



(RESEARCH ARTICLE)



The correlation between serum ferritin levels and impaired heart function in children with transfusion dependent thalassemia

Carrina Nenggar Dewanti *, I Ketut Alit Utamayasa and IDG Ugrasena

Department of Child Health, Faculty of Medicine, Universitas Airlangga / Dr. Soetomo General Hospital, Surabaya, Indonesia.

GSC Biological and Pharmaceutical Sciences, 2021, 16(02), 190–195

Publication history: Received on 11 July 2021; revised on 18 August 2021; accepted on 20 August 2021

Article DOI: <https://doi.org/10.30574/gscbps.2021.16.2.0239>

Abstract

Background: Paediatric patients with transfusion dependent thalassemia require regular lifelong red cell transfusions. Blood transfusions increase the risk of iron overload, which can lead to cardiac hemosiderosis. Serum ferritin can be a parameter for evaluating systemic hemosiderosis.

Objective: To evaluate the correlation between serum ferritin levels and impaired heart function in children with transfusion dependent thalassemia

Methods: A cross sectional study was conducted with transfusion-dependent thalassemia who attended a cardiology and hemato-oncology outpatient clinic from January to December 2018 and had undergone more than 10 transfusion periods. Serum ferritin levels were taken from the mean of 3 measurements before echocardiography. Echocardiography examination was performed by a cardiologist using a 3D Doppler tool to evaluate ejection fraction (EF), tricuspid annular plane systolic excursion (TAPSE) and E / A ratio by calculating the initial diastole (E wave) and atrial contraction (wave A). Data analysis used the Spearman correlation with $p < 0.05$.

Results: There were 45 children with a median age of 10 (2-17) years and had received a median of 18 (10-51) blood transfusions. The mean serum ferritin level was 4,321 (1,168-15,233) ng / mL. Blood transfusion frequency was associated with an increase in serum ferritin ($\rho = 0.74$, $P < 0.005$). From echocardiography examination, approximately 3/45 children had a feature of dilated cardiomyopathy. The mean value of EF 70 (SD 14.32), TAPSE 1.97 (SD 0.57) cm and an E / A ratio 1.68 (SD 0.46). Serum ferritin was negatively correlated with the ejection fraction ($\rho = -0.78$, $P < 0.001$), TAPSE ($\rho = -0.65$, $P < 0.001$) but positively correlated with the E / A ratio ($\rho = 0.67$, $P < 0.001$).

Conclusion: Paediatric patients with TDT have decreased cardiac systolic and diastolic function, and serum ferritin correlates with the decreased cardiac function.

Keywords: Transfusion Dependent Thalassemia; Impaired Heart Function; Serum Ferritin; TAPSE; E/A ratio

1. Introduction

Thalassemia are a group of congenital disorders of haemoglobin synthesis, which is characterized by mutations in the two globin chains alpha or beta and causing a disturbance in the balance of the globin chains [1]. Paediatric thalassemia case in Dr. Soetomo academic general Hospital reached 686 people within 5 years, and 80% of them were transfusion dependent thalassemia (TDT) patients. TDT is a terminology used in a group of thalassemia patients who require regular and lifelong blood transfusions to maintain optimal haemoglobin levels. The recurrent transfusions will cause

* Corresponding author: Carrina Nenggar Dewanti

Department of Child Health, Faculty of Medicine, Universitas Airlangga / Dr. Soetomo General Hospital, Surabaya, Indonesia.

complications of iron overload which will eventually lead to systemic iron accumulation (hemosiderosis). Iron begins to build up in target organs and causes progressive damage, including damage to the heart, liver, lungs, kidneys, and endocrine organs [2]. Cardiac hemosiderosis is the most serious complication of TDT, with a morbidity rate of 63.6% and a mortality rate of up to 71% [3]. Iron overload cardiomyopathy is the most common cause of impaired heart function in TDT patients with various clinical manifestations [4,5]. Serum ferritin levels are thought to have a correlation with impaired heart function due to cardiac hemosiderosis. Studies have identified a significantly lower risk of cardiac disease and death in at least two-thirds of cases where serum ferritin levels have been maintained below 2,500 µg/L [2,6]. Cardiac complications are difficult to avoid, but can be controlled with early screening methods and the use of adequate iron chelation therapy. Echocardiography is a non-invasive device that widely available, relatively inexpensive and easy to perform to detect impaired heart function in TDT patients [2,5]. This study aimed to evaluate the correlation between serum ferritin levels and impaired heart function in children with transfusion dependent thalassemia.

