

ORIGINAL ARTICLE

Comparative Efficacy of Deferiprone, Deferoxamine and Combination of Deferiprone and Deferoxamine on Serum Ferritin Value in Beta-Thalassemia Patients

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Abstract:

Background: Iron overload is a predictable and life-threatening complication in patients with thalassemia. Effective and convenient iron chelation remains one of the main targets of clinical management of thalassemia major. The development of a safe and effective chelator has been the goal for many years. **Aims and Objective:** It was aimed to compare the effect of deferiprone, deferoxamine and combination of deferiprone and deferoxamine on serum ferritin value in beta-thalassemia patients. **Material and Methods:** This controlled clinical trial was conducted on 46 major beta-thalassemic patients. Fifteen patients in deferiprone group received deferiprone 75mg/kg/day three times a day orally. Nineteen patients in deferoxamine group received deferoxamine 30-50 mg/kg/day subcutaneously for 8-12 hours/day and 5 days per week. Twelve patients in combined therapy group received deferiprone 75 mg/kg/day three times a day orally with deferoxamine 30-50 mg/kg subcutaneously every other day. Serum ferritin value was measured at the beginning and at the end of 6th and 12th months of study. **Results:** The mean of serum ferritin value in deferiprone group insignificantly increased from 2731± 1398.5 µg/L at the beginning to 2788.5 ± 978.6 µg/L and to 3331.8 ± 1833.9 µg/L at the end of 6th and 12th months of study, respectively. The mean of serum ferritin value in deferoxamine group insignificantly increased from 2883.5 ± 1598.1 µg/L at the beginning to 2935.3 ± 1258.2 µg/L at the end of 6th month of study and decreased to 2773.8 ± 1216.1 µg/L and 12th month of study. The mean of serum ferritin level in combined therapy group significantly decreased from 7498.7 ± 3512.9 µg/L at the beginning to 4839.9 ± 2698.2 µg/L (P < 0.001) and to 4298.2 ±

2288.7 µg/L (P < 0.001) at the end of 6th and 12th months of study, respectively. **Conclusion:** Combined therapy significantly decreases serum ferritin level. Study suggests deferiprone as a significant addition to support therapy in patients with betathalassemia major on regular transfusion regimens.

Keywords: Deferiprone, Deferoxamine, Ferritin, Beta-thalassemia

Introduction:

Iron overload is a predictable and life-threatening complication in patients with thalassemia and other haematological disorders whose successful management depends on the regular transfusion of red blood cells. In the absence of effective iron chelation therapy, chronic transfusion cause iron accumulation in the liver, various endocrine organs and the heart. The resulting iron deposits in the target organs then lead to tissue damage and complications such as cardiomyopathy, diabetes, liver fibrosis and cirrhosis, hypothyroidism, hypoparathyroidism, hypogonadism and adrenal insufficiency [1]. Consequently, the use of an effective iron chelator to promote the excretion of the excess iron from those target organs is essential to prevent the morbidity and early mortality observed in patients with thalassemia major [2-7].

Over the past three decades, iron chelation therapy with deferoxamine (DFX) has been shown to prolong survival, improve growth and sexual maturation, and reduce hepatic, cardiac and endocrine dysfunction in iron-overloaded patients

[8]. One study suggested that in patients able to use a DFX regimen sufficient to control body iron load, survival after 15 years of therapy exceeded 95%. Conversely, in patients who were unable to achieve body iron reduction, the probability of survival to age 25 was less than 30% [9].

Although DFX can effectively stabilize or reduce body iron load, compliance with the demanding dosing regimen can be an issue. DFX is generally administered five to seven times a week as an 8-to 12-hour subcutaneous infusion (generally overnight). This mode of administration is frequently associated with local irritation at the site of the DFX infusion. DFX has also been associated with a variety of dose-related toxicological effects such as visual and auditory neurotoxicity, growth retardation and bone abnormalities. Due to these complications and the demanding administration regimen, many patients are non-compliant with DFX therapy and fail to achieve adequate chelation, increasing the risk iron-induced complications and early death [9-13]. In addition, some patients who remain compliant with DFX therapy will nevertheless develop cardiac dysfunction and die prematurely of cardiac disease [14].

