

Comparison of Magnetic Resonance Imaging T2 Results in Beta-Thalassemia Patients Treated by Deferasirox or Combination of Deferoxamine and Deferiprone

Nargesbeigom Mirbehbahani MD¹, Ghazal Vaseghi MD², Azam Rashidbaghan PhD³, Mohammad Ali Vakili PhD⁴, Azam Jahazi MSc^{5,*}

1. Cancer Research Center, Golestan University of Medical Sciences, Gorgan, Iran.

2. Hematology-Oncology Research Center, Taleghani Hospital, Golestan University of Medical Sciences, Gorgan, Iran.

3. Kermanshah University of Medical Sciences, Kermanshah, Iran.

4. Golestan University of Medical Sciences, Gorgan, Iran.

5. Gorgan Branch, Islamic Azad University, Gorgan, Iran.

*Corresponding author: Azam Jahazi, Master Science of Midwifery, Department of Medicine, Gorgan Branch, Islamic Azad University, Gorgan, Iran. E-mail: ajahazi@gmail.com. ORCID ID: 0000-0001-6462-9471

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Abstract

Background: Iron extra load is an anticipated and lethal consequence of chronic blood transfusion in major beta-thalassemia patients; therefore it is necessary to use an efficient iron chelator drug to stimulate the evacuation of the surplus iron from the body. This trial was performed to compare myocardial and hepatic magnetic resonance imaging T2 (MRI T2*) results of beta-thalassemia patients treated by Deferasirox or combination of Deferoxamine and Deferiprone.

Material and Methods: In this clinical trial, 44 patients who were on combination therapy with Deferiprone and Deferoxamine and complied with the inclusion criteria were randomized to either case (Deferasirox) or control (combined therapy) groups. Twenty-two patients in the case group received Deferasirox. For 22 patients in the control group, prior treatment with Deferiprone and Deferoxamine was continued. Myocardial and hepatic MRI T2* results were assessed before and after the study. Moreover, serum ferritin level (SFL) was evaluated every 3 months.

Results: SFL at the start of the study did not differ significantly in two groups (2158.1± 1012.2 µg/L in the control group vs. 2145.5±1121.4 µg/L in the case group) (P=0.08). SFL at the end of the study did not differ significantly in two groups (2204.4±1143.5 µg/L in the control group vs. 2347.2±1236.6 µg/L in the case group), either (P=0.12). In each group, myocardial and hepatic MRI T2* at the start and at the end of the trial did not differ significantly (P>0.1).

Conclusion: Myocardial and hepatic MRI T2* results were better in the control (combination therapy) group than those in the case (Deferasirox) group. Major beta-thalassemia patients replied to combined treatment better than Deferasirox.

Key words: Beta-Thalassemia, Deferasirox, Deferiprone, Deferoxamine, Magnetic Resonance Imaging

Introduction

Major beta-thalassemia is a widespread genetic disease in Iran (1). The advocated therapy for major beta-thalassemia includes regular red blood cell transfusions all over life, which is generally performed every two to five weeks depending on the transfusion needs of each individual in order to retain the pre-transfusion value of hemoglobin between 9 and 10.5 g/dL. Blood transfusion can lead to iron extra

load in tissues, leading to a major risk of many complications, which are fatal if not prevented, such as fibrosis and cirrhosis in the liver, diabetes mellitus, growth retardation and hypogonadotropic hypogonadism, hypocalcaemia, osteoporosis and arrhythmias, myocarditis, and intractable cardiac failure (2). Iron chelating drugs have significantly enhanced survival rates and reduced morbidities that are relevant to body

toxicity. Therefore, it is necessary to use a potent iron chelator to increase the expulsion of the surplus iron from the body(3-8). Some investigations showed that the combination of Deferoxamine and Deferiprone was an appropriate way for decreasing iron extra load (9-14). Deferasirox is produced to defeat the deficits of preceding iron chelators(15). Deferasirox is usually well tolerated in patients even in children as young as two years old and its safety and efficacy are established. It has shown promise in many clinical trials and other studies since 2003. Many clinical studies have shown a single dosage of Deferasirox 10- 40 mg/kg/day reduces hepatic iron concentration analogous to Deferoxamine (16-20).

MRI is progressively available to estimate heart iron. As iron concentration increases, T2 value in tissues decreases (21). Myocardial T2 <20 ms indicates enhanced heart iron and is associated with reduced left ventricular function (21).

