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Changes of Biologic Marker in Neonatal Sepsis: Is it significance?

Changes of Biologic Marker in Neonatal Sepsis: Is it significance?

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Abstract. Introduction. Neonatal sepsis is the leading cause of death in newborns. The initial symptoms of sepsis are usually unclear, the clinician often judge these conditions based on risk factor and clinical examination. Blood culture is one of the parameters to be checked but the result takes time. It is also usually come with a positive result of 10 - 60% only. Another biologic marker such as hematologic one is used to evaluate the sepsis because it is considered faster enough. The aim of study is to evaluate the significant changes in biologic marker during neonatal sepsis with positive risk factors. **Methods.** This was a cross sectional study. All <72 hours old's neonates with positive risk factors, neonates who admitted in July to September 2015 in the Neonatal Intensive Care Unit (NICU), and clinically suspected of sepsis were included. Laboratory results of each case were recorded. The eight variables of biologic hematologic parameters of the neonates (hemoglobin, leukocytes, platelet counts, IT (immature to total neutrophil) ratio, IM (immature to mature neutrophil) ratio, polymorphonuclear, immature polymorphonuclear, and hematological scoring (HSS)); one variable of C-reactive protein, and one variable culture result were assessed. Each variable will be compared based on culture result using independent T-test of SPSS. **Results and Discussion.** Thirty-six samples were found which consist of twenty-nine negative and seven positive sample of culture results. All statistical variable's results weren't significant (p >0,05). These results showed there is no significant changes to these variables even if there are any risk factors within the neonates. Higher or lower value of these variable did also not prove whether the culture is positive. **Conclusion.** No significant changes in biologic marker during neonatal sepsis with positive risk factors.
Keywords: hematological parameters, Hematologic Scoring system, neonatal sepsis

1. Introduction

Sepsis is the main cause of death in newborns. In developing countries, the average mortality is between 11-68/1000 births, in Bangladesh an average of 42/1000 live births. Early diagnosis of neonatal sepsis is still very important. The incidence of sepsis in the Pediatric Intensive Care Unit (PICU) is 24%. While a recent French study conducted in 36 NICU PICUs, there was an incidence of sepsis of 3%, with a

mortality rate of 30-60%. Of those with sepsis, approximately 49% suffer from bacteriology consisting of 58% with gram (+), and 42% with gram (-) bacteria. World Health Organization (WHO) estimates that 4 million neonates die each year, of which 35% including caused by neonatal sepsis [1, 2].

Neonatal septicemia is a typical clinical syndrome characterized by an infection accompanied by bacteremia in the first month of life. The initial symptoms of neonatal sepsis are usually not clear. Current diagnosis with microbiological culture also requires a long time, which is 3-14 days, with a positive result of 10-60% even if these microbiological parameters have high specificity [3]. Although diagnosis and therapy continue to develop, this condition remains a cause of high morbidity and mortality. The speed of diagnosis of neonatal sepsis is important because neonates who experience pain progression faster than in adults [1].

Another biologic marker such as hematologic one is used to evaluate the sepsis because it is considered faster enough. According author knowledge, study of hematologic biologic marker still few in Indonesia. The aim of study is to evaluate the significant changes in hematologic biologic marker during neonatal sepsis with positive risk factors. This study may become a grounded theory for future.

2. Material and Methods

This was a cross sectional study. All <72 hours old's neonates with positive risk factors, neonates who admitted in July to September 2015 in the Neonatal Intensive Care Unit (NICU), and clinically suspected of sepsis were included. Independent Variables were eight variables of biologic hematologic parameters of the neonates (hemoglobin, leukocytes, platelet counts, IT (immature to total neutrophil) ratio, IM (immature to mature neutrophil) ratio, polymorphonuclear, immature polymorphonuclear, and hematological scoring (HSS)); one variable of C-reactive protein and Dependent Variables neonates culture result. Inclusion criteria were mothers who have a risk of causing sepsis in infant and aged <72 hours with clinical symptoms of sepsis. Exclusion criteria were neonates aged >72 hours, no symptoms of sepsis. Subjects from affordable populations who met the inclusion and exclusion criteria were taken consecutively.

Two milliliters of neonatal venous blood taken was inserted in a tube of vacutainer anticoagulant EDTA (ethelenediamine tetra-acetic acid) for routine blood tests. Reagents for the automatic hematology analyzer and Cat Wright were provided. Used tool were Automated Hematology Analyzer Scan type BC-5800, micropipette, Object glass, Olympus Microscope

Each variable will be compared based on culture result using independent T-test of statistic software and advanced for logistic regression if the requirement was fulfilled.

3. Results and Discussion

Thirty-six samples were found which consist of twenty-nine negative and seven positive sample of culture results. Table below shown the characteristic and results.

