DIPONEGORO MEDICAL JOURNAL
(Jurnal Kedokteran Diponegoro)
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
Volume 9, Nomor 1, Januari 2020

THE RELATION BETWEEN TYPES OF IRON CHELATORS AND FERITIN ON OSTEOCALCIN OF THALASSEMIA PATIENTS WITH REPEATED TRANSFUSIONS

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ABSTRACT

Introduction: Thalassemia is an inherited disorder that decrease the rate of globin synthesis. Multiple blood transfusions in thalassemia patients leading to complications of hemosiderosis and hemochromatosis. Iron chelator aims to remove excess iron in the body. High ferritin levels interfere with 25-hydroxyvitamin-D production and negatively affect bone metabolism, measured with osteocalcin (N-Mid Oc). Study aims to determine the relation between type of iron chelator and ferritin levels to osteocalcin levels in thalassemia patients with history of repeated transfusions. **Method:** An observational analytic cross-sectional study. Research was conducted in May - August 2019 and carried out at Red Cross Semarang, Rembang Hospital, and Purwodadi Hospital. Study subjects were 40 people, then 6 people were excluded to 34 people. Gender are 14 male and 20 female. Subjects were thalassemia patient with repeated transfusions and undergoing iron chelation therapy. Subjects that met the criteria were tested for blood to measure ferritin levels and osteocalcin levels. **Results:** Average ferritin levels was 2842.85 ug/L and average osteocalcin levels was 15.05 ng/mL. There was significant relation between type of iron chelator on osteocalcin levels (p=0.046), but there was no significant relation between type of iron chelator on ferritin levels (p=0.434). There was significant relation between ferritin levels and osteocalcin levels on patient with Deferasirox therapy (p=0.022), but no significant relation on patient with Deferiprone therapy (p=0.432). **Conclusion:** There is significant relation between the type of iron chelator on osteocalcin levels and there is significant relation between ferritin levels and osteocalcin levels on patient with Deferasirox therapy.

Keywords: thalassemia,iron chelator,deferasirox,deferiprone,ferritin,osteocalcin

INTRODUCTION

Thalassemia is a group of hereditary disorders that occurred due to mutations in genes that encode one of the globin chains.[1] This causes a decrease in the speed of hemoglobin synthesis and anemia.[2] Data from the World Bank reports 7% of the world's population are carriers and about 300,000 to 500,000 babies are born with this disorder each year.[3] Data from WHO in 2011, thalassemia was found with high prevalence in Mediterranean countries, Middle East and Southeast Asia.[4]

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Treatment of severe anemia in thalassemia patients is blood transfusion. Its purpose is to achieve normal hemoglobin levels so that no growth disturbance occurs.[5] Blood transfusion every 450 mL will cause 200-250 mg of iron stored in the tissue and it will continue to accumulates.[1] Repeated blood transfusion causes complications of hemosiderosis and hemochromatosis on patients.[6]

Iron chelator therapy aims to remove excess iron from the patient's body. Deferoxamine, Deferasirox, and Deferiprone are iron chelators commonly used in Indonesia.[3] Deferoxamine (DFO or Desferal) has a short plasma half-life, so it is given parenterally. Whereas Deferasirox (DFX) and Deferiprone (DFP) are given orally.[6]

The administration of iron chelator begins after the significant amount of iron deposits in the patient's body. It can be assessed from several parameters such as liver iron concentration (LIC).[1] Combined iron chelators is given if serum ferritin levels >2500 ng/mL persist for at least 3 months, or if cardiomyopathy has occurred, or if cardiac hemosiderosis has occurred on MRI examination, T2 (<20 ms).[3]

Repeated transfusions on thalassemia patients can cause iron accumulation. Excess iron that is not used is stored as ferritin. In thalassemia patients with repeated blood transfusion showed high value of ferritin levels.[7]

Research conducted by Gombar in 2018 was investigating differences between ferritin levels and vitamin D levels. The results showed a significant increase in ferritin levels and a significant decrease in vitamin D levels in thalassemia patients group compared to healthy controls group.[8]

Free iron is toxic to cells, because free iron is the catalysis of free radicals formation from Reactive Oxygen Species (ROS) through fenton reaction. Impaired production of 25-hydroxyvitamin D negatively affects bone metabolism in the body.[9]

Osteocalcin (N-Mid Oc) is a marker for bone formation produced by osteoblasts.[10] Research conducted by Zoga in 2014 on thalassemia patients assessed the relation between several bone parameters with bone mineral density. The study found that in thalassemia patients diagnosed with osteoporosis, there were low serum vitamin D levels, high N-Mid Oc levels, and high β-CTx levels.[11]

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So far there has not been much research on the relation between iron chelator and osteocalcin levels, and the relation between ferritin levels and osteocalcin levels. The authors would like to know the relation between types of iron chelator and ferritin levels on osteocalcin levels in thalassemia patients with a history of repeated transfusions.

METHOD

An observational analytic cross-sectional study. Research was conducted in May - August 2019 and carried out at PMI Semarang, Rembang, Purwodadi, and GAKY Laboratory, Diponegoro University.

Study subjects were 40 people, then 6 people were excluded to 34 people. Gender are 14 male and 20 female. Subjects were thalassemia patient with a history of repeated transfusions and were undergoing iron chelation therapy. Subjects that met the criteria were tested for blood to measure ferritin levels and osteocalcin levels.

Ethical clearance was obtained from the Medical and Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Diponegoro University. The inclusion criteria were male and female thalassemia patients, has received transfusions more than 10 times, has received iron chelation therapy, and were willing to become research respondents. Exclusion criteria were leukocytosis, fever, and was receiving vitamin D supplementation.

