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Resistive Index Value of Superior Mesenteric Artery In Preterm Infants With Necrotizing Enterocolitis

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ABSTRACT

Aims: *to find out the comparison of RI values of superior mesenteric artery in premature infants with NEC and without NEC.*

Material and methods: *This study was an observational analytic study, with a case-control study design, where the sampling method was using consecutive sampling in the NICU Room, Anturium and Radiology Department Dr. Hasan Sadikin General Hospital Bandung from September to October 2019. Data processing uses unpaired T-test.*

Results: *The total sample was 22 subjects, consisting of 11 with positive NEC and 11 negative NEC, with an average gestational age of 31.36 weeks and an average birth weight of 1490.45 grams. In the positive NEC group, the average RI value was 0.90 and in the negative NEC group, the average RI value was 0.70. Statistical test results with unpaired T-test showed that there was a statistically significant increase in the value of superior mesenteric artery RI in premature infants with NEC compared to premature infants without NEC with a p-value = 0.0001 (p-value < 0.05).*

Conclusion: *There was an increase in the value of superior mesenteric artery RI in premature infants with NEC compared to premature infants without NEC with a value of p = 0.0001 (p-value <0.05).*

Key words: Necrotizing Enterocolitis–Superior Mesenteric Artery–Ultrasonography

1 INTRODUCTION

Necrotizing enterocolitis (NEC) is a life-threatening neonatal gastrointestinal condition characterized by inflammation, ischemia and bacterial translocation to the gastrointestinal wall [1] . The most common NEC (85% of cases) occurs in premature infants weighing less than 2500 grams and gestational age less than 37 weeks. Clinical presentations often begin to appear on days 3 to 5 of life, with bloody diarrhea (25%) or flatulence, can be signs of sepsis, and vomiting, apnea, or lethargy. The occurrence of NEC is associated with hypoxia, stress, low blood pressure, and infection [2] .

The incidence of NEC is estimated to reach 1% - 8% of all neonates treated in the neonatal intensive care unit (NICU) [3] . The secondary death rate to NEC is around 20% - 30%, making it one of the leading causes of death in premature neonates. Although the exact etiology of NEC is unknown, the researchers concluded the cause was multifactorial. Prematurity (with an imperfect gastrointestinal tract) is a major risk factor; ischemia and/or reperfusion injury, exacerbated by the activation of the proinflammatory intracellular cascade, can play an important role. Neonatal sepsis is considered a risk factor for NEC [4] .

The diagnosis of NEC is based on clinical criteria and radiographic findings. An abdominal x-ray remains the standard imaging modality for diagnosing NEC. The role of ultrasonography is increasing in the diagnosis and follow-up of NEC. With advances in ultrasonography technology, color doppler ultrasonography can assess blood flow from the superior mesenteric artery [5] . The superior mesenteric artery is the second main branch of the abdominal aorta and its origin is just below the celiac truncus in the ventral wall of the aorta. The superior mesenteric artery is a blood vessel that supplies small and large intestinal bleeding [6] . Color

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Doppler ultrasound assessment includes peak systolic flow velocity (PSV), end-diastolic flow velocity (EDV), pulsatility index (PI) and resistive index (RI) [7] . RI is a measure of pulsatile blood flow that reflects resistance to blood flow caused by microvascular located distal from the measurement location [8] . Toll-like receptors 4 (TLR4) are more expressed in the premature digestive tract than are full-term in mice, humans and other species. Activation of TLR4 in the lining of the premature digestive tract by gram-negative bacteria that form bacterial colonization causes several adverse effects, including increased enterocyte apoptosis, impaired mucosal healing and increased release of proinflammatory cytokines, which leads to the development of NEC. Then translocation of gram-negative bacteria through the gastrointestinal mucosa activates TLR4 in the endothelium lining of the mesentery of the digestive tract prematurely, causing a decrease in blood flow and the occurrence of ischemia and necrosis of the digestive tract [9] . Gastrointestinal ischemia is one of the risk factors for NEC in premature infant . The occurrence of ischemia in the gastrointestinal tract causes a decrease in gastrointestinal surface perfusion, with a decrease in gastrointestinal surface perfusion there will be an increase in resistance of the arteries that supply the digestive tract, namely the superior mesenteric artery [3, 10, 11] . Increased superior mesenteric artery resistance can be assessed by color Doppler ultrasonography by calculating RI values. The results of Urboniene et al (2015) RI values $>$ 0.75 have a sensitivity of 96.3% and a specificity of 90.9% in predicting the occurrence of NEC. Color doppler ultrasound assessment on the first day of the life of a premature infants can be a useful non-invasive procedure for predicting premature neonates at high risk for NEC [3] .

Murdoch et al. (2006) explain that neonates with increased mesenteric arterial resistance using color doppler ultrasonography will increase the risk of NEC. These results are in accordance with a research by Khodair et al (2014) and Urboniene et al (2015) [3, 5, 12] .

