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Original Article

Comparison of cardiac dysfunction in thalassemia major patients using deferoxamine or deferiprone as an iron-chelating agent

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Abstract

Background In thalassemia major (TM) patients, major mortality is due to cardiac hemosiderosis. Several types of iron chelating agent available recently are given to overcome this problem

Objective To compare cardiac dysfunction in thalassemia major patients who used subcutaneous deferoxamine (DFO) to those who used oral deferiprone (DFP) as an iron-chelating agent.

Methods This cross-sectional study was held at the Thalassemia Center, Department of Child Health-Cipto Mangunkusumo Hospital (DCH-CMH), Jakarta. We included TM patients aged 10-18 years with a mean pre-transfused hemoglobin level of ≥7 g/dL in the prior year, and who had used DFO or DFP for at least 1 year with good compliance, at a standard dose of DFO at 40-60 mg/kg/day for 5 days a week or DFP at 50-100 mg/kg/day. We excluded TM patients with congenital heart disease or overt heart failure. Trans-thoracal echocardiography was performed at the Integrated Cardiac Service, CMH by a pediatric cardiologist using the conventional method and tissue Doppler imaging (TDI) consecutively, and within 2 weeks of the subject's receiving a packed red blood cell (PRBC) transfusion. The 57 TM subjects consisted of 19 DFO users and 38 DFP users.

Results In our subjects, diastolic dysfunction was more commonly seen than systolic dysfunction, especially moderate diastolic dysfunction. In the DFO group, diastolic dysfunction only was detected in 3/19 subjects, systolic dysfunction only in 1/19 subjects, and both diastolic and systolic dysfunction in 15/19 subjects. None of the DFO users had normal cardiac function. In the DFP group, diastolic dysfunction only was seen in 6/38 subjects, and both diastolic and systolic dysfunction in 30/38 subjects, while 2/38 subjects had normal cardiac function.

Conclusion Diastolic and/or systolic dysfunction was detected in the majority of subjects, but with preserved global cardiac function. We found that cardiac dysfunction was not significantly different in the two iron chelator groups. For all subjects, diastolic dysfunction was seen in 89% of cases, while systolic dysfunction was detected in 77% of cases. **[Paediatr Indones. 2012;52:272-9]**.

Keywords: *thalassemia major, deferoxamine, deferiprone, diastolic dysfunction, systolic dysfunction, conventional echocardiography, TDI*

Thalassemia is the most common genetic disorder worldwide.[1] Chronic hemolytic anemia forces TM patients to depend on life-long transfusion therapy for their survival.[2] Mortality in TM is mainly (up to 71%) caused by cardiac hemosiderosis.[3] Cardiac dysfunction, which leads to cardiomyopathy, mostly begins in the second decade of life.[2,4-6] Subclinical cardiac iron deposition is typically silent for many years. Progressive deterioration occurs rapidly by the time

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heart failure manifests clinically. High mortality due to cardiac hemosiderosis suggests that the condition is not recognized until the advanced stage of the disease. By that time it is too late for effective intervention.[6]

Regular and adequate iron-chelation therapy can prevent and improve cardiac dysfunction in TM patients.[7-8] Several iron-chelating agents are available, but controversies remain on which iron-chelating agents better preserve cardiac function.[7,9-17] DFP, as the world's first oral iron-chelating agent, has been used widely at the Thalassemia Center, DCH-CMH since 2007, while subcutaneous DFO as the world's first iron chelating agent has been used since 1987.[18] DFO is a hexadentate chelator and has an excellent affinity to plasma free iron. DFP is a bidentate chelator with a lower molecular weight than that of DFO (only 1/3 that of DFO). DFP's lipophilic nature allows it to more easily penetrate cells to bind intracellular free iron.[9-10]

The gold standard tool for detecting cardiac hemosiderosis in TM patients are T2* MRI images.[19-22] Since T2* MRI is costly and not widely available, echocardiography remains the preferred method of evaluation.[23-25] In conventional echocardiography, signals are from transmitral blood flow, while in TDI, signals are from myocardial wall movement.[26-28] Aypar *et al*.[29] found that pulsed-wave TDI had high sensitivity and specificity when correlated with T2* MRI in predicting myocardial siderosis in TM patients with normal systolic function.

