INDONESIAN HEALTH JOURNAL
https://ihj.rivierapublishing.id/index.php/rp
Volume 2 Number 2 June 2023
P-ISSN: 2963-3044
E-ISSN: 2963-3036

CORRELATION BETWEEN ADHERENCE THERAPY OF IRON CHELATION WITH ANTHROPOMETRIC STATUS IN MAJOR BETA THALASSEMIA PATIENTS

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Received: 09-05-2023 Accepted: 21-05-2023 Published: 13-06-2023

ABSTRACT

Thalassemia is a condition in which hemoglobin undergoes hemolysis due to impaired synthesis of hemoglobin or globin chains. Growth failure is a common occurrence in patients with thalassemia. Iron overload due to repeated transfusions will cause disturbances in anthropometric status in children with thalassemia. 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 the level of adherence to iron chelation treatment and anthropometric status in patients with thalassemia beta major at Kediri District General Hospital. This type of research is observational analytic with a cross-sectional design. This research was conducted at the SMF Pediatrics (IKA) RSUD Kediri Regency on 16 subjects with β-thalassemia major using a total sampling technique that met the inclusion criteria. The research instruments used in this study were the Morisky Medication Adherence Scale-8 questionnaire and an examination of anthropometric status. The research analysis used the Spearman correlation test. A p-value <0.05 was considered significant. The results showed that there was a significant results between adherence to iron chelation consumption and height for age (p-value = 0.049 > α 0.05), significant results between adherence to iron chelation consumption with weight for age (p-value = 0.036 < α 0.05), and significant results with weight for height (p-value = 0.001 < α 0.05). This study implies that adherence to iron chelation therapy is essential for thalassemia patients. This study shows that patients more adherent to iron chelation treatment have better anthropometric status.

Keywords: anthropometric status, level of medication adherence, thalassemia beta major.

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INTRODUCTION

Thalassemia is a disease caused by a genetic syndrome in which there is a decrease in the synthesis of one of the chains in the primary hemoglobin (Hb A), often found worldwide (Peslak & Sayani, 2023). The World Health Organization WHO (2012) states that approximately 7% of the world's population has the thalassemia gene, with the highest incidence rate of up to 40% of cases in Asia. A high prevalence of thalassemia belt region, including Indonesia. Based on data from YTI (Indonesian Thalassemia Foundation) and POPTI (Association of Parents with Thalassemia) in 2014, 699 people (5.8%) were carriers of the trait from 12,038 people examined (Rahayu et al., 2016).

Patients with thalassemia have chronic anemia, hemolytic processes, and decreased hemoglobin synthesis (Hb), so patients with thalassemia require lifelong transfusions (Solomou et al., 2022). Management of lifelong transfusions and the occurrence of cell damage due to chronic anemia causes iron accumulation in the patient's body resulting in the dysfunction of organs such as the heart, liver, muscles, and endocrine glands (Solomou et al., 2022). Repeated blood transfusions can also result in iron overload due to the continuous accumulation of iron, while the body's ability to excrete iron

is limited (Ganz & Nemeth, 2023). Iron chelation therapy to remove excess iron due to routine blood transfusions (Putri et al., 2015). Iron chelation begins when the serum ferritin level is ≥ 1,000 ng/mL or the patient has received 10-15 blood transfusions and 3 liters of blood (Hoffbrand & PAH, 2013).

Optimum administration of iron chelation can reduce iron deposits in patients with thalassemia. This is expected to improve the growth of sufferers. Children who suffer from thalassemia and receive repeated transfusions will cause iron deposits (hemosiderosis) in the endocrine system, including the thyroid gland (Cappellini et al., 2014).