Some studies suggest that myocardial T2* is valuable to compare the cardiac efficacy of chelators(2-4). Therefore, we compared myocardial and hepatic magnetic resonance imaging T2 (MRI T2) results and serum ferritin level (SFL) in beta-thalassemia patients treated by Deferasirox or combination of Deferoxamine and Deferiprone.

Materials and Methods

This randomized clinical trial, was performed from September 2015 to March 2016, in the hematology–oncology center of Taleghani Hospital of Golestan University of Medical Sciences in Gorgan (a city located in the north of Iran). Male or female major beta-thalassemia patients who aged ≥ 2 years old that had been treated with combination therapy with Deferoxamine and Deferiprone were qualified for entry in the trial. Pediatric patients should have appropriate weight (9.4 kg in patients who took 20 mg/kg/d) to take the smallest tablet of Deferasirox.

Patients that had inclusion criteria of the study (mentioned above) were randomized to either case (Deferasirox) or control (combined therapy) groups. Patients in the case group (Deferasirox) were also required to have a serum ferritin level (SFL) of <500 ng/mL.

In the case group (Deferasirox), patients with cardiovascular, hepatic or renal complication that leading to disorder in metabolism or repulsion of Deferasirox were excluded. In both groups, patients who did not consent to the study were also excluded.

The sample size was calculated according to Gao et al.'s study (22). Regarding the estimated decrease in SFL of case and control groups, the confidence level of 95%, the statistical power of 80%, the sample size was calculated 26 patients in each group on the basis of the below formula. Since the sample may lose up to 10%, the sample size was determined as 29 patients in each group.

$$N = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta} \right)^2 (s_1^2 + s_2^2)}{d^2}$$

In the case group, routine treatment in iron extra loaded patients (Deferoxamine 30-60 mg/kg/day every other day and Deferiprone 50-100 mg/kg/day TDS orally) was stopped, and Deferasirox 20-40 mg/kg/day was prescribed orally for one year.

In the control group (combination therapy), routine treatment in iron extra loaded patients (Deferoxamine 30-60 mg/kg/day every other day and Deferiprone 50-100 mg/kg/day TDS orally) was continued.

In groups, aspartate aminotransferase (AST), alanine aminotransferase (ALT), complete blood count with differential (CBC diff), platelets count (PLT), and SFL were examined at the start of the trial. CBC was done monthly. SFL was tested in a laboratory of Gorgan city by ELISA method at the start and the end of the 3rd,

the 6th, the 9th and the 12th months of the trial. Myocardial and hepatic MRI T2* imaging was done by Pardisnoor Medical Imaging Center in Tehran. Hepatic iron concentration was examined before and after Deferasirox and combination treatment (one year) by doing hepatic MRI. Based on prior trials (23,24), values > 6.3 ms (<2 mgFe/gdw) were supposed normal, 2.8–6.3 ms (2–5 mgFe/gdw) were considered mild, 1.4–2.7 ms (5–10 mgFe/gdw) were considered moderate, and values < 1.4 ms (>10 mgFe/gdw) were supposed severe iron extra load. Moreover, heart MRI T2* was done before and after the treatment. Values > 20 ms were supposed normal, 14–20 ms were considered mild, 10–14 ms were considered moderate, and values < 10 ms were supposed severe iron extra load.

The two groups were matched for the mean of age, sex, basal SFL, and interval of blood transfusion. Data containing patients' demographic characteristics, initial and periodic laboratory test results (SFL, CBC and liver function tests), MRI T2* values, medication side effects such as nausea, vomiting, arthralgia, etc. were noted on the study forms.

Data were analyzed by SPSS version 21.0 and reported as mean \pm standard error (SE). Between-group comparisons were done by Student's t-test. Within-group comparisons were performed by compared the t-test. A P-value <0.05 was supposed statistically significant.

The researcher undertook telephone and face-to-face interviews with patients to be sure that they used drugs regularly and to persuade patients to do laboratory tests. Medication side effects were chiefly asked for and registered. The study was approved by the Golestan University of Medical Sciences Research and Ethics Committee and the code of ethics 3107869312247 was issued. Written informed consent was taken from all patients and from the parent of patients who were <18 years old.

