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ORIGINAL RESEARCH

Achievement of Pre- and Post-Transfusion Hemoglobin Levels in Adult Transfusion-Dependent Beta Thalassemia: Associated Factors and Relationship to Reduction of Spleen Enlargement

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Introduction: The achievement of blood transfusion hemoglobin targets in transfusion-dependent beta-thalassemia patients is influenced by several factors such as genotype, hypersplenism, blood compatibility, donor blood adequacy, and transfusion interval. Failure to achieve these targets leads to an increase in the size of the spleen. Meanwhile, the post-transfusion hemoglobin of thalassemia patients that is not regularly evaluated has made it difficult to determine donor adequacy. Therefore, this study aims to determine the proportion of patients who achieve optimal pre- and post-transfusion hemoglobin levels, determine the factors involved, and the relationship between achieving hemoglobin levels with spleen enlargement in adult transfusion-dependent beta-thalassemia patients.

Methods: This retrospective cohort study was conducted using total sampling of adult thalassemia transfusion-dependent patients at Cipto Mangunkusumo Hospital. Data were obtained through medical records.

Results: A hundred and ten study subjects fulfilled inclusion criteria. The results showed that the blood transfusion deficit <30 mL/kg/year was associated with achieving pre- and post-transfusion hemoglobin targets ($p = 0.008$). Furthermore, there were significant differences between the groups that achieved the pre- and post-transfusion target hemoglobin levels on the reduction of spleen enlargement in centimeters ($p < 0.001$). However, thalassemia genotype, blood compatibility, and transfusion interval did not correlate with the achievement of pre- and post-transfusion hemoglobin.

Conclusion: The achievement of pre- and post-transfusion hemoglobin levels in adult transfusion-dependent beta-thalassemia patients significantly reduced spleen enlargement and contributed to better patient outcomes.

Keywords: transfusion-dependent beta-thalassemia, target hemoglobin level, risk factors, spleen enlargement

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Introduction

Transfusion-dependent thalassemia (TdT) is comprised of beta-major thalassemia and severe beta-HbE (β/HbE) thalassemia, which occurs majorly in the Southeast Asian region.[1] In Indonesia, thalassemia is among the 5 catastrophic diseases namely kidney failure, cancer, heart disease, and hemophilia, with approximately 8000 patients which cost nearly US$ 30,000/person/year. A previous study showed

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that US$ 33 million was mainly for transfusion and iron chelation in 2016 alone, with 18,000 liters/year total donor blood consumption.[2]

The main therapeutic modality in TdT is blood transfusion supported by adequate iron chelation.[3] Moreover, blood transfusion aims to overcome chronic anemia by increasing Hb levels to normal physiologic levels (>13 gr/dl in men and >12 gr/dl in women) and suppress ineffective erythropoiesis to ensure optimal growth and development.[4,5] Although several transfusion target thresholds have been reported to suppress bone marrow expansion and reduce spleen size in pediatric patients, there are limited data in adults.[6–8] Current recommendations from Thalassemia International Federation (TIF) suggested pre-transfusion hemoglobin targets 9–10.5 g/dl with transfusion interval every 2–5 weeks.[3] Cazzola et al also reported that an average pre-transfusion hemoglobin level of 9–10 g/dl (moderate transfusion regimen) can suppress erythropoiesis activity and prevent cardiac as well as endocrine complications due to excessive iron loading.[9]

Adequate blood transfusion reduces the proportion of abnormal red blood cells which leads to a decrease in phagocytosis in the spleen and reverses the splenomegaly.[10] In clinical practice, an adequate volume of blood transfusion is not achievable due to the limited availability of blood donors.[1,11] Also, post-transfusion hemoglobin is not measured routinely due to financial restraint. Therefore, it is difficult to determine whether the low pre-transfusion is due to thalassemia or a previous inadequate blood transfusion, which leads to lower hemoglobin levels.

Studies in the Pediatric Thalassemia Clinic of Dr. Cipto Mangunkusumo General Hospital showed that the mean pre-transfusion hemoglobin levels in beta-major and beta-HbE thalassemia were 6.2 and 6.3, respectively.[12] Preliminary data from a study in adult TdT patients in RSCM showed that only 38.7% and 38.1% of the population achieved the recommended pre- and post-transfusion hemoglobin targets, respectively.[13] According to Kurniawan et al,[14] the inability to maintain post-transfusion hemoglobin levels was related to the presence of alloantibodies (78.6%) and autoantibodies (72.7%). Meanwhile, previous studies have shown that non-splenectomized patients have higher packed red cell transfusion volume requirements compared to patients who have undergone splenectomy.[3]