Deferiprone (L_1) is a bidentate 3-hydroxypyridin-4-one chelating agent that has a high affinity for ferric iron [iron (III)], to which it binds to form neutral 3:1 (deferiprone: iron) complexes that are stable over a wide range of pH values [15, 16]. That is given as 25 to 33 mg/kg body weight, orally, in three doses a day for a total daily dose of 75 to 100 mg/kg body weight. L_1 is rapidly absorbed by the upper part of the gastrointestinal tract, appearing in the blood within 5 to 10 minutes [17].

The side effects of L_1 are agranulocytosis, arthropathy, myopathy, zinc deficiency, nausea, vomiting, headache, anorexia and liver test disorders. Agranulocytosis is the most serious complication of deferiprone. It is observed in approximately 1% of patients [18]. The potential adverse events with L_1 are manageable, and for

patients with iron overload the benefits of reducing the risk of serious iron-induced organ damage outweigh the risks of chelation therapy [19].

Some studies showed that administration of L_1 is a suitable way for decreasing iron overload especially in patients with DFX incompliance [20-31]. In another study, serum ferritin value decreased in DFX group. It non-significantly increased in the L_1 and combined therapy groups [32]. Another studies showed that administration of deferiprone with subcutaneous injection of deferoxamine is a suitable way for decreasing iron overload especially in patients with deferoxamine non-compliance [33-37]. Fishers current review study (2013) demonstrates that deferiprone is indicated for treating iron overload in people with thalassaemia major when deferoxamine is contraindicated or inadequate [38]. El-Beshlawy *et al.* studied the effect of deferoxamine, deferiprone, and a combination of them on the serum ferritin level. After 1 year of study, serum ferritin level decreased in all groups. Compliance was better in combined therapy group. The most prevalent complications seen with combined therapy were transient arthropathy, nausea and vomiting, and combined therapy was considered the best therapy option [39].

The rate of non-compliance with DFX and complications associated with the administration are such that the use of an effective drug with better compliance is necessary. This study was designed to compare the effect of L_1 , DFX and combination of them on serum ferritin value in beta-thalassemia patients.

Material and Methods:

This controlled clinical trial was conducted between 1st July 2007 and 1st July 2008 in hematology-oncology center of Talghani Hospital of Golestan University of Medical Sciences in Gorgan (a city located in the north of Iran).

The study was approved by the Golestan University of Medical Sciences Research and ethics Committees. A written informed consent

was obtained from all patients and from the parent of patients who were less than 18 years old.

Face-to-face and telephone interviews were undertaken to ensure regular drug usage and to encourage laboratory tests. Drugs side effects were specifically asked for and patients were advised to report any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms immediately.

The combined therapy group included 14 patients (7 men, 7 women) and the L₁ group included 20 patients (7 men, 13 women) randomly selected from major beta thalassemia patients referred to the center for transfusion. Patients older than 7 years with negative hepatitis B, C, and HIV tests were eligible for enrollment. In combined therapy group, L₁ manufactured by Avecina drug company (IRAN) was prescribed 75 mg/kg/ day three times a day (TDS) orally with DFX 30–50 mg/kg subcutaneously by an infusion pump every other day. In L₁ group, L₁ was prescribed 75mg/kg/day (TDS) orally. In both group, Complete blood count with differential (CBC diff), alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count (PLT), and serum ferritin value were tested at the beginning of study. CBC diff and ALT were tested weekly until 2 months then every 2 weeks until 2 months then monthly on patient's circumstances.

In response to liver enzymes elevation L₁ dosage was decreased to 50mg/kg/day. After 7-10 days, laboratory tests were done again. If this did not lead to an improvement or if there was an associated neutropenia (neutrophil <1500) or thrombocytopenia (PLT<100 000) deferiprone would then be stopped until recovery occurred.

DFX group included 20 patients (9men, 11women) selected from beta-thalassemia patients that were on DFX therapy before the study. DFX was prescribed 30-50 mg/kg by a subcutaneous infusion pump for 8-12 hours/day and 5 days per week.

Data including patients demographic

characteristics, primary and periodical laboratory tests results, CBC and liver function tests, drug side effects such as nausea, vomiting, abdominal pain, arthralgia and arthritis were recorded on physical exam and interview forms. In each group, serum ferritin value was measured in a laboratory of Gorgan city by ELISA method at the beginning and at end of 6th and 12th months of study. Other laboratory tests were done in Talghani hospital laboratory.