Results

A whole of 58 patients were recruited into the trial. In each group, seven patients excluded from trial because of disagreement and ultimately 44 patients (22 patients in each group) were studied. The mean age, SFL, AST, and ALT at the start of the trial did not significantly differ between case and control groups (Table I). SFL at the start of the trial (2158.1 ± 1012.2 $\mu\text{g/L}$ in control group vs. 2145.5 ± 1121.4 $\mu\text{g/L}$ in case group) did not significantly differ between case and control groups ($P=0.08$). SFL at the end of the trial (2204.4 ± 1143.5 $\mu\text{g/L}$ in the control group vs. 2347.2 ± 1236.6 $\mu\text{g/L}$ in the case group) did not differ significantly between case and control groups ($P=0.12$). In the control group, SFL (2158.1 ± 1012.2 $\mu\text{g/L}$ at the start vs. 2204.4 ± 1143.5 $\mu\text{g/L}$ at the end of the trial) was significantly different ($P=0.038$). In the case group, SFL (2145.5 ± 1121.4 $\mu\text{g/L}$ at the start vs. 2347.2 ± 1236.6 $\mu\text{g/L}$ at the end of the trial) was significantly different ($P=0.03$). SFL in both groups increased significantly at the end of the trial. However, SFL in the case group decreased until the sixth month gradually but increased in the ninth and the twelfth months. In the control group, SFL increased in the third month then decreased until the ninth month gradually, and then increased at the end of the trial (Table II).

In the case group, ten patients had normal basal heart iron load, four had a mild extra load, one patient had a moderate iron extra load, and seven patients had severe heart iron concentration. After receiving Deferasirox, all patients with normal basal values remained normal. Out of four patients with mild iron extra load, one promoted to moderate levels, while three remained the same. In the severe iron extra

loaded patients, one patient progressed into moderate values and six remained severely extra loaded (Figures 1,2). Heart MRI T2* findings at the start and the end of the trial did not significantly differ (P=0.558). In the case group, four patients had a normal basal hepatic iron load, six had a mild extra load, ten patients had a moderate iron extra load, and two patients had severe hepatic iron concentration. After receiving Deferasirox, all patients with normal basal values remained normal. Out of six patients with mild iron extra load, two improved into the normal level and two promoted to moderate values, while two remained the same. In the severely iron extra load group, one participant progressed into moderate values and one remained severely extra loaded. Thus, thirteen patients were in moderate values (Figures 1,2). Hepatic MRI T2* at the start and the end of the trial did not differ significantly (P=0.261).

In the control group, six patients had normal basal heart iron load, two had a mild extra load, nine patients had a moderate iron extra load and five patients had severe heart iron concentration. After receiving Deferasirox, two patients with mild iron extra load, progressed into normal levels. From nine patients with the moderate iron extra load, three improved into normal values and two improved into mild values and four remained the same. All patients with severe basal values remained severe (Figures, 1 and 2). Heart MRI T2* findings at the start and the end

of the trial did not differ significantly (P=0.221).

In the control group, three patients had a normal basal hepatic iron load, nine had a mild extra load, four patients had a moderate iron extra load, and six patients had a severe hepatic iron concentration. After receiving Deferasirox, five patients with the mild iron extra load progressed into normal levels. All patients with moderate basal values remained moderate iron extra load. In the severely iron extra loaded patients, two patients progressed into the moderate values and four remained severely iron extra loaded. Thus, six patients improved into the moderate values (Figures 1, and 2). Hepatic MRI T2* at the start and the end of the trial did not differ significantly (P=0.139)

Mean of AST at the start of the trial (43.4±14.2 in case group vs. 38.8±14.4 in the control group) and the end of the trial (49±18.3 in case group vs. 40.5±14.4 in the control group) did not differ significantly between case and control groups. Mean of ALT at the start of the trial (43.6±16.1 in the case group vs. 37±12.8 in the control group) and at the end of the trial (49.7±19.2 in the case group vs. 32.9±15 in the control group) did not differ significantly between case and control groups.

No main adverse event was observed with either iron chelators. In the case group, four patients developed liver enzymes elevation. They were excluded from the study.

Table I: Basal characteristics of the study participants

Variable	Case group	Control group
Mean age (range)	22.2±5.3 (10–30 years)	20.3±5.3 years (10–34 years)
Female : male, (n)	16:6, (22)	15:7, (22)
AST	43.4±14.2	38.8±14.4
ALT	43.6±16.1	37±12.8

Table II: SFL ($\mu\text{g/L}$) in the study groups (Mean \pm SD)

Time	Case group	Control group
Start	2145.5 \pm 1121.4	2158.1 \pm 1012.2
Third month	2130 \pm 1015.6	2214.5 \pm 1108.2
Sixth month	2084.2 \pm 1044.3	2160.1 \pm 1031.4
Ninth month	2265 \pm 1135.3	2154 \pm 1035.1
Twelfth month	2347.2 \pm 1236.6*	2204.4 \pm 1143.5*

*P<0.05 in comparison with values at the start.