The objective of this study was to compare the proportion of cardiac dysfunction in TM patients who had used subcutaneous DFO to those who used oral DFP as iron-chelating agents. DFP subjects were expected to have fewer echocardiographic abnormalities than DFO subjects.

Methods

This cross-sectional study was conducted at the Thalassemia Center, DCH-CMH, Jakarta, from March to May 2011. We included TM patients aged 10-18 years with a mean pre-transfused hemoglobin level of ≥7 g/dL in the past year, and who had used DFO or DFP for at least 1 year with good compliance, at a standard dose of DFO 40-60 mg/kg/day for 5 days a week or DFP 50-100 mg/kg/day. TM patients with congenital heart disease or overt heart failure were excluded. Trans-thoracal echocardiography was performed with informed consent at the Integrated Cardiac Service, CMH using a General Electric Vivid-7 (1.5 – 4 MHz transducer) by a pediatric cardiologist using conventional and TDI methods consecutively, and within 2 weeks of PRC transfusion. The required sample size was calculated by hypothesis testing against a two proportion formula (α=5%, β=20%, P_1-P_2=20%, n=35 for each group).[30] This study was approved by the Ethics Committee of the University of Indonesia Medical School. Data was analyzed using SPSS for Windows version 11.5.

In this study, only left heart function was assessed, since left-sided heart failure is more common than right-sided heart failure in young populations, and five-fold more common than right-sided heart failure in TM patients.[31] Conventional echocardiography parameters were used, including ejection fraction (EF, %) to represent systolic function and E/A ratio to describe diastolic function. The TDI parameters used were Sa (myocardial velocity in cm/s during systole), Ea (myocardial velocity in cm/s during early diastole), and Aa (myocardial velocity in cm/s during late diastole), all of which were taken at the mid-septal and mid-lateral left ventricular locations.[32-37]

In the TDI method, systolic dysfunction was determined based on receiver operating characteristic (ROC) curve of EF ≤ 55% against mid-septal Sa < 8.5 cm/s (sensitivity 83%, specificity 43%) or mid-lateral Sa < 10 cm/s (sensitivity 83%, specificity 29%) in all subjects.

The presence of systolic dysfunction was determined by either low EF or low Sa. Combined echocardiography parameters could not be used to determine grade of systolic dysfunction.

In the TDI method, diastolic dysfunction cut-off point criteria was based on Ea value, which correlated with abnormal T2* MRI as the gold standard in predicting cardiac hemosiderosis in a study by Aypar *et al*. Mid-septal Ea < 13 cm/s had 100% sensitivity with 92% specificity, while mid-lateral Ea < 20 cm/s had 100% sensitivity with 83% specificity.[29]

We determined the presence of diastolic dysfunction by one of two ways:

1. Single parameter: either abnormal E/A ratio or low Ea

2. Combined parameters: high E/Ea ratio

Grading of diastolic dysfunction was further determined by E/Ea ratio and E/A ratio as shown in **Table 1**.

Results

A total of 57 TM subjects were recruited; there were 19 subjects in the DFO group and 38 subjects in the DFP group. **Table 2** describes the subjects' characteristics of both groups.

The cardiac dysfunction test results of the left side of the heart by iron chelator groups is described in **Table 3** and **Table 4**.

The majority of subjects had both diastolic and systolic dysfunction (45/57 total subjects), while 9/57 total subjects had diastolic dysfunction only, 1/57 total subjects had systolic dysfunction only, and only 2/57 total subjects had normal cardiac function. In this study, the proportion of subjects with subclinical cardiac dysfunction were not significantly different between the DFO and DFP groups.