2. Methods

This is an analytic observational research using cross sectional design. Subjects were children under 18 years old with thalassemia, who attended cardiology and hemato-oncology outpatient clinics in Dr. Soetomo General Hospital. Samples were taken during January - December 2018. Total sampling was performed in this study, with 45 children who met the inclusion criteria. Inclusion criteria were thalassemia patients who had received transfusions more than 10 times per year, had serum ferritin data, and had undergone echocardiography examination. The exclusion criteria were patient with sepsis and using inotropic support. Informed consent was obtained from all individual participants included in the study. Serum ferritin examination was carried out in the clinical pathology laboratory in the Dr. Soetomo General Hospital. Serum ferritin levels were taken from the mean of 3 measurements before echocardiography. Echocardiography was performed within 1–2 months after the last serum ferritin measurement. Paediatric cardiologist using a 3D Doppler Echocardiography to assess cardiac dysfunction. Assessment of cardiac dysfunction is divided into impaired cardiac systolic and cardiac diastolic function. Cardiac systolic function was assessed using the ejection fraction (EF) and tricuspid annular plane systolic excursion (TAPSE) parameters. Cardiac diastolic function was assessed using the parameter E / A ratio by calculating the initial diastole (E wave) and atrial contraction (wave A). Data analysis used the Spearman correlation with p-value less than 0.05 was considered statistically significant. All the statistically significant results were analyzed by SPSS 17.0 software (IBM SPSS).

Ethical issues. Ethical clearance was obtained from the Ethics Committee of Dr. Soetomo General Hospital (ERC 0990 / KEPK / III / 2019). Parental written informed consent was obtained prior to data collection.

3. Results

Table 1 Baseline Characteristic

Characteristic	N (%)
Gender	
Boy	25 (55.6)
Girl	20 (44.4)
Age	
2 - < 5 years	11 (24.4)
5 - 12 years	20 (44.42)
> 12 - 18 years	14 (21.12)
Chelation Therapy	
Deferiprone	32 (71.1)
Deferasirox	7 (15.6)
Deferiprone + Deferoxamine	4 (8.9)
Deferasirox + Deferoxamine	2 (4.4)

Ferritin Serum	
≤ 10000 ng/mL	38 (84.4)
> 10000 ng/mL	7 (15.6)
Frequency of transfusion	
≤ 20 kali / tahun	29 (64.4)
> 20 kali / tahun	16 (35.6)

The baseline characteristics of the patients are presented in Table 1. Of the 45 TDT patients, 25 were boys, with the 5-12 year age group dominating the study subjects. Iron chelation monotherapy with deferiprone was the most widely used in 71% of subjects. Mean serum ferritin levels > 10000 ng / mL were found in 7 patients.

Heart functions were examined from echocardiography profile (Table 2). The mean value of EF, TAPSE, and E/A ratio were $70 \pm 14.32(\%)$, 1.97 ± 0.57 (cm), and 1.68 ± 0.46 respectively. Meanwhile there were 3 patients with cardiomyopathy based from EF value less than 45%. Table 3 express the correlation between serum ferritin and echocardiography profile that represented the cardiac function. Serum ferritin was negatively correlated with the ejection fraction ($\rho = -0.78$, $P < 0.001$), TAPSE ($\rho = -0.65$, $P < 0.001$) but positively correlated with the E / A ratio ($\rho = 0.67$, $P < 0.001$).