Furthermore, a previous study showed that the majority of the patients (83.4%) in the clinic have splenomegaly (≥6 cm), while one-third have thrombocytopenia and leukopenia due to hypersplenism.[13] Pancytopenia is a sign of a hypersplenism condition that makes transfusion targets difficult to achieve. Therefore, patients remain in a state of chronic anemia with splenomegaly and hypersplenism that worsen over time. Meanwhile, splenomegaly and its effects are overcome with optimal management through adequate blood transfusion and iron chelation.[15]

Since splenomegaly caused by inadequate transfusion is reversible, it is expected to be avoided by re-evaluating patients' blood transfusion adequacy.[3] Studies proved that adequate blood transfusion is associated with a reduction in spleen enlargement.[1] Similarly, Karpathiosos et al[16] also reported a significant reduction in spleen size 7–10 days post-transfusion, which indicated the success of blood transfusion. Although annual transfusion requirements determine whether a patient needs to be splenectomized or not, the exact threshold to indicate splenectomy is difficult to determine since it is influenced by factors such as degree of hypersplenism, alloimmunization events, patient genotypes, and baseline donor hematocrit. Furthermore, there are concerns about the risk after splenectomy such as infection, pulmonary hypertension, and thromboembolic events.[3,17–19]

Excessive destruction of red blood cells with extramedullary hematopoiesis activity leads to splenomegaly, causing increased blood transfusion requirements. Therefore, this study aims to determine the proportion of patients who achieve the optimal pre- and post-transfusion hemoglobin level, determine the factors involved, and the relationship between the achievement of hemoglobin levels and spleen enlargement in adult transfusion-dependent beta-thalassemia patients.

Materials and Methods

This retrospective cohort study involved adult thalassemia patients who received regular blood transfusions at the RSCM-Kiara thalassemia clinic, Jakarta. Moreover, the inclusion criteria were adults ≥18 years old, diagnosed with beta-major or beta-HbE thalassemia, while exclusion criteria were patients with active gastrointestinal bleeding and a history of splenectomy. The data were from patients' medical records, which include age, diagnosis, sex, education, occupation, age at the beginning of transfusion, frequency of blood transfusion, the volume of blood demand and transfused, as well as spleen size (both in centimeters and Schuffner scale). Furthermore, the laboratory data included pre- and post-transfusion blood counts and donor

compatibility. The subjects were recruited through total sampling and the results obtained were recorded and analyzed and all patients provided written consent. This study was conducted in line with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.

Achievement of Pre- and Post-Transfusion Target Hemoglobin

Achievement of pre- and post-transfusion target hemoglobin data were extracted from medical records and monitored from June 2017 to June 2018. The values were averaged to obtain mean pre- and post-transfusion hemoglobin levels in one year to determine whether the subject achieved the target. In this study, the gender-adjusted World Health Organization (WHO) and TIF reference values for the hemoglobin targets were used.

Spleen Measurement and Hypersplenism

Spleen enlargement data were taken from the medical records and was followed from June 2017 to June 2018. Spleen enlargement was recorded in centimetres on the Schuffner scale. The values in centimeters were measured from the costal arc to the tip of the palpable spleen. Moreover, the delta spleen size was defined as the difference in enlargement in centimeters (cm) at the beginning and the end of the cohort, while hypersplenism is defined as thrombocytopenia and/or leukopenia with annual blood requirement ≥250 mL/kg/year.

Blood Transfusion Deficit

Blood transfusion deficit is the discrepancy between requested blood volume and transfused blood volume in mL/kg/year.

Factors Related to the Achievement Hb Targets Pre- and Post-Transfusion

The data on thalassemia genotypes, presence of hypersplenism, blood compatibility, donor blood adequacy, and frequency of blood transfusions were taken from medical records and followed from June 2017 to June 2018, and were categorized based on the achievement of the subject's transfusion target level

Data Analysis

The data were analyzed using the SPSS® 20 for Windows™ program and the basic features of the subject characteristics was clearly described. Furthermore, bivariate analysis was performed using chi-square.

Results

Characteristics of the Subjects

This study involved 110 adult patients with beta-major and beta-HbE TdT that regularly visit the adult thalassemia outpatient clinic. The subjects were monitored in a cohort within 1 year from June 2017 to June 2018 and the characteristics are shown in Table 1.

Associated Factors for Achieving Pre- and Post-Transfusion HemoglobinLevel Targets

After obtaining pre- and post-transfusion hemoglobin levels, the subjects were divided into those who have achieved the Hb targets based on gender (WHO criteria) and those who did not achieve the targets. Furthermore, a chi-square analysis was conducted to determine the associated factors for achieving pre- and post-transfusion hemoglobin level targets. The results showed that blood transfusion deficit <30 mL/kg/year was associated with the achievement of pre- and post-transfusion hemoglobin targets ($p = 0.008$), as seen in Table 2.

