RESEARCH ARTICLE

Renal Function in Children with β-Thalassemia Major Treated with Iron Chelating Agent

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Abstract

BACKGROUND: Thalassemia is a disorder of inherited blood and inticated by the abnormal hemoglobin. Transfusion and iron chelation are part of thalassemia management. Iron chelating agent reduces complications due to the excess iron as a result of repeated transfusions, hence, increasing the survival rate. However, prolonged intake of iron chelating agent may increase the risk of renal function impairment. To date, evaluation of renal function in children with β-thalassemia in Medan has never been reported. The objective of this study was to evaluate renal function and other factors in children with β-thalassemia.

METHODS: Fourty-five children with β-thalassemia was recruited in this study. Renal function, represented by estimated glomerular filtration rate (eGFR)and serum ferritin levels were examined. The measurement of eGFR was using Schwartz method.

RESULTS: Decreased eGFR observed in some the children (2 patients) with β-thalassemia major treated with iron chelating agent. None of the factors examined had association with serum creatinine level. Children's age and duration of iron chelating agent intake had positive correlation with their eGFR (r=0.506, p<0.001 and r=0.518, p<0.001, respectively). However, serum ferritin levels was not a predictor for renal function impairment.

CONCLUSION: Most of children with β-thalassemia major treated with iron chelating agent have normal renal function, nevertheless, decreased renal function is observed in few children. Highlighted, renal function examinations should be performed routinely as iron chelating agent administration is a long-term therapy in children with β-thalassemia major.

KEYWORDS: β-thalassemia major, renal function, serum ferritin levels, iron chelating agent

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Introduction

Thalassemia major is a condition in which imbalance globin-chain synthesis of globin affects the hemoglobin production, and therefore interferes with red blood cells production.(1) As one the highest frequency of β-thalassemia carrier in the world, South-east Asia has a major public health problem since elevation number of patients with severe HbH disease and fetus with Hb Barts hydrops foetalis.(2) Based on data from Indonesian Ministry of Health on 2007, the highest frequency of thalassemia was in Aceh (13.4%), followed by DKI Jakarta (12.3%), Sumatera Selatan (5.4%), and the lowest was in Lampung, Kalimantan Barat and Sulawesi Utara (0.1%). Out of 85 patients with β-thalassemia major in Sumatera Utara, the Department of Pediatrics, H. Adam Malik Hospital serves approximately 50 children with β-thalassemia major who receive regular blood transfusion.

As an inherited hematologic disorder, thalassemia has imbalance of α/β-globin chain that leads to insufficient

of hemoglobin synthesis and ineffective hematopoiesis. In correction of anemia, thalassemia, especially β thalassemia major as the most severe form, requires long-term blood transfusions. Those regular blood transfusions may increase event of iron overload because of no physiologic active mechanism for the excretion of iron.(3) Excess iron accumulates in various organs, like heart, spleen, and liver, hence leads to overproduction of free radicals which furthermore causes various organs damage. Unfortunately, patients can not increase iron excretions spontaneously as compensation for iron overload. Therefore, the excess iron in the body must be removed therapeutically, using namely iron chelating agents.(4-6)

Children with β-thalassemia major have been reported to develop abnormalities of renal function, such as high flow of renal plasma, low ability of concentrating urine, and acidosis of renal tubular.(7) Renal function in thalassemia patients may also affected by iron chelating agent therapy. (8-10) To date, there are no specific data regarding renal function among children with β-thalassemia major receiving iron chelating agent therapy in Sumatera Utara. The objective of this study was to assess the correlation of iron chelating agent with renal function among children with β-thalassemia major in Medan, Sumatera Utara, Indonesia.

Methods

Study Design

An observational analytic cross sectional study was conducted at Haji Adam Malik Hospital, Medan, from February to August 2019. All parents of children involved in this study signed an informed consent prior to enrollment of this study. Ethical clearance had been approved by ethical committee of Faculty of Medicine, Universitas Sumatera Utara – Haji Adam Malik General Hospital Medan (No. 301/TGL/KEPK FK USU-RSUP HAM/2019) in accordance with the principles of the Helsinki Declaration.