Table 2 Echocardiography profile

Echocardiography profile	Mean / Median (SD)
Ejection Fraction; EF (%)	70 ± 14.32
TAPSE (cm)	1.97 ± 0.57
E/A ratio	1.68 ± 0.46

Table 3 Correlation between serum ferritin levels and echocardiography profile

Echocardiography Profile	Ferritin Serum Value (Correlation Coefficient)	p
Ejection Fraction (EF)	- 0.787	0.000*
TAPSE	- 0.648	0.000*
E/A ratio	0.667	0.000*

4. Discussion

In this study, boy have higher prevalence than girl. Some studies showed the same result [1,7,8]. Other studies found that female are more common to thalassemia [9,10]. Thalassemia are inherited in an autosomal recessive pattern and does not involve sex chromosomes. It causes males and females to inherit the relevant gene mutations equally with no preference for gender [11]. Deferiprone monotherapy was mostly used in our hospital (71.7%), as well as in several other study centres. This is probably due to minimal side effects and drug availability [9,12]. Retrospective studies show that the use of deferiprone monotherapy provides a protective effect against heart function and increases the survival rate compared to routine deferoxamine therapy.[13,14] Deferiprone administration of 92mg / kg / day can reduce iron deposit levels in the heart by 2.2% in a period of 1 month. Deferiprone also has a significant effect on increasing LVEF compared to deferoxamine [15]. Our study found that 29 patients (64.4%) received transfusions 11-20 times a year, while the remaining 16 patients (35.6%) received transfusions more than 20 times per year. Several studies conducted on transfusion-dependent thalassemia patients showed that the average patient required transfusions of more than twice in a month, and more than 10 times per year [16,17]. Meanwhile, a local study conducted at the Thalassemia

Foundation in Banyumas district showed that the average patient had minimal blood transfusion once a month with a cumulative transfusion frequency more than twelve times / year [8].

The mean value of EF (%) in this study was 70 ± 14.32 . Several studies showed varied EF values in TDT patients, but on average, they showed a decrease in the mean EF when compared to controls who did not suffer from TDT.[18,19] EF describes the fraction of the volume of blood pumped by the heart in each contraction. EF is mostly used to assess left heart systolic function, and although rarely it can also be used to assess systolic function of the right heart to the pulmonary circulation [20]. Trends in the value of the left ventricular ejection fraction (LVEF) and dimensions of the heart are useful for evaluating therapy. LVEF can be an indicator of subclinical cardiotoxicity. Decreased heart function is a poor prognostic sign of ongoing treatment and is an indicator for intensification of therapy. If the LVEF value does not improve after adequate therapy, cardiomyopathy may be considered [21].

The right ventricle has a unique geometric shape, making it difficult to measure systolic function. TAPSE describes a shortened apex to basal fraction of the right ventricle, making it more specific and easier to use for measuring right ventricular systolic function than the EF parameter [22]. The normal value of TAPSE depends on age, but some experts formulate the mean normal value of TAPSE to be 2.3 ± 0.5 mm. The median TAPSE value in this study was 1.97 ± 0.57 mm. A TAPSE value of <16 mm in adults and <10 mm in children is an indication of systolic dysfunction [23,24]. The mean E / A ratio in this study was 1.68 ± 0.46 . The normal value of the E / A ratio in children 12-18 years is 1.88 ± 0.56 . [24] The E / A ratio describes the diastolic activity of the heart by measuring the flow of blood through the mitral valve using Doppler echocardiography. Wave E represents passive ventricular filling in the early diastolic phase (preload dependent) and wave A represents active ventricular filling in the late diastolic phase as a result of atrial contraction. A slowing E / A ratio <0.8 indicates impaired cardiac relaxation [24,25].

There was a significant correlation between serum ferritin and heart function profile (table 3). Echocardiographic parameters change with increasing levels of ferritin. Ferritin serum levels have a negative correlation with the EF value, in which the higher the ferritin level the lower the EF value ($r = -0.787$, $p = <0.05$). A study in Iran showed an association between serum ferritin levels and a significant reduction in EF values with $r = 0.3$ and $P = 0.05$ [26]. LVEF decreased significantly in thalassemia patients with high ferritin levels when compared to the control group who had normal ferritin levels [1]. Systolic dysfunction in the right heart can be seen from the decreasing TAPSE value and inversely proportional to the serum ferritin level ($r = -0.648$, $p = <0.05$). Studies in Italy found consistent results of TAPSE values < 15 mm with cardiac diastolic dysfunction, but no precise results on serum ferritin levels [27]. Hamdy et al compared TAPSE value in thalassemia patients with ferritin levels above and below 2000ng / mL, and found that the TAPSE value at ferritin levels > 2000 ng / mL was higher [28]. Diastolic dysfunction is expressed by the value of the E / A ratio, which is directly proportional to the serum ferritin level ($r = 0.667$, $p = <0.05$), in which the higher the ferritin level, the slower the E / A time. Studies in Greece show that ferritin levels have a significant correlation to the E / A ratio parameter [19].