Optimum assessment of child growth can be measured using child anthropometric standards. Children's Anthropometric Standards is a collection of data on size, proportion, and body composition to assess children's nutritional status and growth trends (Cochrane et al., 2017). The advantages of anthropometry include that the procedure is simple, safe, and can be performed on many samples. Relatively does not require experts. The tools are cheap, easy to carry, durable, and can be ordered and made locally. Precise and accurate because it can be standardized, detect or describe nutritional history in the past, and generally identify moderate, poor, and poor nutritional status because there are clear thresholds (Istiany, 2013).

In Indonesia, few studies have examined the relationship between the level of adherence to iron chelation and anthropometric status in patients with thalassemia beta major. Research conducted by Shobri found that there is a significant relationship between compliance with consumption of iron chelation to the growth of children with thalassemia ("Hubungan Kepatuhan Konsumsi Kelasi Besi Terhadap Pertumbuhan Anak Dengan Thalassemia," 2020). Another research conducted by Bellawati found that compliance with blood transfusion and consumption of iron chelation affects the growth of children with major beta thallasemia (Bellawati & Ismahmudi, 2021). This study aimed to determine the relationship between the level of iron chelation adherence and anthropometric status 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 study sample was 16 β-thalassemia, significant patients. The sample was taken using the total 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. The exclusion criteria were patients with fever characterized by an increase in temperature ≥ 380 C, acute infection, inflammation chronic disease, splenectomy, and malignancy based on medical records and physical examination. This research has obtained Ethical Clearance from the Research Ethics Committee of Kediri General Hospital.

The data collection instrument in this study used the Medication Adherence Scale-8 (MMAS-8) questionnaire. MMAS-8. The level of adherence was divided into 2, namely the adherent category if the total score of the MMAS-8 questionnaire was equal to 6-<8 (a combination of moderate and high degrees) and the non-adherent category if the total score of the MMAS-8 questionnaire was less than 6. Meanwhile, data on the patient's serum ferritin level was 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 16 samples of beta thalassemia primary patients who met the inclusion and exclusion criteria. The general characteristics of β thalassemia significant patients at Kediri District Hospital are shown in Table 1.

Table 1. General characteristics of the sample of β-thalassemia significant patients at Kediri District Hospital

Sample Characteristics	Amount (n)	Percentage (%)
Gender		
Man	7	43.75 %
Woman	9	5 6.6 2%
Age		
<5 years	2	1 2.50 %
5 - <10 years	4	25.00 %
10 - < 15 years	3	18.75 %
15 - < 18 years	7	43.75 %
Ferritin levels		
< 2500ng/mL	7	4 7.75 %
≥ 2500ng/mL	9	5 6.25 %
Abdomen Examination		
Splenomegaly	9	56.25 %
Hepatosplenomegali	7	47.75 %
Classification Therapy		
Deferiprone	10	62.5 %
Deferasirox	6	37.5 %

Table 2. Level of adherence to iron chelation consumption and anthropometric status on β thalassemia significant patients at Kediri District Hospital

Sample Characteristics	Amount (n)	Percentage (%)
Adherence Level		
Adherence	2	11.76 %
Non adherence	14	88.24 %
Height for Age		
Severely stunted	0	0 %
Stunted	14	82.35 %
Normal	2	11.75 %
Weight for Age		
Severely underweight	3	17.65 %
Underweight	12	70.59%
Normal	1	5.88 %
Weight for Height		
Severely wasted	3	17.65%
Wasted	11	64.71%
Normal	2	11.76 %

Table 3. Results of the Spearman correlation test on the level of adherence and anthropometric status

	Height For Age	
	P	R
	0.049	0.429
	Weight For Age	
Adherence Level	P	R
	0.036	0.460
	Weight For Height	
	P	R
	0.001	0.702

Based on the study's results, the level of adherence and anthropometric status was obtained, as shown in Table 2. The result of the Spearman correlation test between the adherence level of iron chelation treatment and anthropometric status are shown in Table 3. There is a significant result with moderate correlation between adherence to iron chelation treatment with height for age (p-value of 0.049 < α 0 .05) and an r-value of 0.429, there is significant result with very low a correlation between adherence to iron chelation treatment with weight for age (p-value of 0.036 < α 0.05) and r-value of 0.036, and there is significant result with strong correlation between adherence to iron chelation treatment with weight for height (p-value of 0.001 < α 0.05) and an r-value of 0.702. These results can be concluded that the level of adherence to iron chelation treatment and anthropometric status has a correlation.