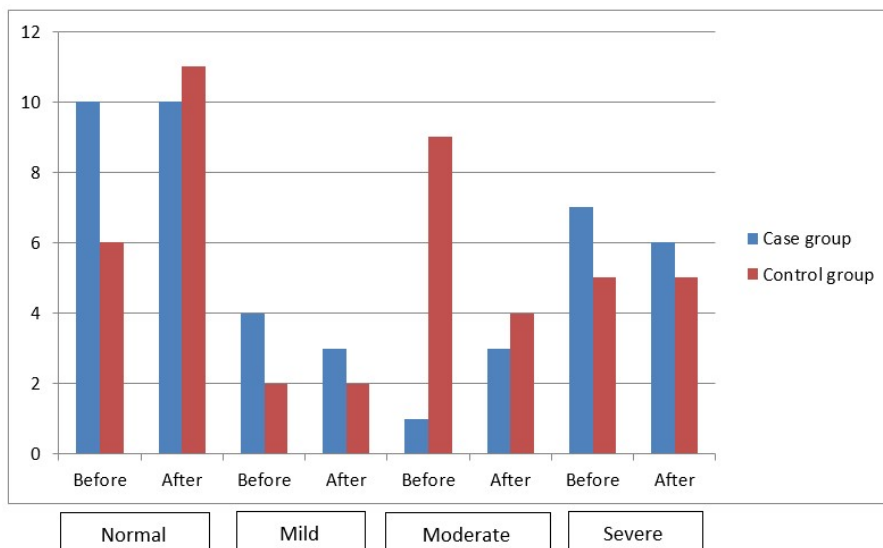


Figure 1. Heart MRI T2* levels before and after the trial in case and control groups.

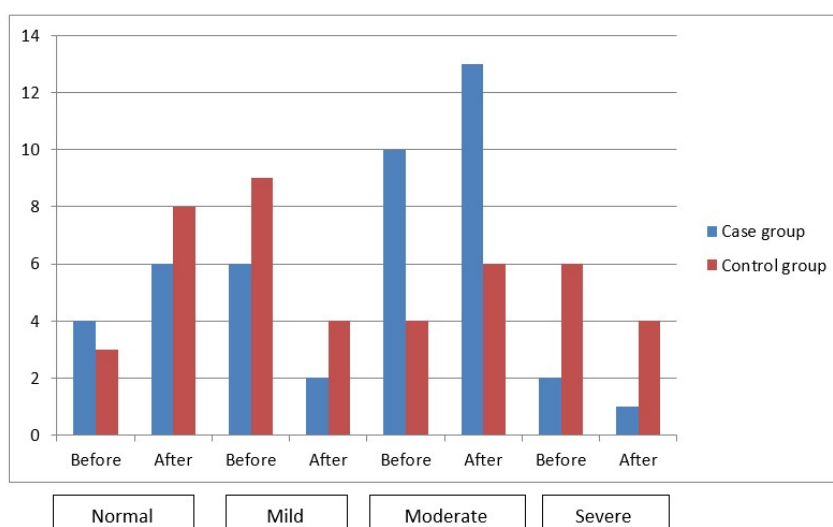


Figure 2: Hepatic MRI T2* levels in case and control groups before and after study.

Discussion

This trial was designed to compare heart and hepatic magnetic resonance imaging T2 results of beta-thalassemia patients treated by Deferasirox and/or combination of Deferoxamine and Deferiprone. Particular measures, including myocardial and liver iron extra load have been examined to determine the body iron load appropriately. MRI is progressively available to estimate heart iron to detect cardiac siderosis former to becoming symptomatic (2,25). Therefore, MRI T2* was used in this trial to specify cardiac outcomes. This can be considered as the power of this trial, as many existent studies (12,26) could not report cardiac outcomes.