Data were analyzed by SPSS software v: 16.0 for windows. t-Student, compared t, Wilcoxon and Mann-withney tests were used for data analysis.

Results:

Finally, a total of 15 patients in L₁ group, 19 patients in DFX group and 12 patients in combined therapy group were analyzed. Total of 5 patients from L₁ group because of arthropathy (n=3), nausea, vomiting (n=1) and heart failure (n=1), 1 patient from DFX group because of disagreement and 2 patients from combined therapy group because of nausea, vomiting (n=1), and arthropathy (n=1) were excluded. The mean of age [16 ± 6.2 (8-33 y) in L₁ group vs. 16.8 ± 7.1 (8-35 y) in DFX group vs. 17.2 ± 5.3 (10–30 y) in combined therapy group] was not significantly different between the three groups. Serum ferritin value at the beginning of study was not significantly different between DFX and L₁ groups (Table 1).

In L₁ group, the mean of serum ferritin value increased non-significantly by 57.5 and 600.8 µg/L at the end of 6th and 12th months of study in comparison to the beginning, respectively. The rise in serum ferritin (543.3 µg/L) was non-significant at the end of 12th month in comparison to 6th month (Table 1).

In DFX group, the mean of serum ferritin value decreased non-significantly by 109.7 and 161.5 µg/L at the end of 12th month of study in comparison to the beginning and to 6th month, respectively. The rise in serum ferritin (51.8 µg/L) was non-significant at the end of 6th month in comparison to the beginning (Table 1).

Table 1: Serum Ferritin Values ($\mu\text{g/l}$)

Group Time	DFX(N=19) (mean \pm SD)	L ₁ (N=15) (mean \pm SD)	DFX+L ₁ (N=12) (mean \pm SD)
Beginning	2883.5 \pm 1598.1	2731.0 \pm 1398.5*	7498.7 \pm 3512.9
After 6 months	2935.3 \pm 1258.2	2788.5 \pm 978.6*	4839.9 \pm 2698.2**
After 12 months	2773.8 \pm 1216.1	3331.8 \pm 1833.9*	4298.2 \pm 2288.7**,***

* $p > 0.05$ when compared with DFX group, ** $p < 0.001$ When compared with values at beginning, *** $p > 0.05$ When compared with values at 6 months after study.

The mean of serum ferritin level in combined therapy group decreased by 2658.8 and 3200 $\mu\text{g/L}$ ($P < 0.001$) at the end of 6th and 12th months of study in comparison to the beginning, respectively. There was a non-significant decrease of 541.7 $\mu\text{g/L}$ at the end of 12th month of study in comparison to 6th month (Table 1).

No adverse effects were noted in group receiving DFX. However, at 5th and 7th months of study, 2 patients out of 19 patients (10.52%) in L₁ group developed mild transient neutropenia and 4 (21%) had mild elevation in liver enzymes. Also, a transient thrombocytopenia was seen in 5 patients (26.32%). By decreasing L₁ dosage to 50mg/kg/day all of these side effects were removed. So these side effects were mild and transient that they be managed.

Discussion:

Recently, some studies suggest that use of combined therapy with deferoxamine and deferiprone decreases serum ferritin level of beta-thalassemic patient by a synergistic effect [21,27,37,40-42]. Also some studies suggest that using of L₁ decrease serum ferritin value of beta-thalassemia patient [20-31].

In our study, the mean serum ferritin level in combined therapy group decreased from 7498.7 \pm 3512.9 $\mu\text{g/L}$ at the beginning of study to 4839.9 \pm 2698.2 $\mu\text{g/L}$ and to 4298.2 \pm 2288.7 $\mu\text{g/L}$ at the end of 6th and 12th months of study respectively, whereas the mean of serum ferritin value in L₁ group increased non-significantly from 2731 \pm

1398.5 $\mu\text{g/L}$ at the beginning to 2788.5 \pm 978.6 $\mu\text{g/L}$ and to 3331.8 \pm 1833.9 $\mu\text{g/L}$ at the end of 6th and 12th months of study. The mean of serum ferritin value in DFX group increased non-significantly from 2883.5 \pm 1598.1 $\mu\text{g/L}$ at the beginning to 2935.3 \pm 3940.9 $\mu\text{g/L}$ at the end of 6th month and decreased non-significantly to 2773.8 \pm 1216.1 $\mu\text{g/L}$ at the end of 12th month of study.