Relationship Between Achieving Pre- and Post-Transfusion Hemoglobin Level Targets and Reduction of Spleen Enlargement

The results obtained on the centimeter delta measurement scale ($p < 0.001$, Table 3) showed that there were significant differences between the groups which achieved the pre- and post-transfusion target hemoglobin levels on the reduction of spleen enlargement.

Discussion

The results showed that there were more female subjects (53.6%) than males (46.4%) with beta-major and beta-HbE TdT in a ratio of 1.16. Similarly, a study conducted by Sharma et al[20] also reported more females than males in beta-dependent transfusion thalassemia patients in India. Compared to other studies related to blood transfusion targets which included pediatric patients,[6–8] we specifically studied adult patients aged ≥18, with the most adults subjects in this study (86.4%) were in the age group 18–30 years old. This is because those within the age

Table 1 Subject Characteristics

Characteristics	N = 110
Sex, n (%)	
Male	51 (46.4)
Female	59 (53.6)
Age group, n (%)	
18–30 Years Old	95 (86.5)
>30 Years Old	15 (13.5)
Education, n (%)	
High-school equivalent or lower	94 (86.3)
Higher education	15 (13.7)
Occupation, n (%)	
Employed	46 (41.8)
Unemployed	64 (58.2)
Thalassemia genotype, n (%)	
β-Mayor	53 (48.2)
β-HbE	57 (51.8)
Leukopenia, n (%)	
Yes	27 (24.5)
No	83 (75.5)
Thrombocytopenia, n (%)	
Yes	54 (49.1)
No	56 (50.9)
Hypersplenism, n (%)	
Yes	36 (32.7)
No	74 (67.3)
Blood transfusion deficit (mL/kg/year), n (%)	
<30	60 (54.5)
≥30	50 (45.5)
Transfusion Interval (weeks), n (%)	
1–2	39 (35.5)
3–5	71 (64.5)
Patients achieving recommended pretransfusion hemoglobin target, n (%)	
Yes	18 (16.4)
No	92 (83.6)
Patients achieving recommended posttransfusion hemoglobin target, n (%)	
Yes	22 (20.0)
No	88 (80.0)
Patients achieving both recommended pre- and post-transfusion hemoglobin target, n (%)	
Yes	8 (7.3)
No	102 (92.7)
Blood product used, n (%)	
Leukodepleted Packed Red Cells	92 (82.1)
Washed Erythrocyte	20 (17.9)
Median spleen enlargement, cm (min−max)	9,25 (0–28.5)
Median spleen enlargement, Schuffner scale (min −max)	3 (0–7)

Abbreviations: β, beta; HbE, hemoglobin E; mL, milliliters; kg, kilogram.

Table 2 Associated Factors for Achieving Pre- and Post-Transfusion Hemoglobin Level Targets

Variables	Achievement of Pre- and Post-Transfusion Hemoglobin Targets		RR (CI 95%)	p
	Yes	No		
Genotype, n (%)				
β-Mayor	6 (11.3)	47 (88.7)	3.226 (0.68–15.29)	0.151
β-HbE	2 (3.5)	55 (96.5)		
Compatibility, n (%)				
Compatible	8 (9.6)	75 (90.4)	–	0.196
Incompatible	0 (0.0)	27 (100.0)		
Blood transfusion deficit (mL/kg/year),				
<30	8 (13.3)	52 (86.7)	–	0.008*
≥30	0 (0.0)	50 (100.0)		
Transfusion interval (weeks), n (%)				
1–2	2 (5.1)	37 (94.9)	0.607 (0.13–2.86)	0.710
3–5	6 (8.5)	65 (91.5)		

Note: *p < 0.05.
Abbreviations: RR, relative risk; CI, confidence interval; β, beta; HbE, hemoglobin E; mL, milliliters; kg, kilogram.

group are the productive pool of the population and inadequate blood transfusion will render them unfit to work, causing unproductivity in most of the working areas. Thalassemia patients usually have difficulties in obtaining proper jobs due to frequent blood transfusions breaks. Therefore, low hemoglobin will make the patients perform poorly and pose the risk of losing jobs, which can reduce their quality of life.

Although most of the subjects were in the productive age,[21] only 48.6% were employed, which poses serious concerns on the quality of life of thalassemia patients.

Table 3 Correlation Between Target Achievement of Pre- and Post-Transfusion Hemoglobin Levels with Reduction of Spleen Enlargement

Variables	Achievement of Pre- and Post-Transfusion Hb Levels		p
	Yes	No	
Spleen Size (Schuffner scale), median (min−max)	0 (0–4)	3 (0–7)	0.282
Delta Spleen Size (cm), median (min−max)	1 (0–5)	0 ([−10] – 3)	0.005*

Notes: Independent sample (Mann–Whitney). *p < 0.05.
Abbreviations: Hb, hemoglobin; cm, centimetres.

