

Relationship Between Heparanase Levels and Hematological Parameters in Dengue Infection Patients

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Abstract

Background: Dengue infection caused by dengue virus and transmitted through the bite of *Aedes aegypti* mosquito causes thrombocytopenia due to bone marrow suppression. Increased Platelet Distribution Width (PDW) and Mean Platelet Volume (MPV) values are associated with platelet activation, destruction, and consumption. Hematocrit levels increase due to hemoconcentration that occurs together with plasma leakage, which is common in dengue infection. Leukopenia occurs due to bone marrow suppression, either directly by the virus or indirectly through the production of proinflammatory cytokines.

Objective: Analyzing the relationship between heparanase and hematological parameters in dengue infection patients

Method: Observational analytical study with cross-sectional approach and consecutive sampling data collection in 100 patients. Heparanase levels were examined using enzyme link immunoassay (ELISA), platelet counts, PDW values and MPV values were examined using the impedance method. Hematocrit levels and leukocyte counts were examined using the lowcytometry method. Statistical analysis used the Spearman correlation test ($p < 0.005$).

Results: Heparanase levels were negatively associated with platelet count ($r = -0.405$, $p = 0.001$), and positively with PDW ($r = 0.250$, $p = 0.012$), MPV ($r = 0.247$, $p = 0.013$), and hematocrit ($r = 0.269$, $p = 0.003$). However, there was no significant association with leukocyte count ($r = -0.077$, $p = 0.448$).

Conclusion: There is a weak positive relationship between heparanase levels and PDW values, MPV values and hematocrit levels. There was a weak negative relationship between heparanase levels and platelet counts and there was no significant relationship between heparanase levels and leukocyte counts.

Keywords: Dengue Infection, Heparanase, Platelets, Hematocrit, and Leukocytes

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INTRODUCTION

Dengue infection is a disease caused by the dengue virus through the bite of the aedes mosquito, especially aedes aegypti. Dengue infection is a mosquito-borne disease, which is growing the fastest in the world. Tropical and subtropical countries are at high risk of transmission of the virus. This is associated with high temperature increases and changes in the rainy and dry seasons are suspected to be risk factors for dengue virus transmission¹. Dengue infection can affect all age groups, from infants to the elderly. The majority of cases are reported to occur in children under the age of 15 years with a proportion of 86 to 95%. The morbidity and mortality rates in children tend to increase, so more attention needs to be paid to clinical symptoms and laboratory test results.²

Based on Ministry Health of Republic Indonesia (Kemenkes) data, there were 1,236 cases of death due to dengue fever (DBD) in Indonesia in 2022. This number has jumped by 75.32% compared to the previous year which had 705 deaths. If the number of DBD sufferers is 143,184 people, it can be seen that the death rate (case fatality rate) due to the disease in the country is 0.86% in 2022.³ As many as 63% of deaths are dominated by children aged 0-14 years. In 2023, the number of dengue cases in Indonesia reached 31,380 cases with 246 of them declared dead.⁴ Data from the World Health Organization (WHO) in the last two years has seen an eightfold increase in dengue cases in 2000-2022. Dengue cases increased from 500 thousand cases to 4.2 million.⁵

DHF caused by one of dengue virus (DENV 1-4). The four serotypes of dengue virus belong to the genus flavivirus with the family flaviviridae.^{6,7} Infection with the DENV virus can cause several pathological conditions, ranging from mild and asymptomatic dengue fever, dengue fever with flu, to DHF and dengue shock syndrome (DSS) which can be fatal.^{8,9}

Plasma leakage is one of the signs of DHF that plays a role in the process of dengue shock. Plasma leakage can occur during the fever phase, generally for three days, then the patient will enter the critical phase. Plasma leakage is influenced by disruption of microvascular endothelial permeability so that albumin moves from within the plasma to the extravascular space.¹⁰

Heparanase (HPSE) is a β -D-endoglucuronidase that degrades Heparan sulfate (HS), both in the extracellular space and inside the cell. Heparan sulfate is

an important component in the extracellular matrix (ECM) and on the surface of the vascular endothelium, functioning to maintain the stability of the matrix structure as a place for cell adhesion to the basement membrane. Heparanase as an enzyme has the ability to trigger different signaling pathways by interacting with transmembrane proteins. In normal and physiological conditions, heparanase shows low expression levels limited to keratinocytes, trophoblasts, platelets, mast cells and leukocytes. On the other hand, in pathological conditions, such as tumor development and metastasis, inflammation and fibrosis, heparanase is overexpressed.^{3,4}

