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Correlation between Adherence Therapy of Iron Chelation Levels with Serum Ferritin Levels in Major Beta-Thalassemia Patients at Kediri District General Hospital

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ABSTRACT

Repeated transfusions, increased absorption of iron, and ineffective erythropoiesis in patients with β thalassemia major cause iron overload, characterized by increased ferritin levels. Iron chelation therapy is needed to overcome iron overload in patients with beta-thalassemia major. The level of adherence affects the success of iron chelation therapy. This study aims to determine the relationship between adherence to iron chelation treatment and serum ferritin levels in patients with thalassemia beta major at Kediri District General Hospital. This type of research is an observational analytic with a cross-sectional design conducted on 17 subjects of β-thalassemia major patients at Pediatric Health Sciences (IKA) RSUD Kediri Regency who met the inclusion and exclusion criteria in December 2022-January 2023. The interviews used the Morisky Medication Adherence Scale questionnaire. -8, while the serum ferritin examination was obtained from the patient's medical record. There were 17 respondents who obeyed 11.76%; the non-compliant category was carried out by Spearman's correlation test and obtained a value of p = 0.01 and a value of r = -0.559. This shows significant results, and there is a moderate correlation between the level of adherence to iron chelation treatment and serum ferritin levels in beta-thalassemia major patients at Kediri District Hospital.

Keywords: thalassemia beta major, treatment adherence level, serum ferritin.

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INTRODUCTION

Beta thalassemia major is caused by a homozygous mutation (beta-zero thalassemia) of the beta-globin gene, resulting in the total absence of beta chains. It manifests clinically as jaundice, growth retardation, hepatosplenomegaly, endocrine abnormalities, and severe anemia requiring life-long blood transfusions. The condition in between these two types is called beta-thalassemia intermedia with mild to moderate clinical symptoms (Bajwa and Basit, 2022). The infant with β-thalasemia major usually can be seen within the first year of life and early childhood with pallor, failure to thrive, variable degree of jaundice, looks weakness and fatigue, recurrent infection, abdominal enlargement due hepatosplenomegaly and slow growth during puberty (Hamizah, et al., 2017).

The prevalence of thalassemia carriers in Indonesia reaches 3-8%, which means that 3-8 out of 100 people are thalassemia carriers (Indonesia, 2012). The number of cases of thalassemia major in Indonesia has increased from 2012 to 2018. In 2012 there were 4,896 cases of thalassemia, and in 2018 there were 8,761 cases (Indonesia, 2012).

Patients with β thalassemia major require regular blood transfusions throughout their lives to maintain haemoglobin levels above 9-10.5 g/dL to suppress ineffective erythropoiesis activity in the bone marrow and prevent growth disorders (Ouadghiri et al., 2023). However, repeated blood transfusions can result in iron overload due to the continuous accumulation of iron, while the body's

ability to excrete iron is limited (Ganz & Nemeth, 2023). In addition, the excess iron experienced by patients with beta-thalassemia major is also caused by increased iron absorption in the gastrointestinal tract due to ineffective erythropoiesis. (Basu et al., 2021) . Excess iron accumulation is toxic to tissues and can cause heart failure, cirrhosis, growth disorders, and endocrine disorders (Pietrangelo & Torbenson, 2024). Therefore, in addition to repeated transfusion therapy, patients with β thalassemia major also require iron chelation therapy to reduce excess iron. This therapy is carried out by excreting iron through urine or faeces using chelating agents (Cappellini et al., 2014).

Ferritin is considered the major iron storage protein which maintains a large iron core in its cavity and has ferroxidase activity (Arosio et al., 2017)). Serum ferritin examination is one of the tests that is often performed to measure the number of iron stores in thalassemia patients undergoing transfusion therapy. Beta thalassemia major patients should maintain their serum ferritin levels below 1500 ng/ml to minimize the possible complication of iron overload (Karunaratna et al., 2017).

Iron chelation therapy's challenge is achieving adherence to a lifelong treatment regimen (Chat Chai et al., 2021). Poor adherence to treatment can increase disease conditions or even death. The level of adherence to long-term therapy in chronic diseases in developed countries is around 50%, while in developing countries, it can be worse. Usage of Deferiprone or Deferasirox as oral chelator is more preferable due to its ease of use, with several studies presenting higher compliance rate in patient with oral chelator compared to injection chelator (Wahidiyat et al., 2018).

In Indonesia, few studies have examined the relationship between the level of adherence to iron chelation and serum ferritin levels in patients with thalassemia beta major. This study aimed to determine the relationship between the level of adherence to iron chelation and serum ferritin levels in patients with thalassemia beta major at Kediri District General Hospital.