Subject Selection

The β-thalassemia major children aged 2-18 years old underwent regular blood transfusions and treated with iron chelating agent, were recruited. Subjects who received ≥8 units of packed red blood cells per year were defined as having regular blood transfusions. Subjects were treated with iron chelating agent, namely deferiprone or deferasirox. Due to the availability of the agents in our center, one subject may receive either deferiprone or deferasirox randomly, and may be administered interchangeably on behalf of their regular treatment. Deferiprone was prescribed as dose of 25 mg/kg body weight, three times daily and deferasirox was prescribed as dose of 20-40 mg/kg, once daily. None of the subject received deferoxamine as the infusion pump device was limited. Subject with renal function impairment and received combination therapy of iron chelating agents (consumption of deferiprone or deferasirox simultaneously in certain period of time) were excluded. Duration of disease is defined as the time between age of diagnosis established (not necessarily right after birth) to the time of enrollment in this study. Duration of iron chelating agent intake is defined as the time between the initiation of iron chelating agent intake to the time of enrollment in this study.

Renal Function Examinations

All subjects underwent renal function examinations including serum ureum and creatinine levels. The parameters were obtained along with extraction of blood specimen for routine complete blood count prior to subsequent transfusions (approximately two weeks relative to the last transfusion). Approximately 2 mL of venous blood sample was acquired for serum creatinine measurement. Serum creatinine was measured with Jaffe reaction using alkaline picrate. Serum sample was centrifuged with 1.500 rpm for 10 minutes to form supernatant and subsequently analyzed with colorimetric method. The primary outcome measuresment was estimated glomerular filtration rate (eGFR). Schwartz method was used to calculate eGFR (eGFR (mL/min/1.73 m^2) = constant (k) x height (cm)/ serum creatinine (mg/dL)). The constant factors (k) divided as follows: (1) <1 year old = 0.45; (2) 1-12 years old = 0.55; (3) female 13-21 years old = 0.55; and (4) male 13-21 years old = 0.70 (Schwartz formula). Renal function impairment, normal renal function, and hyperfiltration were defined as eGFR <90 mL/min/1.73 m^2, 90-140 mL/min/1.73 m^2, and >140 mL/min/1.73 m^2, respectively. Serum ferritin levels was divided into <2,000 ng/mL and >2,000 ng/mL.

Statistical Analysis

Descriptive statistics were conducted for the main characteristics of the subjects. The paired sample t-test was performed to evaluate for association of the two groups of serum ferritin levels with eGFR and serum creatinine levels. To evaluate the factors affecting eGFR and serum creatinine levels, we conducted Spearman correlation test. Significant statistical had been considered for p-values<0.05. This study was using SPSS Version 23.0 (IBM Corporation, New York, USA) for statistical analysis.

Table 1. Subjects' characteristics.

Variable	n = 45	Mean (SD)	Median (IQR)
Gender			
Male, n (%)	24 (53.3)		
Female, n (%)	21 (46.7)		
Patients' age, years			9 (6-14)
Serum hemoglobin levels, g/dL			7.0 (6.6 – 8.0)
Serum creatinine levels, mg/dL		0.43 (0.06)	
eGFR, mL/min/1.73m^2			
Decreased (in 2 patients)		74 (8.48)	
Normal (in 35 patients)		112.47 (13.25)	
Increased (in 8 patients)		156.27 (12.72)	
Duration of disease, years			3.1 (1.5 – 6.0)

Results

We obtained data from 45 subjects with β-thalassemia major admitted to the Pediatric Haematology ward in Haji Adam Malik Hospital, through·out 2018. The median age of the subject was 9 years old. All subjects were transfusion dependent and treated with iron chelating agents.

Out of 45 subjects, 35 subjects (77.7%) maintained normal eGFR, while 2 subjects (4.44%) had decreased eGFR, and 8 subjects (17.7%) had increased eGFR. The subject characteristics were described in Table 1. Serum ferritin levels of the subjects were classified into two groups, value of <2,000 ng/mL and ≥2,000 ng/mL. Our study showed composition of 24 (53.3%) male and 21 (46.7%) female. The median age of the subjects was 9 years old. The mean duration of iron chelating agent intake was 5 years. The median serum hemoglobin levels was 7.08 g/dL.

Table 2 described factors affecting eGFR and serum creatinine levels. None of these factors were significantly related to serum creatinine levels. The age of subjects and duration of iron chelating agent intake were positively correlated to eGFR (r=0.506, p<0.001 and r=0.518, p<0.001, respectively). Mewnwhile, Figure 1 showed the scatter plot of eGFR with the age of subjects, duration of disease, duration of iron chelating agent intake, and dose of iron chelating agent.