Hematology parameter examination is an examination that is often performed as a diagnostic support and to monitor the condition of DHF patients. Some of the important ones are hematology parameters, namely platelet count, PDW value, MPV value, hematocrit level and leukocyte count. Dengue infection patients can experience a decrease in platelet count. Thrombocytopenia in dengue infection occurs through bone marrow suppression mechanisms and destruction and shortening of platelet lifespan.¹¹

In the early phase of infection, the bone marrow picture shows a hypocellular state and megakaryocyte suppression, which is characterized by a decrease in the number of hematopoietic cells and an increase in the hematopoiesis process, including megakaryopoiesis, although thrombocytopenia occurs, thrombopoietin levels in the blood actually increase, this indicates stimulation of thrombopoiesis as a compensatory mechanism for the body to overcome the decrease in platelet count.¹³ Platelet destruction occurs through binding of C3g fragments, the presence of anti-NS1 antibodies to dengue virus, platelet consumption during the coagulopathy process and sequestration in the periphery. Platelet function disorders occur through the mechanism of impaired ADP release, increased levels of b-thromboglobulin and platelet factor4 (PF4) which are markers of platelet degranulation.^{6,11}

Platelets has an important role in maintaining the integrity of the vascular endothelium, the release of heparanase in pathological conditions can increase plasma leakage. This mechanism contributes to the relationship between platelet activation, plasma leakage and increased heparanase activity in dengue infection and can affect PDW and MPV values, which often show reversed changes along with decreasing platelet counts, reflecting an imbalance in the hemostasis process.^{7,13}

There are parameters in the form of platelet indexes that can be known using an automatic hematology analyzer, namely Platelet distribution width (PDW) and Mean platelet volume (MPV).^{3,10} Platelet distribution width (PDW) examination measures the variation in the size of platelet circulating in peripheral blood. High PDW values can be found in sickle cell disease and thrombocytosis, while low PDW percentages can indicate platelet that have small sizes and have a reference value of 8.3-56.6%.^{4,11}

Platelet distribution width (PDW) is also called the platelet density index describes platelet degranulation. Platelet degranulation occurs due to increased platelet activation. The higher the platelet activation, the lower the PDW value. PDW describes the variation of the platelet density index.¹⁴

Mean platelet volume (MPV) examination is a marker of platelet function and is related to thrombopoiesis activity. Mean platelet volume is one of the inexpensive parameters and is widely performed in laboratories and hospitals. This parameter assesses the average size of platelet diameter circulating in peripheral blood and can assess thrombopoiesis activity.^{15,16} Pathogenesis of dengue infection is related to platelet destruction in the periphery by anti-platelet antibodies and direct suppression of the bone marrow resulting in thrombocytopenia.^{14,15} MPV value can describe the level of platelet activation in the periphery and the bone marrow response as a response to thrombocytopenia that occurs during the course of dengue infection with a reference value of MPV of 7.5-11.5 fl.

Another important parameter in cases of dengue infection is the hematocrit level to determine the total volume of erythrocytes in 100 cells/L of blood and is expressed in%. An increase in hematocrit values describes a state of hemoconcentration and is found in patients with dengue infection.¹⁷ This shows that examination of hematocrit values is one indicator of plasma leakage, so it is necessary to conduct hematocrit examinations periodically.¹⁷ Generally, a decrease in platelets precedes an increase in hematocrit. Hemoconcentration with an increase in hematocrit $\geq 20\%$ reflects increased capillary permeability and plasma leakage. Hematocrit values are affected by fluid replacement or bleeding. Reference value for normal hematocrit values according to Dacie for adult men is 40 - 54% and for adult women is 37 - 54%.¹⁸

Parameter of the number of leukocytes is also an important parameter in cases of dengue infection. Several studies have shown that leukopenia occurs in

dengue infection.¹⁹ Research by Marissa et al. (2020) stated that there was a decrease in the number of leukocytes on days 1-3 of fever. Leucopenia peaks before the fever subsides and returns to normal on the 5th day after the fever subsides. The occurrence of leukopenia in dengue virus infection is caused by bone marrow suppression due to direct viral infection or due to an indirect mechanism through the production of pro-inflammatory cytokines that suppress the bone marrow.²⁰

RESEARCH METHODS

This research is an observational analytical study with a cross-sectional approach and consecutive sampling data collection. The research sample was patients infected with dengue (IgM and/or IgG positive) who were hospitalized at Diponegoro National Hospital, Semarang, and met the inclusion and exclusion criteria of the study.