METHODS

This type of research is observational analytic with a cross-sectional design. The research was conducted at the SMF Pediatrics (IKA) Regional General Hospital (RSUD) Kediri Regency in December 2022-January 2023. The population in this study were all patients aged 1-18 years who were diagnosed with β thalassemia major at SMF IKA RSUD Kediri Regency. The study sample was 17 thalassemia major thalassemia patients. The sample was taken using a purposive sampling method based on inclusion criteria, namely pediatric patients aged 1- 18 years old who had self-examination and was diagnosed with β-thalassemia major, had blood transfusions ≥ 10 times at SMF IKA RSUD Kediri Regency, and their parents gave their consent to participate in the study and the exclusion criteria were patients with fever characterized by an increase in temperature ≥ 38^0 C, acute infection, chronic inflammation, splenectomy, and malignancy based on medical records and physical examination. This study has received Ethical Clearance from the Research Ethics Committee of Kediri District Hospital.

The data collection instrument in this study used the Medication Adherence Scale-8 (MMAS-8) questionnaire. MMAS-8. The level of adherence is divided into 2, namely the adherent category if the total score of the MMAS-8 questionnaire is equal to 6-<8 (a combination of moderate and high degrees) and the category of non-adherence if the total score of the MMAS-8 questionnaire is less than 6. Meanwhile, data on the patient's serum ferritin level is taken from secondary data derived from medical records. Data analysis to determine the correlation between the two variables using the Spearman correlation test with a significance value of $p < 0.05$. The statistical processing computer program Statistical Package for Social Science (SPSS) 26.0 is used.

RESULTS AND DISCUSSION

There were 17 samples of beta thalassemia major patients who met the inclusion and exclusion criteria. The general characteristics of β thalassemia major patients at Kediri District Hospital are shown in Table 1.

Table 1. General Characteristics of Beta Thalassemia, Major Patients at Kediri District Hospital

Sample Characteristics	Amount (n)	Percentage (%)
Gender		
Man	7	41.18%
Woman	10	58.82%
Age		
<5 years	2	11.77%
5 - <10 years	4	23.54%
10 - < 15 years	3	17.64%
15 - <18 years	8	47.05%
TB/U		
Normal	7	29.41%
Short	10	70.59%
Abdomen Examination		
Splenomegaly	5	41.18%
Hepatosplenomegaly	12	58.82%
Classification Therapy		
Deferiprone	10	58.82%
Deferasirox	7	41.18%

Based on the study's results, the adherence level and serum ferritin level are shown in Table 2. The results of the Spearman correlation test between the adherence level of iron chelation treatment and ferritin levels are shown in Table 3.

Table 2. Values of ferritin levels and MDA levels

Sample Characteristics	Amount (n)	Percentage (%)
Compliance Level		
Obey	2	11.76
Not obey	15	88.24%
Ferritin Levels		
< 1000ng/mL	2	11.76%
1000-2000ng/mL	2	11.76%
>2000ng/mL	13	76.48%

The level of adherence to iron chelation treatment and serum ferritin levels had a p-value of 0.01 <α 0.05 and an r-value of -0.559, so it can be concluded that the level of adherence to iron chelation treatment and serum ferritin levels had a significant and moderate correlation.

Table 3. Results of the Spearman Correlation Test on Adherence and ferritin levels

	Serum Ferritin Levels
Compliance Level	R -0.559
	p.s. 0.01
	n 17

Characteristics of the sample based on the data obtained showed that the number of female samples was more than male. Namely, ten samples (66.7%) were female, and seven (33.3%) were male. According to Mendel's law, thalassemia is passed from parent to child in an autosomal recessive

manner. The pattern of autosomal recessive inheritance is a horizontal line so that there are many sufferers in one generation, but not for every generation. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Heterozygotes (i.e., carriers) may be slightly anemic but are clinically asymptomatic (Origa, 2021). The characteristics of the sample based on age obtained the highest number of samples aged 15-<18 years with eight samples (47.05%). Patients with β thalassemia major usually appear normal at birth. Symptoms will be found in children aged 2 to 6 years (Cappellini et al., 2014).

The characteristics of the sample according to height per age were ten samples (58.82%) with short height and seven samples (41.18%) of normal height. The anterior pituitary gland is very sensitive to iron accumulation, so it interferes with the secretion of hormones. If there is an accumulation of iron in the anterior pituitary, it will interfere with the synthesis and secretion of Growth Hormone (GH) so that the growth of people with thalassemia can be disrupted (Joshi & Phatarpekar, 2013). In addition, iron buildup can interfere with osteoid maturation and precipitate into hydroxyapatite crystals, disrupting normal bone metabolism (Moiz et al., 2018).