Table 1. Cardiac dysfunction criteria based on echocardiography findings

	Diastolic dysfunction	Systolic dysfunction
Conventional echocardiography	E/A ratio < 1.43 or > 2.33	EF ≤ 55%
TDI	Mid-septal Ea < 13 or Mid-lateral Ea < 20 (cm/s) Septal or lateral E/Ea > 8	Mid-septal Sa < 8.5 or Mid-lateral Sa < 10 (cm/s)
Combination methods[37,39-41] (conventional and TDI)	**Grading of diastolic dysfunction**[37,39-41]**:** Mild dysfunction (impaired relaxation): E/Ea < 8 with E/A < 1.43 Moderate dysfunction (pseudonormal pattern): E/Ea > 8 with normal E/A Severe dysfunction (restrictive pattern): E/Ea > 8 with E/A > 2.33	

Table 2. Demographic and clinical characteristics of subjects by iron-chelator group

Characteristics	Chelator groups		Total (n=57)
	DFO (n=19)	DFP (n=38)	
Sex, n			
Male	5	20	25
Female	14	18	32
Nutritional status* , n			
Malnourished	15	30	45
Normal weight	4	5	9
Overweight	0	3	3
Type of thalassemia major, n			
- β homozygote	10	22	32
- β/HbE	9	16	25
Mean duration of illness, n			
≥10 years	14	27	41
< 10 years	5	11	16
Mean serum ferritin within most recent year, n			
≥2500 ng/mL	18	28	46
< 2500 ng/mL	1	10	11

* measured by mid-upper arm circumference

Table 3. Cardiac dysfunction by iron chelator group based on echocardiography modality

	Echocardiogram		P value	RR	CI 95%
	Dysfunctional	Normal			
Conventional echocardiography					
Diastolic function					
DFO	7	12	0.922	1.08	0.52 – 2.25
DFP	13	25			
Systolic function *)					
DFO	1	18	0.652	0.40	0.05 – 3.19
DFP	5	33			
TDI					
Diastolic function *)					
DFO	17	2	0.703	1.10	0.88 – 1.36
DFP	31	7			
Systolic function *)					
DFO	16	3	0.510	1.14	0.87 – 1.50
DFP	28	10			
Combined evaluation methods					
Diastolic function *)					
DFO	16	3	0.389	0.91	0.74 – 1.13
DFP	35	3			

Note : *) Fisher's exact test

Table 4. Proportion of subjects with cardiac dysfunction by iron chelator group

	DFO (n=19)		DFP (n=38)		P value
	n	(%)	n	(%)	
Normal	0	(0)	2	(5)	0.548
Diastolic dysfunction only	3	(16)	6	(16)	1.000
Systolic dysfunction only	1	(5)	0	(0)	0.333
Diastolic and systolic dysfunction	15	(79)	30	(79)	1.000

Discussion

In our study, female subjects were almost equal to male subjects (32 vs 25 subjects). However, among male subjects, the ratio of DFP to DFO use was disproportionate at 4:1. In general, the oral chelator was preferred over the subcutaneous chelator, because the oral route is more practical, more comfortable, non-invasive and not painful. DFP requires no special administration procedure nor restriction of daily activities. Patients' compliance to the oral chelator was better than that of the subcutaneous chelator, hence there were fewer DFO users.

