Original Article

Combined Therapy with Deferiprone and Desferrioxamine as Compared to Desferasirox on Ventricular Function in Thalassemia Major Patients

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Abstract

Background

Myocardial iron overload is the leading cause of death in patients with beta-thalassemia major. Combined therapy with deferiprone(DFP) and desferrioxamine (DFO)were suggested to be more effective than deferasirox(DFX) for removing heart iron. Deferasirox has recently been made available, but its long-term efficacy on cardiac function has not yet been established. Our study aimed to compare the effectiveness of deferiprone and desferrioxamine with deferasiroxon ventricular function in thalassemia major patients.

Materials and Methods

In this clinical trial study,72 thalassemia major (TM) patients were randomised to receive either deferiprone combined with desferrioxamine and deferasirox ,and thencardiac functions were evaluated. Data were analysed for left ventricular ejection fractions(LVEF)at baselinebyechocardiograpy, following 12 months of treatment.

Results

72 TM patientswere enrolled in this study lasting 12 months, 36 TMwere placed on DFP/DFO (DFP,50–86 mg/kg body weight; DFO, 24–52 mg/kg body weigh), 36 received DFX (range 18–40 mg/kg body weight). In 36 patients receiving combined therapy, left ventricular ejection fraction increased from 59.3+/-5.7% to 63.7+/-5.1% (p=0.001) over 12 months [baseline LVEF values 56-61%]. Deferasirox showed no change in LVEF (p = 0.93).We found improvement of left ventricular ejection fractionsin the deferiprone combined with desferrioxamine versus the deferasirox group (P = 0.008).

Conclusion

The patients treated with combined therapy with deferiprone and desferrioxamine showed better systolic ventricular function compared to the patients treated with deferasirox. The patients treated with combined therapy with deferiprone and desferrioxamine showed better systolic ventricular function compared to the patients treated with deferasirox.

Keywords

beta- thalassemia, deferiprone , deferasirox

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Introduction

Thalassemia major is an inherited hemoglobin disorder resulting in chronic hemolytic anemia and requires frequent blood transfusion (1). Disease prognosis has been modified with regular blood transfusion and iron chelation therapy. Transfusion therapy, together with elevated gasterointestinal absorption of iron, determines iron overload, which causes most of the mortality and morbidity associated with the disease (2). Cardiac failure and sudden death, the latter probably is due to arrhythmias, remain the major causes of death in β-thalassaemia major patients. Iron toxicity in biological system is believed to be associated with its ability to catalyze the generation of free radicals (3). The incidence of iron overload cardiomyopathy ranges between 11.4 and 15.1% in β-thalassaemia patients (2). Blood transfusions is a common standard therapy for patients with β-thalassaemia major (TM) and prevent death, but although clinical status and short term survival improveed, each unit of blood contains about 200-250 mg of iron which the body cannot eliminate, which leads to long term iron accumulation. Patients treated only with blood transfusions may die in the second or third decades of life due to complications of iron overload, in particularly heart failure (3,4). Myocyte damage is related to the production of reactive oxygen species (ROS) formed as levels of labile iron rise, which cause oxidative damage to membranes and mitochondrial respiratory chain enzyme dysfunction (5,6). Chelation therapy can reduce tissue iron levels and the incidence of cardiac complications, but patients at risk need to be accurately profiled for appropriate treatment. Therefore cardiac disorders related to ventricular failure are the most frequent cause of death in thalassemia major patients (7). Desferrioxamine was the first iron chelating agent for clinical use and became standard therapy in the 1970s. It is a large positively charged lipophobic molecule, and is poorly absorbed by the digestive system with a short plasma half life(8, 9). It is therefore administered subcutaneously using a portable syringe system usually overnight typically 5 times per week. This therapy can be very problematic with poor compliance, and a number of factors may be resulted with long-term cardiac iron accumulation (10). The second clinical iron chelator was deferiprone, which is a much smaller neutrally charged lipophilic molecule which allows good gastrointestinal absorption and cellular access (11, 12). The plasma half life is longer allowing oral administration with three doses per day. Direct comparison trials showed that deferiprone combined with desferrioxamine has greater efficacy than deferasirox for reducing myocardial iron loading and improving left ventricular (LV) systolic function (13,14). At present, a common method to detect heart failure in these patients is a measurement of the left ventricular ejection fractions (LVEF) through M-mode echocardiography (15). Our hypothesis was that deferiprone combined with desferrioxamine would improve LV function more than deferasirox.

Materials and Methods

Among 90 major beta thalassemia patients, 18 patients were excluded because of Hepatitis B and cardiac or renal failure. As a result, 72 patients (41 males, 31 females) with major beta thalassemia were randomly selected between 2011 and 2012 for this clinical trial study in Yazd thalassemia center. Inclusion criteria included LVEF greater than 50% based on the lower normal limit for non-anemic subjects from the age 4-31 Y/O. Seventy two thalassemia major (TM) patients were randomised to receive either deferiprone combined with desferrioxamine (36 patients) or deferasirox (36 patients). The mean administered dosages of the three chelators were: 1) deferasirox 26±6.3 mg/kg body weight per day (range 18–40

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mg/kg body weight per day); 2) deferiprone 72±10 mg/kg body weight (range 50–86 mg/kg body weight per day), divided into three doses per day; 3) desferrioxamine 30±9 mg/kg body weight/infusion via subcutaneous route on 3–7 days per week (range 24–52 mg/kg body weighs).The patients were visited regularly each 8 weeks to 12 months and their EF, and probably drug's side effects were determined. M-mode echo-cardiography also was done to evaluat left ventricular fraction by ejection fraction before and after intervention. Echocardiography was performed by a pediatric cardiologist. Ejection fraction was estimated from the parasternal long-axis M-mode measurement according to ejection fraction were compared before and after aggressive therapy. In addition , the relation between systolic function changes, age and sex were evaluated.