We also found studies with different result from ours. Subroto et al. conducted a study on 62 thalassemia patients and found that there was no association between serum ferritin levels and impaired heart function [29]. A similar study conducted in Iran found that there was no correlation between echocardiography results and serum ferritin levels [30]. Meanwhile, research by Eghbali et al found that ferritin levels only correlated with the EF value, but not with the E / A ratio [26].

The limitation of this study is using a retrospective design with incomplete echocardiography record data. This study also did not evaluate the level of adherence to the use of iron chelation therapy. A larger sample size is expected to provide better result.

5. Conclusion

In paediatric patients with TDT there are decreased of cardiac function. There are significant correlation between serum ferritin levels and impaired cardiac systolic and cardiac diastolic function.

Compliance with ethical standards

Acknowledgments

The authors thanks to Dr. Soetomo Academic General Hospital Surabaya for supporting this study. The authors received no financial support for the research, authorship, and/or publication of this article.

Disclosure of conflict of interest

The authors declare no conflict of interest

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

- [1] Shivanna NH, Murthy R, Ramachandrapa GRH, Munirathnam G. Cardiac abnormalities in children with thalassemia major : correlation of echocardiographic parameters with serum ferritin levels. *Int J Contemp Pediatr.* 2016; 3: 12–5.
- [2] Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, editors. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Nicosia (CY): Thalassaemia International Federation. 2014.
- [3] Lekawanvijit S, Chattipakorn N. Iron overload thalassaemic cardiomyopathy: Iron status assessment and mechanisms of mechanical and electrical disturbance due to iron toxicity. *Can J Cardiol.* 2009; 25: 213–8.
- [4] Ladis V, Chouliaras G, Berdousi H, Kanavakis E, Kattamis C. Longitudinal study of survival and causes of death in patients with thalassemia major in Greece. *Ann N Y Acad Sci.* 2005; 1054: 445–50.
- [5] Said Othman KM, Elshazly SA, Heiba NM. Role of non-invasive assessment in prediction of preclinical cardiac affection in multi-transfused thalassaemia major patients. *Hematology.* 2014; 19: 380–7.
- [6] Olivieri N, Nathan D, MacMillan J, Wayne A, Liu P, McGee A, et al. Survival in medically treated patients with homozygous B-thalassemia. *N Engl J Med.* 1994; 331: 574–8.
- [7] Rodrigues A, Guimarães-Filho FV, Braga JCF, Rodrigues CSC, Waib P, Fabron-Junior A, et al. Echocardiography in thalassaemic patients on blood transfusions and chelation without heart failure. *Arq Bras Cardiol.* 2013; 100: 75–81.
- [8] Rejeki DSS, Nurhayati N, Supriyanto S, Kartikasari E. Studi epidemiologi deskriptif talasemia. *Kesmas Natl Public Heal J.* 2012; 7: 139.
- [9] Agouzal M, Quayou A, Benchechrone K, Khattab M. Characteristics of chelation therapy among beta-thalassemia patients in the North of Morocco. *Clin Rev Opin.* 2010; 2: 1-7.
- [10] Alpendurada F, Smith GC, Carpenter JP, Nair S V., Tanner MA, Banya W, et al. Effects of combined deferiprone with deferoxamine on right ventricular function in thalassaemia major. *J Cardiovasc Magn Reson.* 2012; 14: 1–10.
- [11] Weatherall DJ, Clegg JB, editors. The thalassaemia syndromes. 4th ed. Oxford: Wiley. 2001.
- [12] Goulas V, Kourakli-Symeonidis A, Camoutsis C. Comparative effects of three iron chelation therapies on the quality of life of greek patients with homozygous transfusion-dependent beta-thalassemia. *ISRN Hematol.* 2012; 1–8.
- [13] Anderson LJ, Westwood MA, Holden S, Davis B, Prescott E, Wonke B, et al. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. *Br J Haematol.* 2004; 127: 348–55.
- [14] Pepe A, Meloni A, Capra M, Cianciulli P, Prossomariti L, Malaventura C, et al. Deferasirox, deferiprone and desferrioxamine treatment in thalassemia major patients: Cardiac iron and function comparison determined by quantitative magnetic resonance imaging. *Haematologica.* 2011; 96: 41–7.
- [15] Pennell DJ, Udelson JE, Arai AE, Bozkurt B, Cohen AR, Galanello R, et al. Cardiovascular function and treatment in β -thalassemia major: a consensus statement from the american heart association. *Circulation.* 2013; 128: 281–308.
- [16] Shah N, Mishra A, Chauhan D, Vora C, Shah NR. Study on effectiveness of transfusion program in thalassemia major patients receiving multiple blood transfusions at a transfusion centre in Western India. *Asian J Transfus Sci.* 2010; 4: 94–8.
- [17] Abu Taha A, Yaseen A, Suleiman S, Abu Zenah O, Ali H, Abu Seir R, et al. Study of frequency and characteristics of red blood cell alloimmunization in thalassaemic patients: multicenter study from Palestine. *Adv Hematol.* 2019; 1-5.