Subjects was given a brief explanation of the purpose, benefits, and research protocols. Subjects that met the criteria were interviewed and have their blood tested to measure ferritin levels and osteocalcin levels. The collected data was carried out for coding, entry, and editing using computer software.

Data analysis was performed using SPSS. The relation between the type of iron chelator on ferritin levels were analyzed using Fischer Test. The relation between the type of iron chelator on osteocalcin levels were analyzed using Fischer Test. Each numerical variable was tested for normality test. The relation between ferritin levels and osteocalcin levels were analyzed using Correlation test (Spearman test on deferasirox therapy and Pearson test on deferiprone therapy).

RESULTS

Data collected from May to August 2019. Research was conducted at PMI

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Semarang, Rembang, Purwodadi, and GAKY Laboratory of Diponegoro University. Study subjects were 40 people, then 6 people were excluded to 34 people.

The results showed the majority of research subjects were female with total of 20 people (58.8%), meanwhile male with total of 14 people. The subjects of the study consumed iron chelators, mostly Deferasirox by 26 people (76.5%) and Deferiprone by 8 people (23.5%). Average values of ferritin levels and osteocalcin levels were 2842.85 and 15.04892. The mean standard deviation for ferritin levels was 1667.828 and osteocalcin levels was 10.825923. minimum-maximum range of ferritin levels and osteocalcin levels, respectively were (647-9978) and (0.4659-38.382).

Table 1. Relation between Iron Chelators and Ferritin Levels

Iron Chelator	Ferritin Levels		P
	<1000 µg/L	>1000 µg/L	
Deferasirox	3	23	0.434
Deferiprone	0	8	

Based on Table 1, analysis showed the difference between the types of iron chelators and ferritin levels was P = 0.434 (p> 0.05), so it can be concluded that there was no significant relation between the type of iron chelators with ferritin levels in thalassemia patients with a history of repeated transfusions.

Table 2. Relation between Iron Chelators and Ostecalcin Levels

Iron Chelator	Osteocalcin Levels		P
	Low (<11 ng/mL)	Normal (11-43 ng/mL)	
Deferasirox	14	12	0,046
Deferiprone	1	7	

Based on Table 2, the analysis showed that the difference between the type of iron chelators and osteocalcin levels was P = 0.046 (P<0.05), so it can be concluded that there was significant relation between the type of iron chelators with osteocalcin levels in thalassemia patients with a history of repeated transfusions.

Table 3. Relation between Ferritin Level and Osteocalcin Levels

	Relation between Ferritin Levels and Osteocalcin Levels (*Sig. 2-tailed*)
Deferasirox	0.022
Deferiprone	0.432

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Based on Table 3, the value of Spearman correlation between ferritin levels and osteocalcin levels on patients with Deferasirox therapy was P= 0.022 (P<0.05) and it can be concluded that there was significant relation on patients with Deferasirox therapy. The value of Pearson correlation between ferritin levels and osteocalcin levels on patients with Deferiprone therapy was P= 0.432 (P>0.05) and it can be concluded that there was no significant relation on patients with Deferiprone therapy.

DISCUSSION

Iron chelation therapy such as Deferasirox and Deferiprone aims to reduce the accumulation of iron in the body of thalassemia patients.[12] Evaluation of iron load with serum ferritin levels is an easy choice, but it is very easily influenced by other factors such as infection, inflammation, and vitamin C levels.[13] Research done by Wahidiyat in 2017 showed that T2 MRI examination in thalassemia patients could be done as early detection to determine iron accumulation in patients' heart and liver. This examination is also non-invasive compared to liver biopsy which is the gold standard to determine the level of iron load in thalassemia patients.[14] The regulation of iron in the body is also influenced by Hepcidin hormone.[15,16]

The administration of iron chelation therapy begins after significant deposits of iron in the patient's body.[8] Excess iron in the liver can causes the disruption of the production of 25-hydroxyvitamin D which causes bone metabolism to be affected.[9] Osteocalcin (N-Mid Oc) is a marker of bone formation compounds. Research conducted by Zoga in 2014 showed that Thalassemia patients with osteoporosis have high levels of N-Mid Oc.[11] Hemoglobin levels can also affect osteocalcin levels in the body. Research by Lewerin in 2016 showed osteocalcin levels in men with anemia were higher than in men without anemia.[17]

Research conducted by Juanola-Falgarona showed that osteocalcin levels was also influenced by transferrin levels, which is one of the iron biomarkers in addition to ferritin.[18] Osteocalcin is a protein that is dependent on vitamin K and vitamin D. It is produced by osteoblasts and it is the most common non-collagen protein found in bone.[19]

Research conducted by Xifra in 2018 showed the relation between serum

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ferritin, osteocalcin, and CTX was only significant in patients with obesity (BMI ≥ 25 kg/m2) and there was no significant relation appears in people with normal body weight (BMI <25 kg/m2).[20]

CONCLUSION AND SUGGESTION

Conclusion

There is significant relation between the type of iron chelators and osteocalcin levels in thalassemia patients with repeated transfusions, but there is no significant relation between the type of iron chelators and ferritin levels. There is significant relation between ferritin levels and osteocalcin levels in thalassemia patients with Deferasirox therapy, but no significant relation between ferritin levels and osteocalcin levels in thalassemia patients with Deferiprone therapy. Thalassemia patients from this study showed high level of ferritin serum and normal level of osteocalcin.

Suggestion

Suggestion for future research, pay attention to other factors such as medication adherence of iron chelator, body weight of patients, transferrin levels and hemoglobin levels on thalassemia patients.

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