Table 1. Risk Factor description.

No	Risk Factors	Culture Result (n = 36)	
		Negative (n= 29) (80%)	Positive (n= 7) (20%)
1	Mode of Delivery		
	Normal Vaginal	18	4
	Forceps or Vacuum	1	1
	Cesarean	10	2
2	Premature Rupture of the Membrane		
	No	28	7
	Yes	1	0
3	Hypertension in Pregnancy		
	No	27	6

Yes	2	1

Table 2. Statistical Results.

No	Parameter	Culture Result (n = 36)		P
		Positive (n = 7) Median (Min– Max)	Negative (n = 29) Median (Min – Max)	
1	Hemoglobin	16.4 (10.5 – 20.3)	15.9 (11.7 – 20.6)	0.873
2	Leukocytes	15.9 (11.1 – 33.70)	16.7 (8.4 – 261.3)	0.952
3	Platelet	287 (173 – 359)	228 (27 – 554)	0.436
4	IT (immature to total neutrophil) ratio	0.09 (0.04 – 0.24)	0.09 (0.03 – 9.2)	0.936
5	IM (immature to mature neutrophil) ratio	0.09 (0.01 – 0.3)	0.1 (0.01 – 11.5)	0.704
6	Polymorphonuclear,	12.14 (8.77 – 30.67)	12.12 (3.5 – 9724)	0.704
7	Immature polymorphonuclear.	1.02 (0.13 – 7.08)	1.03 (0.09 – 4.25)	0.984
8	Hematological scoring (HSS)	1 (0 – 5)	1 (0 – 6)	0.695
9	C-reactive protein (CRP)			0,645
	Positive	21	5	
	Negative	8	2	

All statistical variable's results weren't significant (p >0,05). These results showed there is no significant changes to these variables even if there are any risk factors within the neonates. Higher or lower value of these variable did also not prove whether the culture is positive. Logistic regression was unable to be done due to lack of requirement of statistical result of bivariate analysis.

Sepsis is a systemic inflammatory system response caused by infection in both the blood and tissue, This response is manifested with two or more of the following symptoms and signs: temperature> 38^0C or <36^0C, tachypnea, tachycardia, <30 torr, leukocytosis (> 12,000/mm3) or or leukopenia (<4,000/mm3) or neutrophil young cell count >10%.[4] Sepsis in children is generally caused by a bacterial infection consisting of 19% nosocomial infection, and bacteriemia in 49% of patients namely gram negative as much as 52% and gram positive 48%. The most common nosocomial infections are due to coagulase-negative staphylococcus, staphylococcus aureus and enterococcus [5]. This study found 36 samples consist of: 29 negative (80%) and 7 positive (20%) culture result with gram positive 2 (28.5%) and gram neg 5 (71.5%)

There are several risk factors that can increase the incidence of sepsis in children are: 1) Host factors, which consist of: malnutrition, immunodeficiency, chronic disease problems, trauma/burns, serious and critical illness. 2). Treatment factors: surgery, invasive procedures, invasive monitoring devices, antibiotics, immunosuppressive therapy, length of treatment and hospital environment. Sepsis alone was distinguished as early sepsis and advanced sepsis where in the early sepsis the mortality rate reached 5-50% [6].

In every infection, both primary and secondary due to nosocomial, the body will hold an acute phase immunological reaction that makes and releases various mediators that can cause changes in the blood. GCSF (Granulocyte Colony Stimulating Factor) mainly plays a role in increasing granulocyte production, especially neutrophils, increasing and releasing leukocytes, especially neutrophils in the bone marrow [7]. Other study said the number of leukocytes less than 5000/ul or more than 25,000/ul can predict neonatal sepsis but the value of the positive predictions of the abnormal leukocyte count is low. The total number of neutrophils is more sensitive than the total number of leukocytes in diagnosing neonatal sepsis [6]. The degree of neutropenia for prediction of neonatal sepsis is according to age, ie total neutrophils are less than 1800/ul at birth, 8100/ul at 12 hours, 7000/ul when 24 hours and less than

1800/ul after 72 hours [2]. The presence of neutropenia is a better indicator of neonatal sepsis than neutrophilia [2, 11]. The total number of immature neutrophils is more than 1100/ul, 1400/ul and 800/ul respectively when born, age 12 hours and above 60 hours is considered abnormal [2].

From the neutrophil index, the ratio of total immature/neutrophil neutrophils (I/T) is the single most sensitive and specific indicator for neonatal sepsis, with a sensitivity value of more than 96% and a specificity of more than 71% [2, 8, 12].

