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Coagulation Defects in Beta-Thalassemia Major Patients at Haji Adam Malik Hospital Medan

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ABSTRACT

Background: The prognosis of patients with beta-thalassemia major has improved in the last few decades, but some complications occur in thalassemia patients such as the prolongation of blood coagulation time. This study aimed to determine the difference in prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT) between beta-thalassemia major patients and healthy children, frequent and infrequent transfusion, and ferritin levels ≥ 2,500 ng/ml and < 2,500 ng/ml.

Method: This was an analytical cross-sectional study performed at Haji Adam Malik Hospital from April to August 2018 including 20 thalassemia patients and 20 healthy children. Patient data consisted of full blood count, transfusion status, coagulation parameters, serum iron, and ferritin level. The difference between coagulation parameters was analyzed using the independent t test.

Result: There was a significant difference in PT and aPTT between patients with thalassemia and healthy children (15.7 ± 1.5 vs. 13.0 ± 1.0; 42.5 ± 4.8 vs. 36.3 ± 4.8 respectively). There was a significant difference in PT between frequent and infrequent transfusion (15.41 ± 1.30 vs. 17.16 ± 2.08). There was significant difference in PT and aPTT between ferritin levels ≥ 2,500 ng/ml and < 2,500 ng/ml (18.97 ± 0.57 vs 15.93 ± 1.18; 52.92 ± 1.17 vs 42.11 ± 3.88 respectively).

Conclusion: There was a prolongation of PT and aPTT in beta-thalassemia major patients and ferritin levels ≥ 2,500 ng/ml. There was also an elongation of PT in patients who had infrequent transfusions.

Keywords: beta thalassemia, blood coagulation, partial thromboplastin time, prothrombin time, thalassemia major.

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INTRODUCTION

Thalassemia is an autosomal recessive inherited blood disorder, found in many Southeast Asia countries.[1] Thalassemia is a major problem in countries around the Mediterranean Sea, Middle East, India, Pakistan, Southeast Asia, Southern Russia, and China. The frequency of alpha (α) carriers of thalassemia extends from Africa to the Mediterranean, Middle East, East and Southeast Asia, whereas the highest beta (β) thalassemia carriers were reported in the Maldives (18%), Cyprus (14%), Sardinia (10.3%) and Southeast Asia (3-5%).[2]

Beta-thalassemia major shows a clear clinical condition, which is severe anemia due to ineffective erythropoiesis. This clear clinical picture causes major thalassemia patients to be examined immediately into health services and quickly diagnosed.[2] Manifestations that appear in childhood can be severe anemia, jaundice, stunted growth, decreased activity, and frequent sleep. Hepatosplenomegaly with the initial sign of the thalassemic face is usually found.[3] With the severity of anemia symptoms that arise, patients with beta-thalassemia major depend on blood transfusions as a major part of its treatment to improve their quality of life and prolong the survival, so that it is classified into the Transfusion-Dependent Thalassemia (TDT) group.[4]

The prognosis of children with beta-thalassemia has improved in recent decades. This is due to advances in medicine in the provision of transfusions, iron chelation therapy, and bone marrow transplants.[5] Morbidity due to iron deposits are liver disorders, hemorrhage, disorders of the hormonal gland, especially the gonadal, thyroid, parathyroid, and pancreatic glands, resulting in symptoms such as stunted physical growth, the absence of secondary sex signs, infertility, diabetes mellitus, and porous bones.[6]

Several studies in the literature mention the occurrence of hypercoagulability and hemorrhage in patients with beta-thalassemia major. The incidence of thromboembolic events in beta-thalassemia major varied between 0.9 – 4.0% in several studies. However, several studies also reported the occurrence of hemorrhage tendencies in beta-thalassemia major.[7] Prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT), reduced levels of coagulation factors such as protein C, protein S, and Anti-thrombin III (AT III) occur in patients with beta-thalassemia major. The mechanism of the occurrence of thrombosis has been widely investigated, but the mechanism of the tendency for hemorrhage to occur is still not fully explained.[8]

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A study in India in 2006 reported the presence of thrombocytopenia, prolongation of PT and aPTT of 40.7% and 46.3% in patients with beta-thalassemia major.[9] This study aimed to determine the difference in PT, aPTT, and thrombin time (TT) between beta-thalassemia major patients and healthy children, frequent and infrequent transfusion, and ferritin levels ≥ 2,500 ng/ml and < 2,500 ng/ml.

MATERIALS AND METHODS

This study was an analytical cross-sectional study carried out in the Clinical Pathology Department of the Faculty of Medicine, University of Sumatera Utara/Haji Adam Malik General Hospital in Medan in collaboration with the Pediatrics Department of the Faculty of Medicine, University of Sumatera Utara/Haji Adam Malik General Hospital in Medan. The study was conducted from April 2018 to August 2018, including 20 people with beta-thalassemia major and 20 normal controls.