DATA ANALYSIS TECHNIQUES

The data obtained were edited, coded, and entered into computer files. After clearing, the data were analyzed statistically with the help of the SPSS program. Descriptive analysis displays the mean value and standard deviation of the data normality test variables carried out with Kolmogorov-Smirnov test before hypothesis testing. Non-normal data distribution will be transformed. Correlation test using Pearson correlation test on normal distribution data, Spearman correlation test on non-normal distribution data. Significance value in research with analysis results $p < 0.05$.

RESULT

Total 112 dengue fever patients were included in the study. A total of 12 patients were excluded because there were 5 patients with typhoid fever, and 7 patients received thrombocyte concentrate (TC) transfusion. A total of 100 patients who met the inclusion and exclusion criteria were followed in the study consisting of 44 males (44.0%) and 56 females (56.0%). The distribution of subject characteristics is presented in Table 1. A total of 93 (93.0%) with positive dengue IgM, 85 (85.0%) with positive dengue IgG and 78 (78.0%) with positive dengue IgM and IgG

Correlation test analysis showed that there was a significant relationship between hematology levels and platelet counts, PDW values, MPV values and

hematocrit values. However, there was no significant relationship between heparanase levels and leukocyte counts. Spearman rank test between heparanase levels and platelet counts showed weak negative correlation between heparanase levels and platelet counts ($r = -0.405, p = 0.001$).

Correlation test between heparanase levels and PDW values show that there was a weak positive correlation between heparanase levels and PDW values ($r = 0.250, p = 0.012$). There was a weak positive relationship between heparanase levels and MPV values ($r = 0.247, p = 0.013$). Positive correlation was found between heparanase levels and hematocrit levels ($r = 0.269, p = 0.003$). Correlation test showed that there was no significant relationship between heparanase levels and leukocyte counts ($r = -0.077, p = 0.448$).

Table 1. Characteristic Subject of Research

Variable (n = 100)	Frequency (%)	Mean ± SD	Median (min – max)
Gender			
Male	44 (44%)		
Female	56 (56%)		
IgG			
Positive	85 (85%)		
Negative	15 (15%)		
IgM			
Positive	93 (93%)		
Negative	7 (7%)		
Age (years)			20 (1 – 57)
Hb (g/dL)		13,38 ± 1,88	
Leukocyte (x10 ³ /μL)			4,26 (1,23 – 16,10)
Tromocyte (x10 ³ /μL)			87,00 (11,00 – 388,00)
Eritrocyte (x10 ⁶ /μL)			4,80 (3,20 – 6,40)
Hematocyte (%)		37,59 ± 4,87	
MCV (fL)			77,35 (60,50 – 94,30)
MCH (pg)			28,10 (0,40 – 33,20)
MCHC (g/dL)			35,70 (32,10 – 44,60)
PDW (%)		12,70 ± 2,34	
MPV (fL)		10,96 ± 1,07	
RDW-CV (%)			13,00 (10,90 – 140,00)
Heparanase (ng/mL)			0,58 (0,05 – 9,61)

Table 2. Correlation Test Variable

Hematology Parameter	Heparanase	
	<i>p</i>	<i>r</i>
Trombocyte (x10 ³ /μL)	0.001*	-0.405
Plateletes Distribution Width (%)	0.012*	0.250
Mean Plateletes Volume (fL)	0.013*	0.247
Hematocryte (%)	0.003*	0.269
Leukocyte (x10 ³ /μL)	0.448	-0.077

*Significant

DISCUSSION

This study involved 100 subjects with 44 males (44.0%) and 56 females (56.0%). The mean heparanase level in this study was 2.40 ± 2.76 ng/mL with a median of 0.58 (0.05 – 9.61) ng/mL. The mean platelet count in this study was $91.44 \pm 62.71 \times 10^3 /\mu\text{L}$ with a median of 87.00 (11.00 – 388.00) $\times 10^3 /\mu\text{L}$. High PDW value in this study illustrates the variation in platelet size and may be caused by increased activity and platelet consumption in patients with dengue infection. This study obtained a PDW value of $12.70 \pm 2.34\%$ with a median of 12.50 (8.00– 18.10) %. Dengue infection conditions increase excessive platelet use or function with increased MPV values associated with increased megakaryocyte activity that increases platelet cell production and increases the release of young platelets with larger sizes. This study obtained an MPV value of 10.96 ± 1.07 fL with a median of 11.00 (7.40–13.20) fL. Increased hematocrit levels illustrate hemoconcentration always found in dengue infection, is a sensitive indicator of plasma leakage, so it is necessary to check hematocrit regularly.