Many studies have corroborated the safety and efficacy of Deferasirox in major beta-thalassemia patients (3,4,18,23,26). The ESCALATOR study carried out in the Middle East was the first randomized clinical trial that examined the side effects of treatment with Deferasirox in major beta-thalassemia patients (18). The aim of a review study by Wahidiyat et al., (4) was to determine which iron chelator (Deferoxamine, Deferiprone or Deferasirox) was the most efficient in decreasing myocardial and liver iron extra load. Their study showed that Deferiprone therapy alone could better control or reduce myocardial iron extra load and Deferoxamine was superior in controlling or reducing liver iron extra load. Researchers suggested that further trials with longer period of Deferasirox therapy and larger sample sizes should be done to detect the significant effect of Deferasirox. Alavi et al., (26) reported that hepatic MRI results decreased significantly ($P < .05$) after 18-months of treatment with Deferasirox, and 73.33% of cases overtook the initial endpoint in this view. A cohort study by Pepe et al., (3) demonstrated that participants received Deferiprone orally showed lower myocardial iron

concentration and better global systolic ventricular function in comparison with the participants received Deferasirox orally or Desferrioxamine subcutaneously. They retrospectively selected major thalassemia participants who had received only one chelator for longer than one year. In the present trial, in the case group (combined therapy), Hepatic MRI T2* findings at the start and at the end of the trial did not differ significantly ($P=0.261$). In addition, heart MRI T2* findings at the start and at the end of the trial did not differ significantly ($P=0.558$). The first explanation could be that the few numbers of patients with normal hepatic iron extra load at basal indicated that patients were mild, moderate, and severe iron extra loaded despite prior treatment with Deferoxamine. Further explanation could be that patients with the severe iron extra load need an extended duration of therapy to achieve the therapeutic aims, and patients in present trial may achieve a better outcome in a longer duration (17). Thus, the authors concluded that Deferoxamine cannot be replaced by Deferasirox in patients with severe iron extra load. We suggest long-term follow-up investigations in patients with severe iron extra load until determination of Deferasirox efficacy.

In the present trial, the mean SFL in the control group (combination therapy) increased from 2158.1 ± 1012.2 $\mu\text{g/L}$ at the start to 2214.5 ± 1108.2 $\mu\text{g/L}$ at the end of the third month then decreased slowly to 2154 ± 1035.1 $\mu\text{g/L}$ at the end of the ninth month and at last increased to 2204.4 ± 1143.5 $\mu\text{g/L}$ at the end of the trial. However the mean SFL in the case group (Deferasirox therapy) decreased from 2145.5 ± 1121.4 $\mu\text{g/L}$ at the start to 2084.2 ± 1044.3 $\mu\text{g/L}$ at the end of the sixth month then increased to 2347.2 ± 1236.6 $\mu\text{g/L}$ at the end of the trial.

Lately, some investigations propose that combination treatment with Deferoxamine and Deferiprone reduces SFL of beta-thalassemia patients by a synergistic effect

(10-12,27). A study by Hejazi et al., (12) showed that in comparison to the standard treatment with Deferoxamine alone, combination therapy with Deferoxamine and Deferiprone reduced SFL. That method was effective in the clinical management of iron extra load in major beta-thalassemia patients. Daar and Pathare (27) demonstrated that the addition of Deferiprone to iron chelator therapy had analogous efficacy to Deferoxamine treatment alone in reducing the organ's iron concentration.

As explained in the paper (2), SFL>2500 ng/mL is relevant to fatal outcomes, thus this is very important to reduce these values to improve total body iron. Since all of the patients had a basal SFL < 2500 ng/mL, an insignificant decrease in SFL at the end of the trial could be described. Many studies have demonstrated that the efficacy of therapy is dose-dependent; Furthermore, investigators have emphasized the importance of exact dose regulation to achieve therapeutic aims (18,25). The dose must be regulated conforming to the intensity of iron extra load and transfusional iron intake (2,16,29). In this trial, the initial dose was different from 20 mg/kg/day to 40 mg/kg/day, according to basal hepatic iron concentration and ferritin levels. In Taher et al.'s study (18) 78% of patients endured an additional dose up to 25 or 30mg/kg. No important harmful incident was described, and it was considered as a safe treatment that did not have any of the toxicities experimented with other iron chelators (13).

Conclusion

The present trial demonstrated that after twelve months, SFL insignificantly was increased by Deferasirox therapy and that's increase was more than that by combination therapy with Deferoxamine and Deferiprone. We concluded that major beta-thalassemia patients replied to combined treatment more satisfying than

Deferasirox treatment. We suggest a study with a longer period of Deferasirox therapy in major beta-thalassemia patients with certain transfusion plans.

Conflicting of Interest

There is no conflict of interest between the authors

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