The inclusion criteria in this study were: (1) children under 18 years old;[10] (2) had been diagnosed as beta-thalassemia major based on the Thalassemia International Federation criteria in 2014;[4] (3) have undergone regular blood transfusions for at least 1 year; and (4) patients were willing to participate in the study by signing an informed consent. The exclusion criteria in this study were individuals who had liver enzyme increase of more than five times the normal value and individuals who take aspirin or drugs that affect hemostasis.

Blood sampling was done without excessive static. A total of 5 ml of venous blood was taken and divided into two tubes - each 2 ml EDTA vacutainer, and 3 ml citrate vacutainer. Blood with EDTA anticoagulant was examined for FBC using a hematology analyzer to obtain Hemoglobin, MCV, MCH, RDW and platelet counts using Sysmex XN-1000i. Blood with citric anticoagulant was centrifuged at a speed of 3,500 rpm for 15 minutes and examined with Coatron A4 to obtain the values of PT, aPTT, and TT. For demographic data, univariate analysis was carried out so that the distribution of sample characteristics was obtained. Bivariate analysis was used to determine the difference in PT, aPTT, and TT in children with beta-thalassemia compared to healthy controls, frequent and infrequent blood transfusions, and also in beta-thalassemia children who had ferritin values above 2,500 ng/ml and below 2,500 ng/ml. The statistical test used was the independent t test. The analysis was carried out at 95% confidence intervals with a p-value of < 0.05 considered as significant.

RESULTS

The study involved 20 patients with beta-thalassemia major and 20 normal control people. In the patient group, there were 11 males (55%) and nine females (45%). The average age of patients was

Table 1 General characteristics of samples

Characteristics	Units	Patients (N = 20)	Controls (N = 20)
Gender, n (%)			
Male		11 (55.0%)	7 (17.5%)
Female		9 (45.0%)	13 (32.5%)
Age, mean ± SD Transfusion frequency	Years	8.55 ± 4.63	8.17 ± 4.26
Infrequent		4 (20.0%)	-
Frequent		16 (80.0%)	-
Splenectomy			
Non-splenectomy		18 (90%)	-
Post-splenectomy		2 (10%)	-
Erythrocyte index			
Hemoglobin, mean ± SD	g/dL	7.02 ± 1.77	13.0 ± 1.87
MCV, mean ± SD		726 ± 6.31	77.9 ± 4.75
MCH, mean ± SD	fl	23.8 ± 2.67	25.5 ± 1.62
RDW, mean ± SD	%	24.0 ± 6.79	13.6 ± 1.08
Thrombocyte, mean ± SD	10^3/µL	279.75 ± 146.2	323.10 ± 91.8
Iron			
Iron serum, mean ± SD	µg/dL	156.95 ± 54.2	
Feritin, mean ± SD	ng/mL	1,986.5 ± 1,147.5	

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Table 2 **Difference of PT, aPTT, and TT between patients with β thalassemia major and controls.**

Variables	Case (n = 20)	Control (n = 20)	*P-value*
PT	15.7 ± 1.5	13.0 ± 1.0	0.001
APTT	42.5 ± 4.8	36.3 ± 4.8	0.001
TT	14.1 ± 2.1	14.7 ± 1.5	0.273

Table 3 **Difference of PT, aPTT, and TT in β thalassemia major patients between frequent and infrequent transfusion**

Variables	Frequent (n = 16)	Infrequent (n = 4)	*P-value*
PT	15.41 ± 1.30	17.16 ± 2.08	0.04
APTT	42.11 ± 4.39	44.22 ± 6.75	0.44
TT	14.58 ± 2.04	12.35 ± 1.64	0.059

Table 4 **Difference of PT, aPTT, and TT in β thalassemia major patients between ferritin level ≥ 2,500 ng/ml and < 2,500 ng/ml**

Variables	< 2,500 ng/ml (n = 16)	≥ 2,500 ng/ml (n = 4)	*P-value*
PT	15.93 ± 1.18	18.97 ± 0.57	0.001
APTT	42.11 ± 3.88	52.92 ± 1.17	0.001
TT	13.87 ± 1.85	15.17 ± 3.13	0.288

8.55 ± 4.63 years. Complete general characteristics of samples can be seen in Table 1.

In the coagulation parameters, it was seen that PT and aPTT in the patient group were more elongated than the control group (15.7 ± 1.5 vs. 13.0 ± 1.0; 42.5 ± 4.8 vs. 36.3 ± 4.8). As shown in Table 2, there were significant differences in PT and aPTT between thalassemia and non-thalassemia (p = 0.001). In TT, there was no statistically significant difference between thalassemia and non-thalassemia (p = 0.273).