A decrease in platelets precedes an increase in hematocrit levels. This study obtained hematocrit levels of $37.59 \pm 4.87\%$ with a median of 37.50 (24.00–50.00)%. The occurrence of leukopenia in dengue virus infection is caused by bone marrow suppression due to direct viral infection or due to indirect mechanisms through the production of proinflammatory cytokines that suppress the bone marrow. In this study, the number of leukocytes was 4.98 ± 2.76 with a median of 4.26 (1.23 – 16.10).

Relationship between heparanase levels and platelet count

Heparanase is secreted by various cells including circulating blood cells such as leukocytes and platelets. Platelets are known to play a critical role in maintaining vascular integrity during dengue and modulate leukocyte diapedesis through heparanase secretion. DENV NS1 has been shown to initiate inflammatory responses via TLR4 on monocytes and platelets, and also induces the release of cathepsin L, which is essential for the formation of active heparanase. Although plateletson the one hand can maintain endothelial integrity, the release of heparanase from platelets in pathological conditions can increase plasma leakage. This may contribute to the relationship between platelet

activation, plasma leakage and increased heparanase activity in dengue fever.²¹⁻²³

Relationship between heparanase levels and PDW and MPV values

Increased larger young platelet from the bone marrow into the blood circulation, thus increasing platelet size variation with platelet morphology such as spherical and pseudopodia. Another pathophysiological mechanism that may cause higher platelet size variability is hypercoagulability. During the thrombosis process, there will be increased destruction and consumption of platelets, resulting in a decrease in the number of platelets, due to the presence of release of heparanase from platelets in pathological conditions that increase plasma leakage.^{24,25}

Relationship between heparanase levels and hematocrit levels

Damage to the endothelial layer of glycocalyx can disrupt microvascular flow and proteoglycans are considered the most important structure because they are the largest components of glycocalyx. Glycocalyx consists of long glycosaminoglycan chains in the plasma membrane. Pathological conditions (such as tumor development, metastasis, inflammation and liver fibrosis) heparanase is overexpressed and there is a disturbance in the intensity of the extracellular matrix can increase the occurrence of endothelial leakage.

Increased heparanase activity correlates with endothelial dysfunction markers heparan sulfate and syndecan-1, as well as clinical markers of plasma leakage, platelet count levels are inversely correlated with heparanase activity in dengue infection, so that hematocrit levels will increase (hemoconcentration) due to increased blood cell levels or decreased blood plasma volume.

Relationship between heparanase levels and leukocyte count

Heparanase on the vascular endothelium binds chemokines and thereby facilitates their oligomerization and presentation to circulating leukocytes, prevents them from being carried away by the bloodstream, and forms a chemokine gradient necessary for leukocyte migration. Endothelial heparanase can also directly regulate leukocytes by acting as a ligand for leukocyte L-selectin, or by masking other adhesion molecules on the vascular endothelium to make them accessible to leukocyte integrins. Heparanase is present on both endothelial cells and leukocytes. L-selectin is constitutively expressed

by neurophils and monocytes, whereas endothelial cells upregulate P-selectin upon activation.^{26,27}

Heparanase is an enzyme that plays a role in the breakdown of heparan sulfate, one of the important components of the extracellular matrix and proteoglycans found on the cell surface and in the intercellular space, heparanase is involved in biological processes such as cell movement, cell migration, inflammation, and angiogenesis, this enzyme is especially active in cells involved in inflammatory reactions and other pathological processes. Heparanase contributes to the reorganization of the Extracellular Matrix (ECM) and glycocalyx resulting in increased vascular permeability and leukocyte extravasation and releasing heparanase-bound cytokines and growth factors that are usually sequestered in the ECM, thus promoting angiogenesis and inflammation in the surrounding area, especially in promoting metastasis through enzymatic degradation of the extracellular matrix.^{28,29}

CONCLUSION

Significant correlation was found between heparanase levels with Plateletes Count, PDW, MPV and hematocrite in dengue infection patients. Leukocyte is the only one variable that have not significantly correlated with Heparanase levels.

Ethics Statement and Conflict of Interest Disclosures
Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

This study was approved by the Institutional Research Board and Ethics Committee.

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