There was a rise in serum ferritin values after 6 months of chelation with oral L₁ which is in conformity with the results of few earlier workers [43,44]. L₁ was found to be effective only in balancing the iron input due to blood transfusion by excreting urinary iron. Few earlier reported studies demonstrated a fall in serum ferritin values only after at least 18 months of therapy [35-45]. The rise in serum ferritin concentration has been attributed to the rapid glucoronization of the drug in the liver making it ineffective to chelate the stored iron in the body [44].

Taher *et al* (2001) reported a significant decrease in serum ferritin of patients receiving L₁ after 6 months. Serum ferritin showed no changes after 24 months of study. In patients receiving DFX, serum ferritin decreased significantly after 6 and 24 months of study [46].

Gomber *et al* (2004) studied the effect of DFX, L₁ and a combination of them on serum ferritin value. After 6 months of study, serum ferritin value decreased in DFX group. It non-significantly increased in the L₁ and combined therapy groups [32]; whereas Hoffbrand *et al.* study showed that

in patients were on L₁ therapy for mean 39.4 months, serum ferritin value non-significantly decreased from initial mean, 2937 µg/L to final mean, 2323 µg/L [47]. Aydinok *et al.* study demonstrated that liver iron concentration in L₁ group non-significantly decreased whereas in combined therapy group liver iron concentration and serum ferritin significantly decreased after 1 year of study [48].

In the study of Kattamis *et al.* serum ferritin level decreased from 4543 to 3279 µg/L after combined therapy [36] whereas Hashemieh *et al.* study showed that the mean serum ferritin level of 33 patients on deferoxamine therapy before the study non-significantly increased from 1881 ± 257 to 2495 ± 384 µg/L after 6-month deferiprone therapy [49].

Because of deferiprone's lipophilicity, neutral charge at pH 7.4 and low molecular weight, it has a greater potential than DFX to permeate cell membranes and chelate intracellular iron [50]. This ability has further elucidated in the Caco-2 epithelial cell line, in which deferiprone, both free and bound to iron, showed significant mobility into and out of the cells [51]. Thus it is probable that L₁ will be more effective particularly if used in combination with DFX.

In our study, combined therapy was tolerated very well. Only one patient stopped combined therapy because of arthropathy and another because of nausea and vomiting. In four patients transient elevation of liver enzymes occurred but did not require cessation of combined therapy.

Studies have shown that nearly 30% of patients receiving L₁ experience drug side effects, but these complications rarely lead to stopping therapy. Agranulocytosis is the most serious adverse complication associated with L₁ use. It is seen in approximately 1% of patients [18]. In Gomber's *et al.* study (2004) in L₁ group two patients (9.5%) showed arthropathy and 85.7% showed elevation in serum ALT [32]. In order to monitor for this complication, the patient's blood should be tested

every 7-10 days. In our study agranulocytosis was not seen. In the combined therapy group, four patients developed a mild transient neutropenia and liver enzymes elevation but that did not need to stop study. In L₁ group, A mild transient neutropenia and thrombocytopenia was seen in two (13.3%) and five (33.3%) patients, respectively. Nausea and vomiting was seen in one patient (6.7%). This complication can be minimized if the drug is given in divided doses after meals. Arthropathy was seen in three patients (20%) but settled after stopping L₁ therapy. ALT transient elevation that is another common complication of L₁ was seen in 26.7% of our patients but did not require interruption of therapy. Fisher's study (2013) showed that intensified deferoxamine treatment or use of other oral iron chelators, or both, remain the established treatment to reverse cardiac dysfunction due to iron overload. Adverse events are increased in patients treated with deferiprone compared with deferoxamine and in patients treated with combined deferiprone and deferoxamine compared with deferoxamine alone [38].

Conclusion:

L₁ and DFX had similar effect on serum ferritin value. L₁ or DFX therapy alone could not decrease serum ferritin values efficiently. Combined therapy with DFX and L₁ showed significant decrease in the mean serum ferritin levels. That was well tolerated with few significant side effects. Owing to the complications and the demanding administration regimen, many patients are non-compliant with DFX therapy and fail to achieve adequate chelation, increasing the risk of iron-induced complications and early death [9–13]; our study suggests L₁ as a significant addition to support therapy in patients with beta thalassemia major on regular DFX transfusion regimens. Further trials should compare therapeutic effects of DFX and L1 particularly in a long period of time regimen.

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