Table 3 described comparison between eGFR and serum creatinine levels to groups of serum ferritin levels. None of the group of serum ferritin levels had significant association to eGFR and serum creatinine levels (p=0.431 and p=0.605, respectively).

Discussion

This study revealed most of children with β-thalassemia major (77.7%) had normal eGFR, nevertheless, some of them had decreased eGFR (4.4%) and increased eGFR (17.7%). Our findings were in accordance with previous study which found normal eGFR in 140 children with β-thalassemia major.(11) In contrast, other study found

Table 2. Factors affecting eGFR and serum creatinine levels.

Variable	eGFR		Serum Creatinine Levels	
	r*	*p*	r*	*p*
Age	0.506	**<0.001**	0.458	**0.002**
Duration of disease	0.489	**0.001**	0.106	0.494
Duration of iron chelating agent intake	0.518	**<0.001**	0.408	**0.007**
Dose of iron chelating agent	0.339	**0.028**	0.299	0.055
Serum hemoglobin levels	0.042	0.785	-0.056	0.72

*Spearman correlation test.

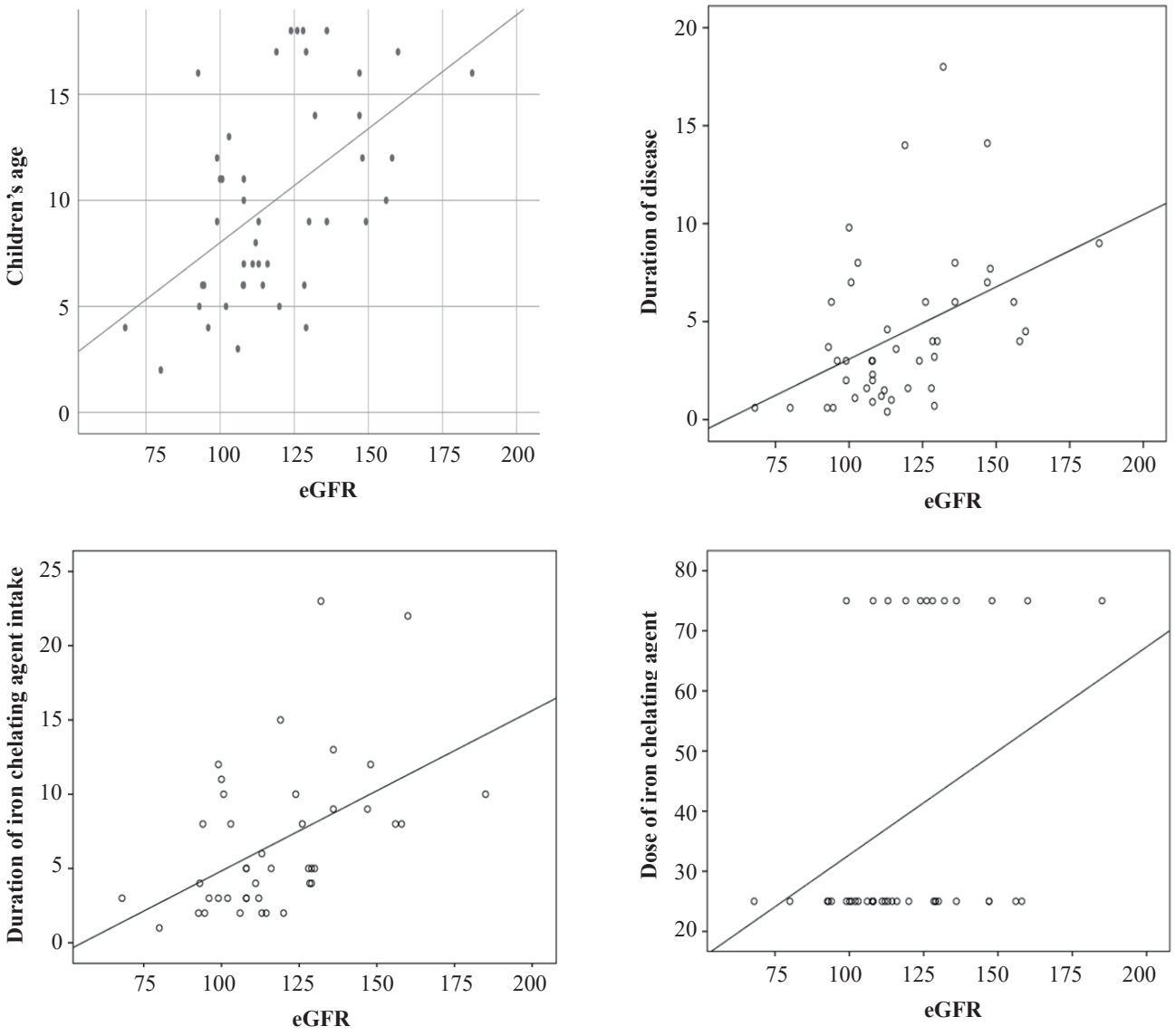

Figure 1. Scatter plot of eGFR with age of the children, duration of disease, duration of iron chelating agent intake, and dose of iron chelating agent.

hyperfiltration was common in patients with thalassemia. (12) This difference could be explained by the difference of measurement methods of serum creatinine levels. Serum creatinine clearance was then measured by 24-hour urine collection, while we estimated serum creatinine clearance by the Schwartz equation. Hyperfiltration could be a consequences of chronic anemia in children with β-thalassemia major, similar as in young children with sickle cell anemia.(13) The decrease in serum creatinine also may be associated with regular blood transfusion and bone marrow suppression.(12) Highlighted, in spite of the proportion of children with β-thalassemia major with decreased eGFR was relatively small (4.4%), this circumstances should be addressed properly, as it may lead to further devastating renal damage.

In this study, we revealed that age of the children and duration of iron chelating agent intake positively correlated with eGFR. In contrast, previous study found no significant correlation between age of the children and duration of iron chelating agent intake with eGFR.(14) Further studies to evaluate the effect of iron chelating agent administration are needed. Variation of serum hemoglobin levels might be associated with increased risk of decline eGFR. Therefore, it is important to maintain pre-transfusion levels of haemoglobin between 9.5-10.5 g/dL. Similar to our findings, other study found significant correlation between duration of iron chelating agent intake and renal tubular disease. Furthermore, impairment of renal function and proximal tubular dysfunction were found in children with β-thalassemia major. There was a correlation between