The mean ages for the DFO and DFP groups were similar: 13.9 (SD 2.3) years and 14 (SD 2.3) years, respectively. Most subjects (41/57) had suffered from thalassemia for more than 10 years. Duration of illness in each DFO group ranges 5.3 – 16.4 years, while that of the DFP group was 4.3 – 17.8 years. Longer duration of illness and and greater number of PRBC transfusions led to a higher risk of transfusional hemosiderosis. Serum ferritin in ranges within the most recent year among DFO subjects was 1663 – 11303 ng/mL, while in DFO group was 1005 – 9906 ng/mL. The majority of subjects, regardless of iron-chelating agent used, had severe iron overload (mean serum ferritin of ≥ 2500 ng/mL). A previous study by Silvilairat *et al*.[42] reported that increasing E/Ea ratio reflects severe cardiac iron overload. They also showed that cardiac function in TM subjects could be preserved if serum ferritin was < 2500 ng/mL. However, we found that nine subjects with mean serum ferritin of < 2500 ng/mL (1 DFO, 8 DFP) already had cardiac abnormalities. The lowest serum ferritin in this study was 1005 ng/mL, in a 10.8 year-old boy who had ß-major thalassemia for 8.3 years and had used DFP in the last 1.4 years. He had received DFO

before it was replaced by DFP. He had severe diastolic dysfunction with normal EF. Bosi *et al.*[43] reported a weak negative correlation between serum ferritin and EF. Serum ferritin, as an acute phase reactant, could be elevated due to inflammation, malignancy, or liver diseases.[44] Serum ferritin reflects only 1% of total body iron.[3] Serum ferritin cannot reliably predict cardiac iron burden. Piga *et al.*[45] showed that thalassemia patients with cardiac dysfunction had high transferrin saturation (> 70%) and high non-transferrin bound iron (NTBI) levels, compared to thalassemia patients without cardiac dysfunction.

The DFO group had used DFO for a longer duration than DFP subjects had used DFP. Ranges duration of DFO use was 1 – 11.3 years, while median duration of DFP use was 1 – 3.7 years. In the Thalassemia Center at DCH-CMH, DFO had been used since 1987, 20 years prior to DFP use.[18] In our study, the mean dose of subcutaneous DFO was 42.8 (SD 4.4) mg /kg/day for 5 days a week, while mean dosage of oral DFP was 70.2 (SD 7.6) mg/kg/day within the most recent year.

Both iron chelators have short half-lives (DFO 20 minutes and DFP 2-3 hours), therefore, patients compliance is crucial to prevent and manage cardiac dysfunction due to iron overload.[10] Piga *et al.*[11] and Delea *et al.*[46] reported that patients had better compliance with DFP than with DFO use. We also found that patient compliance was slightly better with the oral chelator than the subcutaneous chelator, although this difference was not statistically nor clinically significant (average DFO compliance 85.8 (SD 6.5)% and average DFP compliance 87.3 (SD 6.1)%. TM patient education about their illness and its long-term complications, including cardiac hemosiderosis, is needed to motivate them to comply in taking the iron-chelating agents.

In our subjects, cardiac dysfunction detected by echocardiography could have been diastolic, systolic, or a combination of both diastolic and systolic dysfunction. Conventional echocardiography revealed normal global cardiac function in the majority of subjects. However, the TDI method revealed significant cardiac dysfunction in the majority of subjects. Diastolic dysfunction was found in 48/57 (84%) of all subjects, while systolic dysfunction was detected in 44/57 (77%) of all subjects. We found that the presence of either diastolic or systolic dysfunction was not significantly different between the two groups (all P values > 0.05). Low EF of ≤ 55% was found in only 11% of the subjects (1 DFO and 5 DFP subjects). In both chelator groups, diastolic dysfunction was more commonly seen than systolic dysfunction.

A decrease in the regional myocardial wall velocity was typically found before any signs and symptoms of overt heart failure. Hence, TDI may be beneficial in early detection of regional abnormalities before global cardiac dysfunction occurs. Another benefit of TDI is in estimating the left ventricle end diastolic pressure (LVEDP) by E/Ea ratio. An increase in LVEDP is an early marker of diastolic dysfunction. An E/Ea ratio > 8 correlates with an elevation of LVEDP, according to Ommen *et al.*[47] who correlated direct measurement of LVEDP through an invasive catheterization procedure and E/Ea ratio by echocardiography. An increase in E/Ea ratio has been correlated to an increased clinical risk of heart failure.[28]