The purpose of this study was to compare the superior mesenteric artery resistive index (RI) value in premature infants with necrotizing enterocolitis (NEC) and without necrotizing enterocolitis (NEC) at the Dr. Hasan Sadikin General Hospital Bandung.

2 MATERIAL AND METHODS

This study was an observational analytic study with a case-control study design conducted from September to October 2019 in the NICU Room of Dr. Hasan Sadikin General Hospital Bandung with ethical license number LB.02.01/X.6.5/261/2019. Inclusion criteria were premature infants (gestational age $<$37 weeks) and birth weight $<$2500 grams with a diagnosis of NEC and without NEC. Patients with a diagnosis of NEC were included in the NEC group and patients without NEC were included in the control group. Data on the characteristics of the study subjects were obtained from the patient's medical records. The research subjects were selected by consecutive admission, in the order in which patients arrived. To determine the stage of the NEC used the Bell's modification criteria scoring system [13] .

The superior mesenteric artery RI was calculated using Philips Affiniti 50G with a micro-convex C8-5 probe frequency of 8-5 Mhz and GE Logiq S7 Expert with a linear probe L3 - 12 frequencies 3-12 Mhz. The patient is examined in the supine position. RI is calculated using the Pourcelot formula [14] .

Significance test to compare the characteristics of the two research groups used unpaired T-test. Whereas statistical analysis for categorical data was tested with the Chi-Square test. The significance criteria used are the value of p if p$\leq$0.05 is statistically significant, and p$>$ 0.05 is not statistically significant. The data obtained are recorded in a special form and then processed through the SPSS program version 24.0 for Windows.

3 RESULTS

This study was conducted on 22 premature infants from September to October 2019. The overall subject characteristics of the patients were based on gestational age (weeks), sex, birth weight (grams), superior mesenteric artery RI values, and necrotizing enterocolitis grade (Table 1). The mean gestational age was 31.36 $\pm$ 2.854 weeks. For the male infants 11 or 50.0% and girls 11 or 50.0%. The mean birth weight was 1490.45 $\pm$ 436.154 grams. The average superior mesenteric artery RI value is 0.80 $\pm$ 0.114 with the category of superior mesenteric artery RI value increasing 16 or 72.7% and normal 6 or 27.3%. For negative necrotizing enterocolitis as much as 11 or 50.0%, grade I necrotizing enterocolitis as much as 9 or 40.9% and grade II necrotizing enterocolitis as much as 2 or 9.1%.

In the positive NEC group, the average gestational age was 31.72 $\pm$ 2.493 weeks. For the sex of male babies 6 or 54.5% and girls 5 or 45.5%. The average birth weight is 1445.00 $\pm$ 361.333 grams. For grade I NEC 9 or 81.8% and NEC grade II 2 or 18.2%. The NEC group was negative, for the average gestational age was 31.00 $\pm$ 3.255 weeks. For the sex of male babies are 5 or 45.5% and girls 6 or 54.5%. The average birth weight is 1535.90 $\pm$ 514,173 grams. For negative NEC 11 or 100.0%, grade I NEC 0 or 0.0% and grade II NEC 0 or 0.0% (Table 2).

This numerical data analysis was tested using the unpaired T-test. Statistical test results in the above study group obtained information on the value of p on the variable gestational age and birth weight greater than 0.05 (p value$>$ 0.05), which means not statistically significant, thus it can be explained that there are no mean differences which were statistically significant between the variable gestational age and birth weight in the positive NEC and negative NEC groups.

Analysis of categorical data was tested using the Chi-Square test, namely gender and Kolmogorov Smirnov test, namely the NEC variable. Statistical test results in the

Table 1. Clinical characteristics

Variabel	N=22
Gestational age (weeks)	
Mean±Std	31,36 ± 2,854
Median	31,50
Range (min-max)	27,00 – 36,00
Sex	
Male	11 (50,0%)
Female	11 (50,0%)
Birth weight (gram)	
Mean±Std	1490,45 ± 436,154
Median	1470,00
Range (min-max)	850,00 – 2300,00
RI value	
Mean±Std	0,80 ± 0,114
Median	0,81
Range (min-max)	0,60 – 0,96
RI value category	
Increase (>0,75)	16 (72,7%)
Normal (<0,75)	6 (27,3%)
Necrotizing enterocolitis	
Negative	11 (50,0%)
NEC grade I	9 (40,9%)
NEC grade II	2 (9,1%)

Table 2. Comparison NEC positive and NEC negative characteristics

Variable	NEC Positive N=11	Negative N=11	value
Gestational age (weeks)			0,563
Mean±Std	31,72 ± 2,493	31,00 ± 3,255	
Median	32,00	30,00	
Range (min-max)	28,00 – 36,00	27,00 – 36,00	
Sex			0,670
Male	6 (54,5%)	5 (45,5%)	
Female	5 (45,5%)	6 (54,5%)	
Birth weight (gram)			0,563
Mean±Std	1445,00 ± 361,337	1535,90 ± 514,173	
Median	1500,00	1345,00	
Range (min-max)	850,00 – 2100,00	900,00 – 2300,00	
Necrotizing enterocolitis			0,000**
Negative	0 (0,0%)	11 (100,0%)	
NEC grade I	9 (81,8%)	0 (0,0%)	
NEC grade II	2 (18,2%)	0 (0,0%)	

above research group obtained information on the value of p, p on gender variables greater than 0.05 (p value> 0.05) which means not statistically significant so that it can be explained that there is no significant difference in percentage statistics between sex variables in the positive NEC and Negative NEC groups. While the p-value of the NEC variable is smaller than 0.05 (p-value <0.05) which means that it is statistically significant, so it can be explained that there is a statistically significant percentage difference between necrotizing enterocolitis variables in the positive NEC and negative NEC groups.

