

# Comparison between Deferoxamine and Combined Therapy with Deferoxamine and Deferiprone in Iron Overloaded Thalassemia Patients

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## Abstract

**Background:** Iron overload is the main cause of morbidity and mortality in patients with beta thalassemia major. Effective and convenient iron chelation remains one of the main targets of clinical management of thalassemia major. The combined treatment with deferoxamine and deferiprone could have an increased chelation efficacy and allow drug doses and toxicity to be reduced.

**Methods:** Eighty patients with thalassemia major were randomized to receive one of the treatments: deferoxamine given in combination with deferiprone and deferoxamine alone. Changes in serum ferritin and any toxicity were determined.

**Results:** After one year, the mean serum ferritin ( $\pm$ SD) in deferoxamine alone group decreased from 2945 ( $\pm$ 591) ng/ml to 2,451 ( $\pm$ 352) ng/ml ( $p < 0.001$ ). In the group treat with deferoxamine and deferiprone, a dramatical decline was noticed from 2986 ( $\pm$ 612) ng/ml to 2,082 ( $\pm$ 221) ng/ml ( $p < 0.001$ ). A significant improvement was observed after 6 months of combination therapy. The main side-effects were skin reactions (deferoxamine alone), nausea and arthralgia (combined therapy).

**Conclusion:** Combination therapy is a practical and effective procedure to decrease severe iron overload in patients with beta thalassemia major.

**Keywords:** Thalassemia major; Deferoxamine; Deferiprone; Chelation therapy

## Introduction

$\beta$ -thalassemia usually becomes symptomatic as a severe, progressive anemia during the second six months of life. Regular blood transfusions are necessary in these patients to prevent the serious consequences and cardiac decompensation caused by the marked anemia.<sup>1</sup> The recommended transfusion scheme leads to the transfusion of 100-200 mL/kg/year of pure red cells, which is equivalent to 0.3-0.6 mg of iron per kg body weight per day.<sup>2</sup> The lack of a natural mechanism to eliminate the excessive iron causes its accumulation in organs. When the

iron-binding capacity of defensive proteins such as transferrin and ferritin is exceeded, iron can generate harmful free radicals and cause tissue and multiorgan damages.<sup>2</sup> Prevention of iron toxicity, and consequently of iron-induced morbidity and mortality is the main objective of iron chelation therapy in transfusion-dependent patients. Chelation therapy with deferoxamine, the most widely used iron chelator, has been associated with a significant decrease in the rate of iron-induced complications and with a dramatic increase in survival of transfusion-dependent thalassemia patients.<sup>3-5</sup>

However, despite the availability of deferoxamine in most developed countries, one third of the patients develop an excessive body iron load because of the difficulties in complying with the self-administered subcutaneous infusions 5-6 days a week.<sup>5</sup> Therefore, it is not surprising that a proportion of chelated

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patients continue to develop iron-induced complications and/or die from iron-induced cardiac diseases.<sup>5-8</sup>

The development of a safe and effective oral chelator has been the goal for many years. Deferiprone, first synthesized in 1982, is a bidentate chelator which forms a 3:1 chelator/iron complex excreted mainly in the urine.<sup>9,10</sup> The most serious deferiprone-related adverse event is agranulocytosis, which occurs in 0.6/100 patients for each year.<sup>11</sup> Other common side effects are transient gastrointestinal symptoms, arthropathy and a transient rise in serum transaminases.<sup>11,12</sup>

The combined use of both chelators has been suggested to increase iron chelation effectiveness. Wonke *et al.* first reported that combined therapy of daily deferiprone with subcutaneous deferoxamine administered 2-6 days per week resulted in a decrease in serum ferritin concentrations in five patients treated for 7-15 months.<sup>13</sup> It has been suggested that enhanced chelation and a decrease in total body iron stores can be obtained by combining the two iron chelating drugs deferoxamine and deferiprone either sequentially or simultaneously.<sup>13-15</sup> The combined treatment with deferoxamine and deferiprone could have an increased chelation efficacy and sometimes allow drug doses and toxicity to be reduced and the number of days of deferoxamine infusion to be decreased, improving compliance and quality of life.

