International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

The Correlation of PAI-1 level with Regular Blood Transfusion in Children with Thalasemia Beta Mayor at H. Adam Malik Hospital, Medan

Sutiansi[1], Bidasari Lubis[2], Adi Koesoema Aman[3]

[1, 3]Department of Clinical Pathology, Faculty of Medicine, University of North Sumatera / RSUP H. Adam Malik Medan

[2] Department of Pediatric, Faculty of Medicine, University of North Sumatera / RSUP H. Adam Malik Medan

[1]*tiansie84[at]gmail.com*, 08159008253

Abstract: ***Background: Beta Thalassemia is a congenital hemoglobin disorder due to a genetic mutation that causes decreases or absent of beta globin chain synthesis. Patients with thalassemia need regular blood transfusions and iron chelating agent throughout their lives. Plasminogen Activator Inhibitor-1 (PAI-1) is a serine protease inhibitor that serves as the primary inhibitor of tissue Plasminogen Activator (tPA) and urokinase Plasminogen Activator (uPA). Increased PAI-1 is a risk factor for thrombosis and atherosclerosis. Methods: This research is an observational study with cross sectional data collection method. This study took blood samples of 32 pediatric patients with beta thalassemia mayor who regularly transfused at the HAM Hospital. PAI-1 is only checked once before the patient has a blood transfusion. The research was conducted after obtaining ethical approval and informed consent. Result and Discussion: 19 boys (64.7%) and 12 girls (35.3%) with the youngest age 1 year and oldest 18 years old. Using spearman correlation tests showed that there is a significant correlation between the length of transfusion with PAI-1 (p = 0.001) with correlation value (r) 0.546. Using spearman correlation tests it was also found that there was a significant correlation between total transfusions with PAI-1 (p = 0.004) with correlation value (r) obtained was 0.500. These findings indicate that the longer the child's subject transfused, it will be followed by increasing levels of PAI-1. Conclusion and Suggestion: PAI-1 levels increase along with the increasing blood transfusions frequency in pediatric patients with Thalassemia. More research is needed to determine the pathogenesis of thrombosis and aterosclerosis in pediatric patients with thalassemia beta major who regularly blood transfusions.***

Keywords: Beta Thalassemia Major, Regular Blood Transfusion, PAI-1

1. Introduction

Thalassemia β is a congenital hemoglobin disorder due to a genetic mutation that causes a decrease or absence of the synthesis of β globin chains. Thalassemia β major is the heaviest form of thalassemia β that causes severe anemia with ineffective hemolysis and erythropoiesis with clinical symptoms appearing between 6 months to 2 years. Patients with thalassemia β major need regular blood transfusions and iron flatfoot therapy throughout his life. As a result of repeated transfusions in thalassemia β major patients, chronic iron disorders occur so that they are more susceptible to impaired procoagulant status which in turn causes thrombotic events clinically.[1, 2]

Plasminogen Activator Inhibitor-1 (PAI-1) is a serine protease inhibitor (serpin) also known as an endothelial plasminogen activator inhibitor functioning as the main inhibitor of tissue plasminogen activator (tPA) and urokinaseplasminogen activator (uPA). Increased PAI-1 is a risk factor for thrombosis and atherosclerosis.3

2. Aims

This study aims to determine the relationship between PAI-1 levels and the frequency of blood transfusions in pediatric patients with Thalassemia Beta Major at RSUP. H. Adam Malik, Medan. So we know the average level of PAI-1 in pediatric patients with Thalassemia Beta Major.

3. Methods

This research is an observational study with a cross-sectional data collection method. The research was conducted at the Department of Clinical Pathology, Faculty of Medicine USU (FK USU) / RSUP H. Adam Malik Medan in collaboration with the Department of Pediatrics, Faculty of Medicine (FK USU) / RSUP H. Adam Malik Medan, from December 2020 to February 2021. The subject of the study was a pediatric patient with beta major thalassemia which was established based on the criteria of the Thalassemia International Federation who regularly transfusions blood at the Thalassemia Polyclinic of RSUP H. Adam Malik Medan, and had met the inclusion criteria.

The size of the samples in this study was determined as many as 32 samples. The inclusion criteria in this study were pediatric patients diagnosed as beta thalassemia major who received repeated blood transfusions. The PAI-1 examination was carried out at the Department of Clinical Pathology of FK USU / RSUP H. Adam Malik Medan using aChemwell automatic analyzer with the ELISA method.

Data analysis was performed using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) software for Windows. A characteristic picture on the subject of study is presented in the form of a tabulation and is described. The relationship between PAI-1 levels with duration, frequency and total transfusions and total using the Spearman correlation test. All statistical tests with a p-value < 0.05 are considered meaningful.

4. Results

This study was attended by 32 pediatric patients with Thalassemia beta major who regularly transfused blood at the thalassemia polyclinic of RSUP H. Adam Malik Medan from March 2021-May 2021 who had met the inclusion criteria. The characteristics of the subjects of the study are presented in table 1. Male subjects were 19 people (59.4%) with an average age of 10.47 years with the youngest age of 1 year and the oldest age of 18 years. The results of height and weight measurements respectively showed an average of 126.19 cm and 28.41 kg.