In the positive NEC group, for the average RI superior mesenteric artery value was 0.90 ± 0.047. In the negative NEC group, the mean RI superior mesenteric artery value was 0.70 ± 0.072. For the analysis of numerical data this is tested using the unpaired T test. Statistical test results in the above study group obtained information on the value of p on the RI superior mesenteric artery value is smaller than 0.05 (p value <0.05), which means statistically significant, so it can be explained that there are significant differences between the superior mesenteric artery RI values in the positive and negative NEC groups (Table 3).

Table 3. Comparison of RI Values on Positive and Negative NEC

Variable	NEC Positive N=11	Negative N=11	value
RI value			0,0001**
Mean±Std	0,90 ± 0,047	0,70 ± 0,072	
Median	0,91	0,75	
Range (min-max)	0,82 – 0,96	0,60 – 0,80	

4 DISCUSSION

Necrotizing enterocolitis (NEC) is a life-threatening neonatal gastrointestinal condition characterized by inflammation, ischemia and bacterial translocation to the gastrointestinal wall [1]. According to the literature, NEC usually occurs (85% of cases) in preterm infants born less than 37 weeks with birth weights less than 2500 grams, this is in accordance with the results of the study in table 2 can be seen the birth weight of babies with an average NEC of 1445 grams (range between 850-2100 gram) and the average gestational age is 31 weeks (range between 28-36 weeks) [2]. The results of this study are not much different from those of Urboniene et al [3]. An important consideration in the diagnosis of NEC is the gestational age at the onset of clinical symptoms, because there is an inverse relationship between gestational age with the onset of clinical symptoms and the severity of clinical symptoms in patients with NEC. In particular, infants born at 27 weeks gestational age usually have NEC clinical symptoms appear at 4-5 weeks of age and have a much higher risk of developing NEC than infants born at near 37 weeks of gestation, whose onset is usually the first 2 weeks after birth. To understand the reasons why premature infants are at very high risk of NEC compared to term infants, researchers have focused their efforts on understanding the differences between the digestive tracts of premature infants and term infants. These studies have described important differences in bacterial colonization, circulatory micro-perfusion and the maturity of the gastrointestinal immune system [15, 16] .

Toll-like receptors 4 (TLR4) are more expressed in the premature digestive tract than are full-term in mice, humans and other species. Activation of TLR4 in the lining

of the premature digestive tract by gram-negative bacteria that form bacterial colonization causes several adverse effects, including increased enterocyte apoptosis, impaired mucosal healing and increased release of proinflammatory cytokines, which leads to the development of NEC. Then translocation of gram-negative bacteria through the gastrointestinal mucosa activates TLR4 in the endothelium lining of the mesentery of the digestive tract prematurely, causing a decrease in blood flow and the occurrence of ischemia and necrosis of the digestive tract [9, 10] . Gastrointestinal ischemia is one of the risk factors for NEC in premature infants. The occurrence of ischemia in the gastrointestinal tract causes a decrease in gastrointestinal surface perfusion, with a decrease in gastrointestinal surface perfusion there will be an increase in resistance of the arteries that supply the digestive tract, namely the superior mesenteric artery. The RI value is a measure of pulsatile blood flow that reflects resistance to blood flow caused by microvascular located distal from the measurement location [3, 11] . The results in table 3 show that the mean value of the RI superior mesenteric artery in the positive NEC group is higher than the mean value of the RI superior mesenteric artery in negative NEC groups, statistically, this mean difference is significant. These results are in accordance with the studies of Murdoch et al, Khodair et al and Urboniene et al who concluded that there was a significant increase in the RI value of the superior mesenteric artery in preterm infants than in preterm infants without NEC [3, 5, 12] .

5 CONCLUSION

There is an increase in the superior mesenteric arterial resistive index (RI) value of premature infants with NEC compared to premature infants without NEC at Dr. Hasan Sadikin General Hospital Bandung.

This study limitation was a case-control study where only comparing RI values of the superior mesenteric artery in premature infants with NEC and without NEC, so it cannot determine whether RI values of the superior mesenteric artery can be used as parameters to find out the earlier occurrence of NEC.

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Compliance with ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Conflict of interest: Harry Galuh Nugraha, Edwam Akbar, and Atta Kuntara declare that they have no conflict of interest.

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