	PPV (%)	NPV (%)	PLR	NLR
	Positive blood result	Negative blood result						
>0.3mg%	4	6	28	70	40	58	0.95	1.02
<0.3mg%	10	14						

Sn: Sensitivity
Sp: Spesifisity
PPV: Positive Predictive Value
NPV: Negative Predictive Value
PLR: Positive Likehood Ratio
NLR: Negative Likehood Ratio

DISCUSSION

In our study, we found male was higher than female in neonatal sepsis. This is in accordance with previous studies in India in 2002 and 2017 which found predominantly boy in the neonatal sepsis.[11,12] Although the exact reason is unclear, why many male neonates are reported, but it is possible because of the factors that regulate Y-globulin synthesis situated on the chromosomes X. Males only have 1 X chromosome so they are less immunologically protected than females.[13]

In our study, the mean body weight was 2341.1 grams. In a study in Jakarta in 2013 reported the average body weight of neonatal sepsis was 1945 gram.[2] A study in Padang in 2016 reported the average neonatal body weight with sepsis <2500 grams. [14] This is possibly due impaired defense mechanism and low immunoglobulin G in neonates with low birth weight.[11,15]

In our study, the mean age of neonates was 11.5 days. This result was not different in Turkey and India in 2015, the mean age of neonatal sepsis was 10.5 days and 5.5 days respectively.[7,16] This result was different from the research in Iran in 2012 which mostly neonatal sepsis age occured at 1-3 days of life.[17] Late onset sepsis is acquired from the environment where the patient is treated. This condition often found in infants who are treated in intensive care for newborns, premature babies who have long stays, a prolonged duration of parenteral nutrition, infections originating from infant care tools, nosocomial infections or cross infections from other babies or medical personnel who treat babies. [18]

In our study, a mean leukocyte value and platelet was 15,780/mm^3 and 17,8810/mm^3 respectively. This is consistent with the results of research in Italy where the mean leucocyte value and platelet was 16543/mm^3 and 211,900/mm^3 respectively.[9]

In our study, the gestational age predominantly was below 37 weeks (premature). The research in Egypt and Iran in 2012 reported similar findings in neonatal sepsis.[5,17] Maternal-foetal transfer of IgG is still low in pematurity babies. Placental transfer of maternal IgG antibodies to the fetus is increased after 31 weeks gestation and a second increased significant occurred at 40 weeks gestation.[19]

In our study we found low D-dimer levels. This is in contrast to study in India reported that D-dimer levels increased in neonates with sepsis,[7] and study in Italy reported that neonatal D-dimer levels also increased.[9] Research in Turkey reported an increased D-dimer levels in neonatal sepsis.[16] The differences between these studies occured because gestational age at recruitment greater than 37 weeks while in our study most of the gestational age was before 37 weeks. In prematurity infants, the fibrinolytic system is still premature, so that a coagulation disorder occurs then the results of fibrinolytic products can be detected normally produced false negative. In term infants after the first 24 hours of life, the fibrinolysis breakdown products are in normal levels, while an increased levels can be caused by the suspicion of coagulation disorders namely diseminated coagulation disorders, deep venous thrombosis, bleeding or sepsis. [20]

The study in Scotland reported that increased levels of D-dimer were measured in blood from preterm and term, but the mechanism of was unclear. In this study transplacental transfer was not the factor that caused increased D-dimer. This was proved by the examination of D-dimer levels in mothers where the D-dimer level is 0.25mg/l. Fibrin degradation products can be found normally in 65% of term infants.[21]

Since sepsis is a systemic inflammatory response to infection, isolation of bacteria from blood is considered the gold standard for the diagnosis of sepsis. [4] Acute inflammation activates the coagulation system causing deposition of intravascular fibrin. Fibrinolysis due to increased plasminogen activator contributes to fibrin formation. Concurrent depression occurs anticoagulation such as Protein C and Protein S.[22]

D-dimers are formed by the breakdown of cross-linked fibrin which specific marker for fibrinolysis. D-dimer levels is increased in sepsis due to fibrinolysis. Activation of coagulation causes platelet depletion and clotting factors which manifest clinical bleeding and micro thrombus formation that cause organ dysfunction.[23] In this study, the majority of the results of blood cultures were no bacterial growth. Study in Egypt in 2015 and in India in 2017 reported no bacterial growth in clinical sepsis neonates. [5,11]Blood culture is the gold standard for the diagnosis of sepsis. However, it takes 24-48 h culture results. Sepsis cannot always be excluded even when blood cultures are found to be negative. Conversely, isolation of bacteria in a blood culture may reflect asymptomatic bacteremia or contamination. Despite no bacterial growth of blood culture, diagnosis of neonatal sepsis can't be excluded.[4] Positive blood cultures was found

only 8-73% in neonatal sepsis.[24]

This study reported that D-dimer levels have a sensitivity of 28% meaning the levels of D-dimer able to identify neonates with sepsis by 28%. Specificity of 70% means that the D-dimer level able to identify neonates without sepsis by 70%. A positive predictive value of 40% indicates that the D-dimer levels can predict neonates with sepsis by 40% and a negative predictive value of 58% indicating that D-dimer levels can predict neonates without sepsis by 58%. A positive likelihood ratio of 0.75 and a negative likelihood ratio of 1.02 means that no possibility of sepsis. Study in India reported D-dimer as a marker of sepsis in neonates with a sensitivity of 90%, specificity 58.3%, positive predictive value 69.4% and negative predictive value 84.4%.[7] The differences between these studies because the recruitment in India study was carried out in all neonates with positive blood culture results, while in this study was carried out in all neonates with clinical sepsis without awaiting for the blood cultures results.

The disadvantage of this study is the limitations of avaibility reagents to culture microorganisms. The advantages of this study was a diagnostic test by assessing sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio. This is the first study to asess the role of D-dimer levels as a marker of neonatal sepsis in Indonesia.

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