According to Siddiqui et al,[22] approximately 70.3% of transfusion-dependent thalassemia patients worried about their future lives and careers because being unemployed can interfere with their ability to visit the hospital for regular blood transfusion. However, being employed can also hinder regular visits for blood transfusion, especially when the frequency is more than once a month.

There were more subjects with beta HbE thalassemia genotype in this study because it is prevalent in Southeast Asia, particularly in Indonesia.[23] Moreover, beta HbE thalassemia patients usually have lower pre-transfusion hemoglobin levels than those with beta-thalassemia major, and splenomegaly is also more common in beta HbE thalassemia.[24] Hypersplenism in transfusion-dependent thalassemia is characterized by splenomegaly, anemia, hyperplasia of precursor cells (maturation arrest), thrombocytopenia, and/or leukopenia, accompanied by the requirement for blood transfusion >250mL/kg/year.[25] Although most subjects (75.5%) in this study had not experienced leukopenia, approximately 49.1% had thrombocytopenia. Furthermore, there is accelerated destruction of normal cells (90% platelets) in hypersplenism,[26] therefore, thrombocytopenia precedes leukopenia in such patients. Based on this study, 36 (32.7%) subjects had advanced hypersplenism.

The pre-transfusion hemoglobin target was based on the guidelines issued by Thalassemia International Federation (TIF),[3] while the threshold for post-transfusion hemoglobin target was on normal Hb according to WHO.[4] Therefore, achieving normal hemoglobin level post-transfusion is paramount to suppress erythropoietin levels which can stimulate excessive erythroid proliferation, causing splenomegaly.[6,8]

The results showed that only one variable was significantly related to the achievement of pre- and post-transfusion hemoglobin target levels, which is the adequacy of donor blood. This factor is clinically relevant since insufficient blood volume reduces hemoglobin levels. Furthermore, it was discovered that thalassemia genotype, blood compatibility, and transfusion interval did not correlate with the achievement of pre- and post-transfusion hemoglobin.

Furthermore, there was a significant correlation (p = 0.005) between the achievement of pre- and post-transfusion hemoglobin and spleen size shrinkage. The measurement of spleen size enlargement in centimeters is more objective and detailed compared to the use of the Schuffner scale. The spleen enlargement was also quantified using the Schuffner scale to determine whether the clinical examination can be used to quantify spleen shrinkage. However, this study showed that quantifiable reduction in spleen size needs to be measured in centimeters. The result indicated that achieving pre- and post-transfusion hemoglobin can significantly reduce spleen enlargement and lower subsequent transfusion requirements, leading to a better outcome in thalassemia patients.

The results also showed that adequate blood transfusion in adult thalassemia patients achieves the target hemoglobin level and reduces spleen size. This reduction of spleen size lowers the transfusion requirement and frequency, leading to a better quality of life. In the United States, rapid enlargement of the spleen is a strong indication to increase blood transfusion.[27] However, there are many factors, especially in developing countries, which make it difficult to achieve these targets, namely difficulty in accessing healthcare, blood scarcity, and limited access to safe blood transfusion.[28,29]

Another factor that needs to be considered is the genetic profile of thalassemia patients. A recent study in Saudi Arabia by AbdulAzeez et al[30] showed that in female beta-thalassemia patients, the co-inheritance of alpha-globin deletion influenced iron status. Since thalassemia is a genetic disorder, other genetic abnormalities occur simultaneously. In addition, genetic factor that gives concern is the co-inheritance of ATRX mutation, which is associated with mental retardation, as described by Al-Nafie et al.[31] These results showed that besides the factors investigated in this study, genetic factors also played a role in the pathogenesis and outcome of thalassemia patients.

This is the first study that evaluated the pre- and post-transfusion hemoglobin levels in adult thalassemia patients in

Indonesia. Although previous studies focused on pre-transfusion hemoglobin levels in childhood, there was no study in adults, especially involving post-transfusion hemoglobin as an indicator of transfusions adequacy. This makes it important to explore adult patients since they need to work and be productive, unlike children. Moreover, adult thalassemia patients also suffer from chronic complications of thalassemia such as heart failure, endocrine dysfunction, and osteoporosis. Therefore, it is necessary to determine the role of achieving blood transfusion targets to their quality of life.

Indonesia has distinct thalassemia population characteristics compared to other countries, such as a high rate of beta HbE. In this study, beta HbE made up for more than half of the subjects. As described before, patients with beta HbE have been reported to have a higher rate of splenomegaly and lower pre-transfusion hemoglobin.[24] This is one of the novelties of our study. The limitation of this study is the small sample size and the use of clinical measurements of spleen size. Therefore, the use of modern imaging techniques such as CT-scan or MRI to obtain more accurate spleen size measurement is recommended for further study.

Conclusion

The achievement of pre- and post-transfusion hemoglobin levels in adult transfusion-dependent beta-thalassemia patients significantly reduced spleen enlargement and can contribute to better patient outcomes.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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