- [18] Ibrahim MH, Azab AA, Kamal NM, Salama MA, Ebrahim SA, Shahin AM, et al. Early detection of myocardial dysfunction in poorly treated pediatric thalassemia children and adolescents: two Saudi centers experience. *Ann Med Surg.* 2016; 9: 6–11.
- [19] Papadopoulou-Legbelou K, Varlamis SG, Athanassiou-Metaxa M, Karamperis S, Malaka-Zafiriou A. Full resting echocardiographic study of left ventricle in children with β -thalassemia major. *Kardiologia.* 2009; 2: 132–8.
- [20] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2016; 37: 2129–200.
- [21] Davis BA, O'Sullivan C, Jarritt PH, Porter JB. Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major. *Blood.* 2004; 104: 263–9.
- [22] Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, et al. Guidelines and standards for performance of a pediatric echocardiogram: a report from the task force of the pediatric council of the american society of echocardiography. *J Am Soc Echocardiogr.* 2006; 19: 1413–30.
- [23] Kjaergaard J, Petersen CL, Kjaer A, Schaadt BK, Oh JK, Hassager C. Evaluation of right ventricular volume and function by 2D and 3D echocardiography compared to MRI. *Eur J Echocardiogr.* 2006; 7: 430–8.
- [24] Tissot C, Muehlethaler V, Sekarski N. Basics of functional echocardiography in children and neonates. *Front Pediatr.* 2017; 5: 1–13.
- [25] Bornauun H, Dedeoglu R, Oztarhan K, Dedeoglu S, Erfidan E, Gundogdu M, et al. Detection of early right ventricular dysfunction in young patients with thalassemia major using tissue doppler imaging. *Iran J Pediatr.* 2016; 26: 1-9.
- [26] Eghbali A, Taherahmadi H, Bagheri B, Nikanjam S, Ebrahimi L. Association between serum ferritin level and diastolic cardiac function in patients with major β -thalassemia. *Iran J Pediatr Hematol Oncol.* 2015; 5: 83–8.
- [27] Mancuso L, Vitrano A, Mancuso A, Sacco M, Ledda A, Maggio A. Left ventricular diastolic dysfunction in β -thalassemia major with heart failure. *Hemoglobin.* 2018; 42: 68–71.
- [28] Hamdy AM, Zein El-Abdin MY, Abdel-Hafez MA. Right ventricular function in patients with beta thalassemia: relation to serum ferritin level. *Echocardiography.* 2007; 24: 795–801.
- [29] Subroto F, Munthe B, Advani N, Firmansyah A. The correlation between ferritin level and cardiac dysfunction in patients with thalassemia. *Paediatr Indones.* 2003; 43: 24–7.
- [30] Shahmohammadi A, Davari N, Aarabi Y, Meraji M, Tabib A, Mortezaeian H. Echocardiographic assessment of cardiac involvement in patients with thalassemia major: evidence of abnormal relaxation pattern of the left ventricle in children and young patients. *Iran Hear J.* 2006; 7: 1–6.