Thrombocytopenia occurs in 10-60% of cases of neonatal sepsis. Because it is not specific and the thrombocytopenia is slow, this value is not used alone especially for the diagnosis of early onset.[4,6]

Monroe et al provide criteria for neonatal sepsis, namely if found 2 or more of the following, the ratio of immature/neutrophil total neutrophils (I/T) >0.16, absolute neutrophil counts <7500/ul or >14,000/ul, number immature neutrophils >1400/mm [13].

In addition, complement that is activated both classically and alternatively can improve the phagocytic process seen in blood smear as vacuolization. Twelve subjects (33%) in this study with peripheral blood morphology obtained vacuolization neutrophil, normo-blast 3 subjects (8.3%) and 1 subject with toxic granulation (2.8%). TNF mediators produced by lymphocytes and monocytes that are activated due to infection will inhibit the neutrophil maturation process so that more neutrophil young cells form rods in the circulation. Activating Hageman factors due to endotoxin or due to vascular endothelial damage can eventually lead to DIC and thrombocytopenia. Infection can also cause red blood cell hemolysis which ultimately can cause anemia. Other mediators such as IL6 can cause hepatocytes to secrete acute phase reactants, namely CRP [7].

By looking at changes in blood, namely leukocyte shape changes, especially neutrophils (vacuolization, hyper granulation), leukocytosis or leukopenia, increasing I/T ratio > 0.2, increasing I/M ratio, immature neutrophils, red blood cell hemolysis process characterized by the presence of nucleated erythrocytes, thrombocytopenia which can all be calculated by scoring, better known as the Hematologic Score System, can detect suspicion of sepsis. Rodwell provides the hematological score for neonatal sepsis (HSS) as follows: The hematological scoring system according to Rodwell (Table 3) establishes a score of 1 for each significant hematologic finding, but there are exceptions to the number of PMNs, if no PMN is found in a portion of peripheral blood then the score is two [12].

Table 3. Hematological Scoring System [6, 12].

Criteria	Abnormality	Score
Total WBC	≤5.000/ul	1
	≥25.000 at birth	1
	≥30.000-12-24 h	
	≥21.000-Day 2 on ward	
Total PMN Count	No mature PMN seen	2
	Increased/decresed	1
Immature PMN Count	Increased	1
I/T PMN Ratio	Increased	1
Degenerative change in PMN	Toxic granules/cytoplasmic vacuoles	1
Platelet count	≤150,000/ul	1

Table 4. Interpretation of Hematological Scoring System [6, 12].

Score	Interpretation
≤ 2	Sepsis is unlikely
3 or 4	Sepsis is possible
≥ 5	Sepsis or infection is very likely

From the study of 287 neonates with hematological scores, it has 96% sensitivity, 78% specificity, positive predictive value 31% and negative predictive value 99% [14]. Other author reassessed this score with a larger number of samples reaching 1000 neonates with sensitivity 93%, specificity 82%, positive predictive value of 50% and negative predictive value of 98% [15]. If the score is only 0-2 then chances are not 99% sepsis [11]. Philip detected slow onset neonatal sepsis with the following 5 parameters, leukocyte count <5000 / ul, neutrophil ratio I / T 30.2, LED 315mm / hour, CRP (+), Haptoglobulin (+). The diagnosis of sepsis is made when two or more positive test results are found. With this approach the sensitivity is 88%, specificity is 80%, while if all five of these tests are negative (99%) is considered not sepsis [6, 16, 17]. Blood culture is the gold standard in neonatal sepsis, but in the literature, it is mentioned that patients with sepsis only 10-60% give a positive result, with a specificity of 100% [8, 9].

Complete blood count with type count is a very easy and fast laboratory examination for neonatal sepsis. The Manroe criteria state that if there are 2 abnormal values from 3 parameters (total neutrophils, immature granulocytes and I / T ratio) then the baby can be sepsis. C-reactive protein (CRP) is another parameter. CRP has several weaknesses, including liver maturity in infants hasn't mature; and the examination should be done serially, because the process of formation of CRP increases after 4-6 hours, 2x in 8 hours, peak 36 hours - 50 hours, half-life of 4 - 7 hours. While the strength of CRP are good for acute processes, relatively inexpensive, easy, can be obtained in a fast time, and does not require a lot of volume. Both combination of other rapid examination results such as CRP and LED, the accuracy of this blood eradication examination will also be increased, and there is no need to wait for the results of the culture long enough for the diagnosis of sepsis [7, 8, 10].

This study shown this parameter couldn't use as screening and diagnoses. There is no single parameter to diagnose neonatal sepsis, several and combined parameter (including clinical condition) need to assess. A new parameter is needed to develop for faster diagnosis of Neonatal Sepsis. Limitation of study was bigger sample size is needed to comprehend different result.

4. Conclusion

No significant changes in biologic marker during neonatal sepsis with positive risk factors.

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