The results showed that based on the data obtained, the sample characteristics revealed that the number of female samples was more than that of males, namely 10 (66.7%) females and 7 (33.3%) males. According to Mendel's law, thalassemia is passed from parents to children in an autosomal recessive manner (Benz, 2023). The autosomal recessive inheritance pattern is a horizontal line so that there are many sufferers in one generation but not for every generation. Patients with β thalassemia major have a 25% chance that both parents are carriers (Hoffbrand & PAH, 2013). 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).

Characteristics of the samples according to ferritin levels showed that ferritin levels were <2500 ng/mL in 9 samples (56.25%) and samples with ferritin levels ≥ 2500 ng/mL in 7 samples (43.75%). The ferritin levels of the study subjects were far above the normal range. Iron overload occurs if the ferritin level exceeds the average value (World Health Organization, 2017). So it can be said that 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 minimal (Cappellini et al., 2014).

β thalassemia significant 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 anemia in patients with β thalassemia major causes the kidneys to release erythropoietin, a hormone that 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 the extramedullary hematopoiesis tissue in the liver and spleen resulting in hepatosplenomegaly (Potts & Mandleco, 2012). Based on the data obtained, ten samples (62.75%) received Deferiprone iron chelation therapy. Moreover, six samples (37.25%) received Deferasirox therapy. Deferiprone is superior in controlling or reducing myocardial iron load (as proven by T2* MRI) ((Wahidiyat et al., 2018). 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.

In this study, it was known that the anthropometric status consisting of height for age, weight for age and weight for height varied among subjects. The characteristics of the sample according to height per age were grouped into two groups, namely normal by two samples (11.75%) and stunted by 14 samples (82.35%). This is following research at RSUD dr. Moewardi Surakarta, out of 30 samples of thalassemia patients, 22 samples (73.33%) were tall according to the stunted category. Eight samples (26.67%) were normal according to the normal category (Alifprilia, 2018). As a result of impaired

synthesis and secretion of adrenocortical hormones will cause disturbances in the growth and metabolism of patients with β thalassemia major. The growth of people with thalassemia will be relatively normal until 9 to 10 years. Iron buildup can interfere with osteoid maturation and precipitate into hydroxyapatite crystals, disrupting normal bone metabolism (Moiz et al., 2018). In addition, malnutrition in thalassemia patients is caused by ineffective erythropoiesis; rapid turnover of erythrocytes also increases energy requirements (Ayukarningsih et al., 2022).

Characteristics of the sample according to weight for age divided was into three groups, namely Severely underweight in 3 samples (17.65%), underweight in 12 samples (70.59%), and normal in 1 sample (5.88%). The characteristics of the sample weight for height were divided into three groups: 3 samples (17.65%) of severely wasted, 11 samples (64.71%) of wasted, and two samples (11.76%) of noemal. This follows research conducted in the IKA section of RSUP Dr. M. Djamil Padang from February 2012 to March 2013. Based on the results of this study, in percentage terms, the average weight index for age was 60% -80%, which was 66.7%. It can be seen that the majority are classified as undernourished (Putri et al., 2015). Other studies also show that children with β thalassemia major's weight is below average. This study found that most patients with thalassemia beta major had poor nutritional status, amounting to 64.1%, 22.7% good nutrition, and 13.2% malnutrition. The same result was also found in RS. Dr. Kariadi Semarang found that most of the nutritional status of β- primary thalassemia children was undernourished. Another study in 2009-2010 showed the nutritional status of β- beta primary thalassemia children, on average, was good nutrition with a percentage of 55%, and the rest was undernourished, namely 45%. This difference is thought to be due to various factors, such as the treatment effect for each individual is different and is also influenced by nutritional intake (Putri et al., 2015).