From Table 3, it can be seen that there was a significant difference in PT between frequent and infrequent blood transfusions (p = 0.04), whereas in aPTT and TT, there were no significant differences between them (p > 0.05).

An analysis was performed to see the differences in PT, aPTT, and TT between ferritin levels ≥ 2,500 ng/ml and < 2,500 ng/ml. As shown in Table 4, there were significant differences in PT and aPTT between the two groups (p = 0.001). However, in TT, the difference was not statistically significant (p = 0.288).

DISCUSSION

The study was conducted from April to August 2018. Characteristics of the study were age, gender, the frequency of transfusion, splenectomy, erythrocyte index, coagulation factors, serum iron, and ferritin levels. From the results of the study, it was found that the average age of patients with thalassemia was 8.55 ± 4.63 years. The number of males and females in the patient group was 11 people (55%) and nine people (45%) respectively.

From the erythrocyte index, the average hemoglobin level of thalassemia patients was lower than controls, which was 7.02 g/dL and 12.3 g/dL respectively. Low MCV and MCH levels were also found in the patient group, which were 72.6 ± 6.31 and 23.8 ± 2.67 respectively. Decreased hemoglobin levels and globin chain imbalances lead to a decrease in MCV and MCH.[11] Platelets in the patient group were lower compared to the control group, which was 279.75 ± 146.2 vs. 323.10 ± 91.8 µL. The result of this study is almost the same compared to other studies; Naithani et al.[9] found that the number of patients experiencing thrombocytopenia was 33.3%, while Ibrahim et al.[12] found 30.7%. In this study, six people experienced thrombocytopenia (30%).

In this study, there is a prolongation of coagulation factors, which are PT and aPTT. The mean value of PT was 15.76 ± 1.59 vs. 13.09 ± 1.06 with a significant difference between the patient and control group (p = 0.001). The mean value of aPTT was 42.54 ± 4.81 vs 36.3 ± 4.82 with p = 0.001 (p<0.05). This is similar to a study by Faraj that stated extension of PT and aPTT were 54% and 56% respectively. In the study, the elongation of PT levels was present in 10% of patients, and the prolongation of aPTT was present in 45% of patients.[8]

APTT is an indicator of intrinsic track and joint lane activity, and PT indicates extrinsic lane activity (network factors) and shared lanes. The prolongation of PT and aPTT in patients with thalassemia who routinely receive blood transfusions can be caused by liver damage due to iron overload and/or circulating hemolysis.[12,13] Multiple transfusions play a role in the activation of the intrinsic coagulation pathway and intravascular hemolysis. There is a relationship between transfusion, hemolysis, and hypercoagulation status.[13] Iron overload causes activation of tissue-released kallikrein like proteases.[14,15] The study by Maiti et al.[16] found that aPTT was more disturbed compared to PT in younger patients with thalassemia. The intrinsic pathways that were more affected by repeated transfusions and hemolysis are also found in studies by Caocci and Rabiner.[13,14]

In this study, it was found that the mean serum iron level in the patient group was 156.95 ± 54.2 µg/dL and the mean ferritin level was 1986.5 ± 1147.5 ng/mL. Ferritin level above normal indicates that most groups of patients have iron overload. This is

similar to the results of other studies, where poor control and compliance with iron chelation therapy resulted in iron overload and high ferritin levels so that the coagulation process was impaired.[8]

Similar results were also found in the study by Naithani et al., where the elongation of PT and APTT correlated with serum ferritin levels ($p = 0.004$ and $p = 0.05$).[9] Research conducted by Oliviery and colleagues found that beta-thalassemia patients with serum ferritin level ≥ 2,500 ng/ml will be at risk of having heart disease. The study also explained that it is good for patients with beta-thalassemia is to regulate ferritin levels < 2,500 ng/ml, which can be helped by consuming chelation drugs so that patients can survive with a lower risk of heart disease.[17]

In this study, examination of coagulation parameters can be used as a regular screening stage in patients with thalassemia.

CONCLUSION

There was an elongation of PT and APTT in beta-thalassemia major patients and ferritin levels ≥ 2,500 ng/ml. There was also an elongation of PT in patients who had infrequent transfusions.

ETHICAL CLEARANCE

Ethical clearance was obtained from the Health Research Ethics Committee of the Faculty of Medicine, University of Sumatera Utara/ H.Adam Malik General Hospital (No. 553/TGL/KEPK FUSU-RSUP HAM/2018).

CONFLICT OF INTEREST

No conflict of interest to disclose.

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AUTHOR'S CONTRIBUTION

Eduward Situmorang was the owner of the idea, wrote the manuscript, revised the final manuscript, and did the laboratory test. Eduward Situmorang, Adi Koesoema Aman and Bidasari Lubis joined together to establish the study design, collected the clinical and laboratory data, analyzed and interpreted all of the results. Adi Koesoema Aman with Bidasari Lubis was in charge of the sampling process.

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