Statistical Analysis

Collected datas were expressed as mean standard deviation, and data were analyzed using Paired T-test, Student T-test by running SPSS software version 16. $p < 0.05$ was considered as statistically significant.

Results

Seventy two patients (41 males and 31 females), aged 4-31 Y/O, with thalassemia major were entered in the present study.Thirty six patients were placed on DFP/DFO (DFP, 50–86 mg/kg body weight; DFO, 24–52 mg/kg body weighs), thirty six received DFX (range 18–40 mg/kg body weight). The patients were randomly allocated into two groups. Demographic characteristics of patients are shown in table 1. No significant differences in gender (p-value=0.1) and age(p-value=0.09) were observed between two groups. In the current analysis, to summarise, in 36 patients received combined therapy, left ventricular ejection fraction increased from 59.3+/-5.7% to 63.7+/-5.1% (p=0.001) over 12 months [baseline LVEF values 56-61%], it was shown significant difference. For the patients on deferasirox therapy(36 patients), the changes in LV parameters from baseline to 12 months showed no significant difference (60.0% at baseline and 60.9% at 12months p = 0.93) that are shown in table 2. The response in the 2 treatment arms for LVEF showed a significant improvement for patients treated with deferiprone combined with desferrioxamine. However it was not seen with deferasirox (12-month difference between drugs $p<0.05$). The deferiprone combined with desferrioxamine group showed significantly higher left ventricular ejection fraction than the deferasirox groups. Although none of the patients suffered from decompensated heart failure (HF).

Table 1:Demographic caracteristics of the two groups

Caracteristics		Deferiprone&Desferrioxamine	Deferasirox	p-value
Age(year)				
	Number	36	36	**0.09**
	Mean	21.11	18.4	
	SD	7.07	6.37	
Sex				
	Male(Number)	24(66.6%)	17(47.2%)	**0.1**

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Female (Number)	12(34.2%)	19(52.7%)

Groups	Baseline	12 months	p-value
Deferiprone&Desferrioxamine	59.3 ± 5.7	63.7 ± 5.1	0.000
Deferasirox	60 ± 5.1	60.9 ± 4.6	0.93
p.value	0.79	0.79	

Table 2: LVEF parameters at baseline, 12 months (mean ± SD) in the 2 treatment arms

Discussion

Major beta thalassemia is a genetic disorder in which there is a progressive iron overload in various organs, leading to death in early adulthood. This iron overload occurs as a result of increased intestinal absorption and frequent blood transfusion needed for these patients (14). Cardiac muscle is one of the organs affected by iron overload. Cardiac biopsies revealed the presence of disrupted myocytes showing loss of myofibers, dense nuclei, and a variable number of pleomorphic electron dense (15). Left ventricular involvement was reported. Necropsy studies showed that both ventricles are equally affected with hypertrophy and myocyte disruption (16). LVEF is an important predictor of outcome in dilated cardiomyopathy, which is both independents of incremental to LV EF (17). The predictive value of LV function has also been shown in congenital heart disease, (18,19) chronic systolic dysfunction, (20) and ischemic heart failure, (21) with LVEF being shown to be an independent predictor of outcome (22,23). Accordingly, the effects of myocardial iron loading on LV function may be important in thalassemia patients. Anderson et al confirmed that siderotic heart failure is often reversible with intravenous iron chelation with desferioxamine (24). Origa et al showed that there was significant improvement in LVEF (increase) with deferiprone combined desferrioxamine therapy (25). Pepe et al founded that Oral once-daily chelatordeferasirox has recently been made commercially available, but its long-term efficacy on cardiac iron and function has not yet been established (26). There is a few data relating LV function changes with the iron chelators, but a recently published abstract relating to a longitudinal trial on the efficacy of deferasirox in myocardial siderosis, showed a significant improvement in myocardial iron levels with an improvement in RVEF at 1 year, but no change in LV function at 1, (27) 2 and 3 (28) years of follow up. It is possible that the LV response is an early signal of myocardial iron clearance and filling pressure improves. Daaret al showed that the improvement in the LVEF may contribute to the improved cardiac outcomes seen with deferiprone combined

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with desferrioxamine (29). Waldes-Cruz et al demonstrated abnormalities of left ventricular systolic and diastolic function, even in asymptomatic children with β thalassaemia, using computer assisted echo studies (30). Others have reported early cardiac dysfunction in asymptomatic β thalassaemic patients with chronic iron overload, using stress radionuclide angiography. The stress induced alterations of left ventricular systolic performance showed a correlation with the total amount of blood transfusion in these patients. Even in patients with few blood transfusion units, an abnormal response of the left ventricular ejection fraction to exercise was found, while the hemoglobin concentration was not predictive of left ventricular performance (31). In the current study, we showed that major beta thalassemia patients treated with combined therapy with deferiprone and desferriox, result in better systolic ventricular function compared to oral deferasirox treatment. Ggroups analysis showed superiority for combined therapy over deferasirox for the increase in LVEF. The cause for this difference in functional response is not fully understood, but the explanation may lie in the additional effects of deferiprone combined desferrioxamine on restoring normal cardiac mitochondrial function, (22) possibly through effects on reducing reactive oxygen species (23).

Conclusion

The patients treated with combined therapy with deferiprone and desferriox showed better systolic ventricular function compared to the patients treated with oral deferasirox. This improvement in the LVEF may contribute to the improved cardiac outcomes seen with deferiprone combined with desferrioxamine.

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Conflict of Interest

The authors have no conflict of interest.

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