Table 1: Characteristics of Research Subjects

Characteristics of Research Subjects	n = 32
Gender, n (%)	
Male	19 (59, 4)
Female	13 (40, 6)
Age, years	
Average (SD)	10, 47 (5, 06)
Median (Min-Max)	10 (1-18)
Body Height, cm	
Average (SD)	126, 19 (23, 64)
Median (Min-Max)	122 (75-163)
Body Weight, kg	
Average (SD)	28, 41 (13, 81)
Median (Min-Max)	25 (10-56)

The results of the PAI-1 level examination are shown in table 2. The average PAI-1 level is 1.29 pg/mL (SD = 1.25 pg/mL) with the lowest level of 0.12 pg/mL and the highest level of 5.47 pg/mL.

Table 2: PAI-1 levels

Tranfussion Characteristics and PAI-1 Level	n = 32
PAI 1, pg/mL	
Average (SD)	1, 29 (1, 25)
Median (Min-Max)	0, 81 (0, 12-5, 47)

Table 3: Relatioship of Transfusion with PAI-1 Levels

	PAI-1	
	p*	r
Duration of Transfusion	0, 001	0, 546
Frequency of Transfusion	0, 544	-0, 111
Total Transfusion	0, 004	0, 500

The results of the analysis using the Spearman correlation test showed that there was a significant correlation between the duration of the transfusion and the PAI level-1 (p = 0.001). The correlation value (r) obtained is 0.546 meaning that there is a positive and moderate-strength correlation between the duration of the transfusion and pai-1 levels in children with beta major thalassemia who regularly undergo blood transfusions. Using the Spearman correlation test, no significant correlation was found between transfusion frequency and PAI levels-1 (p = 0.544). Using the Spearman correlation test, a significant correlation was also found between total transfusions and PAI levels-1 (p = 0.004) with a correlation value (r) obtained was 0.546 meaning that there was a positive and moderate-strength correlation between total transfusions and PAI-1 levels in children with beta major thalassemia who regularly underwent blood transfusions.

5. Discussion

The number of patients sampled in this study was 32 patients consisting of 19 people (59.4%) men and 13 people (40.6%) women. This is in line with research conducted by Hassan, et al (2010) where it was found that men (54.6 %) suffer more from thalassemia than women (45.4 %).[4]

The youngest age of beta thalassemia sufferers in this study was 1 year old with the oldest age of 18 years. This is in line with research conducted by Mettananda, et al (2020) which conducted a control case study on 288 patients with beta thalassemia from September 2017 to March 2018. The results of their study found the youngest sufferer age 4 years and the oldest age 18 years.[5]

Age greatly affects the need for transfusion blood in people with thalassemia. Every time you increase the age of 1 year, the need for blood will increase by about 0.816 milliliters. As we get older, the frequency of blood transfusions received every month also increases because as you get older, the disease condition worsens so that the need for blood transfusions increases. The need for blood required at each subsequent transfusion also increases. The amount of blood that is administered each transfusion increases with increasing age and with the growth of the child. If the patient has a large spleen, the destruction of blood is faster so they need more blood. However, if the spleen is already removed, their blood needs are slightly reduced.[6]
From this study, the average PAI-1 level was 1.29 pg per mL with the lowest level of 0.12 pg per mL and the highest level of 5.47 pg per mL. Results In line with research conducted by Kumar et al, 2016. They conducted a study of 30 thalassemia major patients aged 12-20 years who routinely received transfusions and 30 healthy individuals as controls. Then each major beta thalassemia patient is subjected to PAI-1 examination. The results of their study showed the average level of PAI 1 in the control population was 3047 ± 414 pg / ml, the value in cases of thalassemia major was 3683 ± 358 pg / ml. Its level increases significantly ($p<0.05$) in cases, compared to controls. High levels of PAI-1 compared to the number of blood transfusions, indicate that the average level of PAI-1 correlates with the number of blood transfusions as well as the frequency of transfusions.[7, 8]

Using the Spearman correlation test, it was shown that there was a significant correlation between the duration of the transfusion and the PAI-1 level (p=0.001) and the correlation value (r) obtained was 0.546, meaning that there was a positive and moderate-strength correlation between the duration of the transfusion and the PAI-1 level in children with Beta Major thalassemia who had regular blood transfusions. This is in line with a study conducted by Angchaisuksiri et al., in 2007 where the increase in PAI-1 or t-PA antigen was a result of a decrease in fibrinolytic activity.[7]

Then, using the Spearman correlation test, it also showed that there was a significant correlation between the total transfusions and the PAI-1 level (p = 0.004) and the correlation value (r) obtained was 0.500, meaning that there was a positive and moderate strength correlation between

total transfusions and PAI-1 levels in children with Beta Major thalassemia who regularly transfused blood. This is in line with a study conducted by Kumar et al., in 2016 where there was an increase in PAI-1 along with frequent blood transfusions in patients with Thalassemia Beta Major who received blood transfusions and had received iron chelation therapy.[8]