Iron deposition may trigger heart failure in TM patients. Iron overload in thalassemia is due to ineffective erythropoiesis, peripheral hemolysis, and an increase in iron absorption through the gastrointestinal tract, but the main cause is repetitive blood transfusions. Each PRBC unit contains 200-250 mg of iron. Repetitive transfusions saturate the body's transferrin, impairing its ability to bind iron. Iron toxicity occurs when free oxygen radicals are produced from free iron, the most toxic form of iron. Reactive oxygen species (ROS) cause perioxidative damage to cell structures, apoptosis of cardiomyocytes, and eventually cardiac dysfunction.[2,19]

In our study, diastolic dysfunction was more commonly seen than systolic dysfunction, similar to several other thalassemia studies[48-52] in which left ventricle diastolic dysfunction usually preceded the onset of systolic dysfunction. Diastolic dysfunction in our subjects was classified as mainly moderate dysfunction (33/57), characterized by "normal" E/A ratio. This "normal" E/A ratio in moderate diastolic dysfunction was a pseudo-normal pattern, because E/Ea ratio was increased when measured by the combined methods. Conventional echocardiography could not be used alone to detect moderate diastolic dysfunction. TDI was needed to confirm all the "normal" E/A ratios found by the conventional method, hence leading to different echocardiogram interpretations.

In the DFO group, diastolic dysfunction only was detected in 3/19 subjects, systolic dysfunction only in 1/19 subjects, and both diastolic and systolic dysfunction in 15/19 subjects. No DFO users had normal cardiac function. In the DFP group, diastolic dysfunction only was seen in 6/38 subjects, both diastolic and systolic dysfunction in 30/38 subjects, while 2/38 subjects had normal cardiac function. The occurrence of cardiac dysfunction, diastolic or systolic, between the two iron-chelator groups were not significantly different (all P values were > 0.05).

We had expected less cardiac dysfunction in the DFP group than in the DFO group, but this was not the case. One reason could be that the majority of DFO users had changed to DFP use after its introduction in the Thalassemia Centre in 2007. According to data from the Thalassemia Center, from 2007 – 2011 about 65% of the thalassemia patients aged 10-18 years changed their chelating agent from DFO to DFP.[18] It is possible that subjects' cardiac dysfunction occured before the change in iron chelators. Furthermore, subclinical cardiac dysfunction may occur before patients enter their second decade of life, but we only recruited TM subjects aged 10-18 years, and grouped them according to the chelator they had taken by in the year prior to the study.

Maggio *et al.*[15] explained that thalassemia patients have individual sensitivities to oxidative damage in their heart tissue due to iron overload. Differences at molecular level and in immunogenetic mechanisms influence the body's resistance to iron toxicity.

The majority of subjects in our study had significant subclinical cardiac dysfunction. Early recognition of these abnormalities before obvious clinical manifestations are seen is important in order to intervene earlier. Optimizing chelation therapy could reverse these abnormalities as much as possible in order to gain better quality of life and increase patients' survival rates.

Since this study was not longitudinal, all factors that might interact and influence the occurrence of cardiac dysfunction, as well as a cause-result relationship could not be explained extensively. Ideally, to determine which chelating agent is superior for protecting cardiac function, a longitudinal study must be done with all participants observed from the first time they receive chelation therapy, at a certain standard dosage, and then monitored regularly until they enter the second decade of life without any change in chelator type. In addtion to the relatively small sample size, especially in the DFO group, compliance levels were assessed only by interviewing subjects and their parents, which may be subject to recall bias.

In conclusion, diastolic and/or systolic dysfunction was detected in the majority of TM subjects, but with preserved global cardiac function. Cardiac dysfunction between the iron chelator groups was not significantly different. Among all thalassemia major patients diastolic dysfunction was seen in 89% of cases, while systolic dysfunction was detected in 77% of cases.

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