Table 3. Comparison of eGFR and serum creatinine levels to serum ferritin levels.

Variable	Serum Ferritin Levels		*p**
	<2,000 ng/mL	≥2,000 ng/mL	
eGFR, mL/min/1.73m^2, mean (SD)	0.41 (0.07)	0.43 (0.06)	0.605
Serum creatinine levels, mg/dL, mean (SD)	115.95 (26.69)	121.61 (19.99)	0.431

*Independent T-test

impairment of renal function with anemia, particularly in patients with hypertransfusion and iron chelation, especially deferoxamine, therapy.(15)

This study showed no correlation between serum ferritin levels to eGFR and serum creatinine levels. In accordance with this study, several studies showed serum ferritin levels was not a predictor for glomerular nor tubular renal disease.(12,16) It was then concluded that iron chelating agent could not be removed sufficiently therefore iron deposition and hemosiderosis may occur. (17) Serum creatinine levels do not reflect renal impairment because it may be interfered with factors unrelated to renal function, such as muscle mass, protein intake, inflammatory illnesses and hepatic diseases. Extensive studies are being conducted to investigate serum markers as predictor of renal function impairment, especially at an early stage.(18)

Some limitations of this study should be noted. First, we did not perform individual evaluation between types of iron chelating agents due to the availability of the agents in our center. Second, we did not utilize other markers aside from serum creatinine and eGFR to evaluate renal function. There are some markers with higher sensitivity and specificity for early detection of renal function. Nevertheless, in our local community setting, serum creatinine and eGFR are the most feasible markers nowadays to be utilized in community. Highlighted, renal function examinations should be performed routinely as iron chelating agent administration is a long-term therapy in children with β-thalassemia major. Further studies utilizing other markers to predict renal function impairment in early stage and long-term follow-up to investigate of the effect of iron chelating agent in renal function parameters are needed.

Conclusion

Most of children with β-thalassemia major treated with iron chelating agent have normal renal function, nevertheless, decreased renal function is observed in few children. Age of the children with β-thalassemia major and their duration of iron chelating agent intake are positively correlated with eGFR. Highlighted, renal function examinations should be performed routinely as iron chelating agent administration is a long-term therapy in children with β-thalassemia major.

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