Characteristics of the samples according to abdominal examination found β thalassemia major patients with splenomegaly without hepatomegaly in 5 samples (29.41%) and hepatosplenomegaly in 12 samples (70.59%). Splenomegaly occurs due to extramedullary erythropoiesis (Andriastuti et al., 2016). Severe anaemia in patients with β thalassemia major causes the kidneys to release erythropoietin. This hormone stimulates the bone marrow to produce more red blood cells resulting in ineffective erythropoiesis. Increased erythropoiesis results in bone marrow hyperplasia and expansion, resulting in bone deformities. Erythropoietin also stimulates extramedullary hematopoietic tissue in the liver and spleen, causing hepatosplenomegaly. Based on the data obtained, ten samples (58.82%) received Deferiprone iron chelation therapy. Moreover, seven samples (41.18%) received Deferasirox therapy. Deferiprone is superior in controlling or reducing myocardial iron load (as proven by T2* MRI) (Wahidiyat et al., 2019). Deferasirox is effective in improving myocardial and hepatic siderosis.(Ansari et al., 2017). Iron chelation therapy is urgently needed in patients with β thalassemia major with repeated blood transfusions (Permono et al., 2012). Iron chelation should be started when ferritin levels rise above 1000 ng/mL or the patient has received 10-20 units of PRC (Prabhu et al., 2009).

From the results of this study, 15 samples (88.24%) were non-adherent in consuming iron chelation, and two samples (11.76%) were obedient. The sample's adherence level was assessed from the Medication Adherence Scale-8 (MMAS-8) questionnaire. So it can be said that the level of adherence to consumption of iron chelation in patients with β thalassemia major at RSUD dr. Kediri district is low. Many factors influence the level of treatment adherence. There are several barriers to adherence to therapy, namely poor communication between patients and drug providers, insufficient knowledge about the drug and how to use it, feeling unsure of the importance of treatment, and fear of side effects of the drug. To improve medication adherence, better communication and better information on the disease and its medication appeared to be the crucial concepts for patients (Kvarnström et al., 2021).

From the results of this study, the lowest ferritin level was 725.2 ng/mL, and the highest ferritin level was 2986.7 ng/mL. Research subjects who had ferritin levels <1000 ng/mL in 2 samples (11.76%), 1000-1000 ng/ml in 2 samples (11.76%) and > 2000 ng/mL in 13 samples (76.48%)). Normal ferritin values range from 20–400 ng/mL (CDC, 2020). The ferritin levels of the study subjects were far above the normal range. Iron overload is called iron overload if the ferritin level is more than the normal value [20]. So the research subject has excess iron. Repeated blood transfusions, ineffective erythropoiesis,

and increased iron absorption through digestion cause iron overload in patients with β thalassemia major. In contrast, the body's ability to excrete iron is limited (Cappellini et al., 2014).

Therapy obtained by patients with β thalassemia major apart from routine blood transfusions is chelation therapy to excrete iron and administration of vitamin C and vitamin E, which are used as antioxidants. Optimal administration of iron chelation can reduce iron deposits in patients with thalassemia (Safitri et al., 2015). However, the lack of adherence to taking the iron chelating drugs given can be a factor that causes this therapy not to be optimal. When repeated blood transfusions are carried out without taking regular iron chelation therapy, it can cause a significant increase in ferritin levels (Satria et al., 2016). This is consistent with previous research, which stated that the non-adherent group in iron chelation treatment had ferritin levels ≥ 1000 ng/ml (Chat Chai et al., 2021). High serum ferritin levels were associated with higher liver and cardiac iron load and the patients with irregular use of iron chelating agents were more likely to have higher cardiac iron load (Sobhani et al., 2019).

The results of data analysis using the Spearman correlation test on the level of adherence to iron chelation treatment with serum ferritin levels in patients with thalassemia beta major at Kediri District General Hospital obtained a p-value of 0.01 and an r-value of -0.559. This shows that there is a significant correlation between the level of adherence to iron chelation treatment and serum ferritin levels in patients with thalassemia beta major and has a moderate correlation. This is consistent with previous research, which states that the higher the adherence to iron chelation treatment, the lower the serum ferritin level. Low adherence in chronic diseases is influenced by lack of knowledge about the causative disease, lack of awareness of the reasons for treatment, anxiety about taking drugs in the long term, fear of side effects of treatment, regimen and type of drug given, age, and the poor doctor-patient relationship (Triwardhani et al., 2022).

CONCLUSION

Based on the results of the conducted research, it can be concluded that there is a significant relationship between the level of compliance with iron chelation therapy and serum ferritin levels with a p-value of 0.01 and a moderate correlation (r=-0.559) in patients with beta-thalassemia major at Kediri Regional General Hospital.

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