Thalassemia patients who get regular blood transfusions have a tendency to experience procoagulant status responsible for the incidence of thrombosis later in life. In line with the research conducted by Silitonga, et al. (2019), the process of changing the inhibition of natural coagulation and fibrinolysis that occurs will be a risk of thromboembolic events in patients with Thalassemia Beta Major even though clinical signs and symptoms have not yet appeared.[8, 9]

In thalassemia major patients who routinely receive transfusions, there will be an increase in PAI levels-1. Elevated levels of PAI-1 in these patients are responsible for an increased risk of thrombosis. There is evidence that in thalassemia patients there is a decrease in coagulation factors and an increase in platelet activation, in addition there is an increase in inflammatory conditions, the presence of endothelial cell injuries, impaired fibrinolysis and a decrease in natural anticoagulants in beta thalassemia. These changes may explain the increased risk of thrombosis in thalassemia major patients who routinely get blood transfusions.[10]
Study conducted by Chuncharunee et al, (2019). They performed autopsies on thalassemia major patients who died, where during their lifetime they routinely received transfusions, they found that there was thrombosis in small blood vessels, especially in the lungs and brain.[10]

6. Conclusion

The incidence of beta major thalassemia by sex is more in males than females. There was a significant correlation between the duration of transfusion and total transfusion with PAI-1 levels in pediatric patients with beta thalassemia major who were regular transfusions.

References

[1] Langhi D, Ubuaki EMA, Marques JFC, Verissimo MA, Loggetto SR, Silvinato A, et al.2016. *Guidelines on Beta-thalassemia major-regular blood transfusion therapy*. [Online]. Available at scielo. br/j/rbhh/a/jwrnQTxMrmJJ9JKTRbQ8GLh, doi: 10.1016/j. bjhh.2016.09.003. Revista Bras HematolHemoter.

[2] Cappelini MD, Farmakis D, Porter J &Taher A.2021. *Guidelines for the management of transfusion dependent thalasemia (TDT)*. Nicosia: Thalassaemia International Federaton Publication.

[3] Kumar A, Batra HS, Banerjee M, Bandyopadhyay S, Saha TK, Misra P, et al.2017. *PAI-1 Study in Thalassemia Major Patients Receiving Multiple Blood Transfusion*. [Online]. Available at springer. com/article/10.1007/s12291-016-0620-7, doi: 10.1007/s12291-016-0620-7. Indian Journal of Clinical Biochemistry.

[4] Hassan SM, Hamza N, Al-Lawatiya FJ, Mohammed AJ, Harteveld CL, Rajab A, et al.2010. *Extended Molecular Spectrum of Beta and Alpha Thalassemia in Oman*. [Online]. Available at tandfonline. com/doi/abs/10.3109/03630261003673147, doi: 10.3109/03630261003673147. International journal for hemoglobin research.

[5] Mettananda S, Pathiraja H, Peiris R, Wickramarathne N, Bandara D, Silva U, et al.2019. *Blood transfusion therapy for Beta thalassemia major and hemogloblin E beta thalasemia: adequacy, trends and determination in Sri Lanka*. [Online]. Available at onlinelibrary. wiley. com/doi/10.1002/pbc.27643, doi: 10.1002/pbc.27643. Pediatric Blood and Cancer.

[6] Apidechkul T, Yeemard F, Chomchoei C, Upala P &Tamornpark R.2021. *Epidemiology of* thalassemia among the hill tribe population in Thailand. [Online]. Available at https: //journals. plos. org/plosone/article?id=10.1371/journal. pone.0246736, doi: 10.1371/journal. pone.0246736. Plos One.

[7] Angchaisuksiri P, Atichartakaran V, Aryurachai K, Archararit N, Chuncharunee S &Tiraganjana A.2007. *Haemostatic and thrombotic markers in patients of hemoglobin E*/thalassemia disease. [Online]. Available at wiley. com/doi/abs/10.1002/ajh.20945, doi: 10.1002/ajh.20945. American Journal of Hematology.

[8] Kumar A, Saha D, Kini J, Murali N, Chakraborti S & Adiga D.2016. *The role of discriminant functions in screening beta thalassemia trait and iron deficiency anemia among laboratory samples*. [Online]. Available at thieme-connect. com/products/ejournals/abstract/10.4103/0974-2727.208256, doi: 10.4103/0974-2727.208256. Journal of Laboratory Physicians.

[9] Silitonga JT, Aman AK &Lubis B.2019. *The hypercoagulation state among major beta thalassemia patients at H Adam Malik Hospital, Medan*. [Online]. Available at balimedicaljournal. org/index. php/bmj/article/view/1400, doi: 10.15562/bmj. v8i2.1400. Bali Medical Journal.

[10] Atichartakarn V, Chuncharunee S, Archararit N, Udimsubpayakul U, &Aryurachai K.2014. *Intravascular Hemolysis, Vascular Endothelial Cell Activation and Thrombophilia in Splenectomized Patients with Hemoglobin E/Beta Thalassemia Disease*. [Online]. Available at karger. com/Article/Full-text/355719, doi: 10.1159/000355719. ActaHaematologica.