From the results of this study, 14 samples (82.35%) were non-adherent in consuming iron chelation, and two samples (11.76%) were adherent. 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. These results are consistent with a study conducted by Triwardhani on 60 patients with β- thalassemia major who received iron chelation therapy at Dr. Hasan Sadikin Bandung, 37 samples (62%) were non-compliant, and 23 samples (38%) were compliant (Triwardhani et al., 2022). The same results were also obtained by Gustiana, who conducted a study on 50 subjects with β -thalassemia major and found 30 samples (60%) who had low adherence to iron chelation consumption and 20 samples (40%) who had a high adherence rate (Gustiana et al., 2020). Many factors influence the level of treatment adherence. There are several barriers to adherence to therapy, namely poor communication between doctors and patients, 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. Long-term drug use is a complex regimen that requires large amounts of drugs with various delivery schedules (Jimmy & Jose, 2011).

Routine blood transfusions can prolong the survival of patients with major β-thalassemia. However, they can cause iron overload, which can cause hemosiderosis which will eventually cause disturbances in various organs, such as the liver, heart, and endocrine organs, which can interfere with children's growth (Robbiyah 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).

The results of data analysis using the Spearman correlation test on the level of adherence to iron chelation consumption with anthropometric status in patients with β-thalassemia major at Kediri District General Hospital showed a positive correlation. From the height-for-age results, the p-value

was 0.429, and the r-value was 0.429; from the weight-for-age results, the p-value was 0.460, and the r-value was 0.036; from the weight-for-height results, the p-value was 0.702, and the r-value was 0.001. This shows a significant correlation between the level of adherence iron chelation consumption and anthropometric status and has a robust positive correlation strength. This follows research conducted by Safitri, which showed that respondents who obediently consumed iron chelation had average growth, namely 31 people (55.4%) (Safitri et al., 2015). The results of this study also follow research (Origa, 2017) which states that using iron chelation in patients with thalassemia major can reduce iron deposits in the thyroid gland. The provision of iron chelation must be given regularly so that the growth of children with thalassemia can be optimal. Administration of drug doses in children with thalassemia is needed. Study that was done by Syobri showed that 30 people stated no adherent with a percentage of 40%. It implied that there is a significant relationship between compliance of iron chelation consumption to growth on children with major beta thalassemia. This also implied that respondents who have adherence with iron chelation therapy have better nutritional status ("Hubungan Kepatuhan Konsumsi Kelasi Besi Terhadap Pertumbuhan Anak Dengan Thalassemia," 2020). Impaired growth and malnutrition are characterized by lower body weight and height in children with major beta thalassemia than in normal children. The existence of nutritional problems in thalassemia sufferers shows that there are still many children who experience impaired physical growth, which can affect nutritional status in the next life cycle period and will also indirectly have an impact on morbidity and mortality (Kusumawati et al., 2017).

Excess iron in the body can be overcome by consuming iron chelation therapy regularly. Low adherence in chronic diseases is influenced by a 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. The results of this study can be used as a reference for educating parents and thalassemia primary patients about complications of organ dysfunction that can occur due to hemosiderosis and the importance of consuming iron chelation.

CONCLUSION

Based on the research results, there is a significant relationship between the level of adherence to iron chelation treatment and anthropometric status, which is divided into three categories. The level of adherence with height for age has significant result (p-value of 0.049) and a moderate correlation (r: 0.429), the level of adherence with weight for age has significant result (p-value of 0.036) and a very low correlation (r: 0.036), the level of adherence with weight for height has a significant result (p-value of 0.001) and a strong correlation (r: 0.702), It can be concluded that the level of adherence to iron chelation treatment is correlated with anthropometric status in thalassemia patients at Kediri District Hospital.

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