## Materials and Methods

Eighty patients with thalassemia major were randomized to receive one of the following two treatments; 40 patients treated with deferiprone (500 mg tablets of deferiprone) given at a daily dose of 75 mg/kg in combination with deferoxamine (40- 50 mg/kg, twice weekly) and 40 patients treated with deferoxamine alone (40-50 mg/kg, 5 days weekly) that were considered as a reference group. All patients received regular blood transfusions at 2-4 weekly intervals to maintain hemoglobin levels above 9 g/dL<sup>16</sup> and all had been treated with deferoxamine prior to the commencement of the study. Iron-overloaded thalassemic

patients at least 10 years old with ferritin levels above 2000 ng/mL over the previous year were eligible to enter the study. Exclusion criteria were lack of compliance, known toxicity or intolerance preventing therapy with deferoxamine and deferiprone, neutropenia (neutrophils  $<1.5 \times 10^9/L$ ), thrombocytopenia (platelets  $<100 \times 10^9/L$ ), renal, hepatic or decompensated heart failure. During therapy, hematological evaluation included hemoglobin, hematocrit, WBC, absolute neutrophil and platelet count measurements every 1-3 weeks and liver and renal function were checked monthly. Serum ferritin levels were controlled every 3 months. Any adverse events and compliances were checked at each transfusion visit.

A two-sample t-test was performed to compare parametric characteristics. A paired t-test was performed to examine the changes in serum ferritin between baseline and last results. A type I error ( $\alpha$ ) of 0.05 was used to determine statistical significance. The study was approved by the Research Committee of the Babol University of Medical Sciences and a written consent was provided from all patients aged >18 years and parents of patients aged <18 years old.

## Results

The efficacy of combined therapy was evaluated in 40 patients treated for 12 months. Baseline characteristics were similar in the two groups (Table 1). There was a statistically significant reduction of serum ferritin values in both groups. After one year, the mean serum ferritin ( $\pm$ SD) in deferoxamine alone group declined from 2945 ( $\pm$ 591) ng/mL to 2,451 ( $\pm$ 352) ng/mL ( $p < 0.001$ ). In group treated with deferoxamine and deferiprone, a dramatical decrease from 2986 ( $\pm$ 612) ng/mL to 2,082 ( $\pm$ 221) ng/mL ( $p < 0.001$ ) was noticed. A significant improvement was visible after 6 months of combination therapy. In the deferoxamine alone group, serum ferritin levels reduced to 2702 $\pm$ 242 ng/mL ( $p < 0.001$ ). In the combination therapy group, the decrease was 2453 $\pm$ 318 ng/mL ( $p < 0.001$ ) (Figure 1).

**Table 1:** Main characteristics of the patients

	Deferiprone with deferoxamine (n=40)	Deferoxamine alone (n=40)	P-value
Females	18 (45%)	19 (47.5%)	0.24
Mean age $\pm$ S.D. (years)	18.7 $\pm$ 4.8	17.8 $\pm$ 6.1	0.44
Mean serum ferritin ng/mL $\pm$ S.D.	2986 $\pm$ 612	2945 $\pm$ 591	0.26

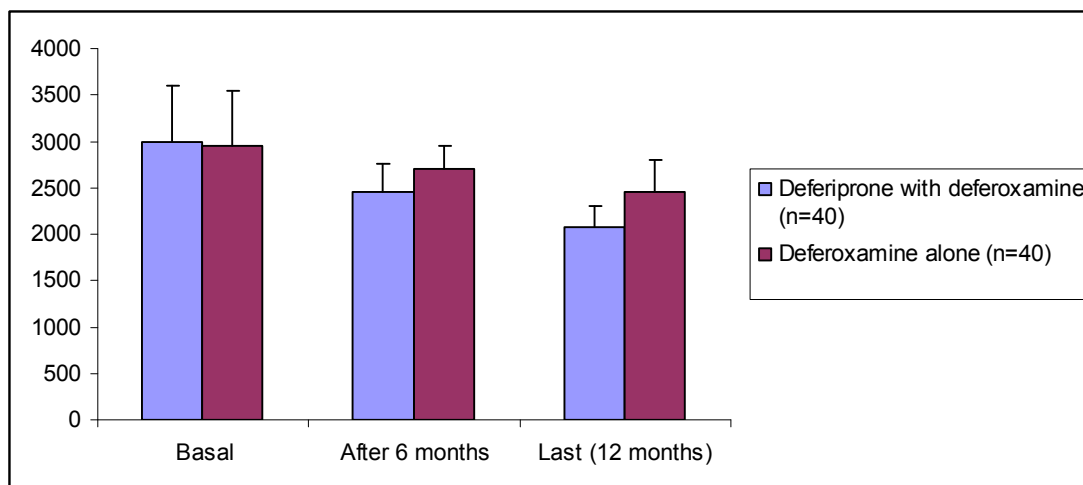


Fig. 1: Mean ferritin levels (ng/mL) in patients

Different adverse drug reactions were found between the two therapies. The combined therapy was associated with episodes of nausea in 12 patients (30%), nausea and abdominal pain in three patients (7.5%), and diarrhea in two patients (7.5%). These events occurred mainly in the first weeks of therapy and were mild/moderate in severity. In these patients, gastrointestinal symptoms resolved without discontinuation of the treatments. Some patients reported improvement of gastrointestinal symptoms when deferiprone was taken after meals instead of fasting. In other patients, the dose of deferiprone temporarily reduced and then gradually increased without recurrence of the gastrointestinal symptoms. Daily infusions of deferiprone were associated with abscess at the site of infusion in one patient (2.5%), and skin allergic reactions in 11 patients (27.5%). There were no episodes of agranulocytosis and neutropenia. The combined therapy was associated with arthralgia in 2 patients (5%). Transient fluctuations in serum alanine aminotransferase (ALT) levels were observed in 8 patients (20%) treated with deferiprone in combination with deferoxamine. In these patients deferiprone therapy was discontinued and the levels of ALT decrease gradually after cessation of deferiprone.

## Discussion

Recently, a number of *in vitro* and *in vivo* studies have suggested that the simultaneous use of deferoxamine and deferiprone is associated with an additive or even synergistic iron excretion in patients with thalassemia major, and that combined therapy could

decrease iron overload in patients who had previously been unable to achieve a satisfactory response to deferiprone or deferoxamine alone.<sup>17-22</sup> It has been suggested that deferiprone, with a low molecular weight, acts as an intracellular chelating shuttle and the large and hydrophilic molecule of deferoxamine serves as an extracellular iron sink.<sup>23</sup> In our study, we evaluated the safety and efficacy of the combined treatment.

The combined treatment has the theoretical advantages of targeting more iron pools and achieving a longer period of chelation coverage. Recent retrospective studies have reported that oral deferiprone has a greater ability to reduce iron loading in the heart and a greater cardioprotective effect than has subcutaneous deferoxamine.<sup>24-26</sup> However, since this study was designed prior to these publications, it did not evaluate the effect of either therapy in removing iron from other tissues such as the heart.

The current study showed that the combined use of deferoxamine and deferiprone is not associated with new safety concerns. All adverse reactions observed have been previously reported. Deferoxamine infusions were associated with skin reactions, while the oral chelation therapy was associated with transient gastrointestinal symptoms. The most serious adverse effect of deferiprone is agranulocytosis which occurs in 0.5% of patients.<sup>27</sup> No agranulocytosis was observed in this clinical study, which could be due to the relatively small number of patients studied for a rarely occurring complication. Arthralgia during combined therapy occurs more frequently than with the use of deferoxamine alone, suggesting a possible decrease in the intra-articular labile iron pool.<sup>27</sup>

In summary, the study emphasizes that beta thalassemia major patients with transfusional iron overload can be successfully treated with a combination of deferoxamine and deferiprone. Continuous deferiprone treatment with intermittent administration of subcutaneous deferoxamine is a practical and effective procedure to decrease severe iron overload in patients with thalassemia major. Most importantly, the data provide support to clinicians who need to give patients a period of time in which chelation with the injectable chelator can be interrupted and replaced

with this oral agent.

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**Conflict of interest:** None declared.

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