The Best Iron Chelation Therapy in Major Thalassemia Patients is Combination of Desferrioxamine and Deferiprone

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Abstract
Introduction: The best and effective iron chelation remain one of the major strategy in clinical management of thalassemia major patients. The purpose of this study was to evaluate the safety and effectiveness of combined therapy with Desferrioxamine and Deferiprone in patients with thalassemia major that undergoing in regular administration of adequate desferrioxamine (5-6 days/week).

Patients and Methods: This study was performed in two groups: one group with combination therapy, that had received oral deferiprone 70 mg/kg /day for 6 days and two days desferrioxamine 40 mg/kg with subcutaneous injection. Other group treated with only desferrioxamine with doses of 40 mg/kg 5- 6 day/week resemble to one year ago. (In past year both groups had regular & adequate administration and consumption of desferrioxamine with doses of 40 mg/kg 5-6 day/week).

Thirty six patients were entered in this study. The efficacy of combined therapy was evaluated in 19 patients that treated with Desferrioxamine and deferiprone and 17 patients that treated with Desferal alone for at least 12 month. In both group the patients were received Desferal in Regular program in one year ago until to start of this study. Age of the patients was over 10 years old. Deferiprone administered orally 70 mg/kg/day in three divided dose and desferrioxamine 40 mg/kg/day by subcutaneous infusion overnight for 8-12 hr twice weekly. Serum ferritin concentrations were measured at base, 6 and 12 month. Full blood count were performed every 15 day for 2 first months and then monthly. The evaluation of cardiac function was performed in regular manner (every 6 months) and all of patients had normal cardiac function.

Results: The mean decreased of ferritin level was 493 µg/L in combination therapy and mean increased in ferritin level was 637.6 µg/L in desferrioxamine group.

Statistical analysis was performed with using T-test, and Paired T-test. There were significant differences between the two groups (p-value= 0.0001).

The most common side effects in combined therapy group were dyspepsia and nausea in 6 patients (18.1%), especially in the first month of treatment. Joint pain and stiffness were observed in 4 cases (13.6%). Significant neutropenia and agranulocytosis were not observed.

The serum ferritin level was increased in 64.7 % of patients that treated with desferrioxamine alone.

Conclusion: The results of this study confirmed that the thalassemia major patients with iron overloaded whom received desferrioxamine as a regular manner (at least 40 mg/kg for 5 days /week) can be safety treated with a combination of deferiprone and desferrioxamine. This combination therapy was effective in reducing iron burden, as assessed by serum ferritin level.

Key words: Thalassemia, Ferritin, Deferoxamine, Deferiprone

Introduction
The patients with thalassemia major are symptomatic during second 6 months of birth. The major and first symptom is progressive anemia and regular blood transfusion is necessary to prevent the serious complication of marked anemia and secondary cardiac complication. This treatment has other complication and major complication is iron
overload. When the iron binding capacity and ferritin is exceeded, iron can generate harmful free radicals and cause of tissue and organ damage.(1)

Prevention of this toxicity is the main objective of iron chelation therapy in transfusion dependent patients. The most widely used iron chelator is desferrioxamine and had significant effect in decreased of iron induced complication.(2, 3, 4)

One third of patients that treated with desferrioxamine developed excessive body iron over load because of difficulties in self administration Subcutaneous infusions 5-6 days/week.(4)

The discovery of an oral agent with best effectiveness and safety has been the goal for many years.

Deferiprone was the first oral chelator agent with 1/3 iron/chelator complex that excreted mainly in the urine.(5, 6) The usage of combination therapy with desferrioxamine and oral iron chelator (deferiprone) revealed a statistically significant reduction of serum ferritin level in many studies.(7, 8, 9, 10)

Adverse effect of deferiprone included: arthralgia, nausea and other gastrointestinal symptoms, fluctuating in liver enzyme level, leukopenia and rarely agranulocytosis. Most of these side effects can be monitored and controlled with supportive care.(11)

Deferiprone acts as an intracellular chelating shuttle and desferrioxamine serves as an extracellular sink.(12)

The aim of this study was the evaluation and comparison of the efficacy and safety and side effect of combination therapy with desferrioxamine and deferiprone in patients with thalassemia major that previously treated with regular program with desferrioxamine (5-6 days/week).

**Patients and methods**

Forty four patients with thalassemia major over 10 years age (10-20) with iron over load and regular consumption of desferal in one year ago and with adequate dosage and prescription were considered for this study. When we described the study, 8 patients after consideration for protocol refuse of treatment and the cause of this decision was afraid of this treatment, because in past the physician said to them that this treatment recommended in patients with cardiac dysfunction only.

All of patients (in both groups) had high ferritin level >1500 (1500-2500). The mean hemoglobin level was 6 gr/dl (4-8) in pretransfusional setting (in both groups). The mean blood consumption in both groups was in closed program in 2 years ago, 2 units/month.(1-3)

In the end of all of investigation 36 patients entered in this study and all of them evaluated for safety, efficacy and toxicity of protocol therapy.(17) patients who received only desferal as same previously treated and 19 cases treated with combination therapy. For all patients of group A subcutaneous infusion of desferal at doses of 40 mg/kg for 5-6 days/week and for all patients of group B (combination therapy) orally deferiprone 70 mg/kg/day in three divided doses/week and desferal 40 mg/kg/day for 2 days/week by subcutaneous infusion over night for 8-12 hr were prescribed.

This study was approved by ethical committee of university.

Exclusion criteria was: kidney disease, severe liver disease, HIV positive, neutropenia.

T-test was used to compare characteristics between different groups of patients and change in serum ferritin level between base line and termination was examined with using a Paired T-test for all patients.

**Results**

After 1 year mean serum ferritin level reduced from 2175±1098 to 1682.8±880 μg/L in combination therapy and elevated from 1764±785.8 μg/L to 2402±1277 μg/L in desferal group. This change in serum ferritin level between two groups has significant difference (P-value <0.0001). (Table-1)

No significant difference in serum ferritin level were seen in between two groups after six month and no significant increase reported in each groups.

### Table-1. Serum ferritin level in combination therapy and desferal groups.

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th>Dose (mean)</th>
<th>Effectivity (%)</th>
<th>Decrease No. (%)</th>
<th>Increase No. (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desferal</td>
<td>493.1 μg/l decrease</td>
<td>14 (73.7%)</td>
<td>5 (26.3%)</td>
<td>0.0007</td>
<td></td>
</tr>
<tr>
<td></td>
<td>637.6 μg/l increase</td>
<td>(1)%</td>
<td>5 (29.4%)</td>
<td>11 (64.7%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### Table-2. Side effects prevalence and causes of drug discontinuation.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Percentage of side effect (%)</th>
<th>Discontinuation of drug (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>18.1%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13.6%</td>
<td>10%</td>
</tr>
<tr>
<td>Total</td>
<td>31.8%</td>
<td>20.6%</td>
</tr>
</tbody>
</table>
In combination therapy serum ferritin level in 14 (75.7%) of patients reduced, and in 5 (26.3%) patients was elevated. (Table-1)
In desferal group serum ferritin level in 11 patients (64.7%) elevated and in 5 cases (24.4%) reduced and in 1 (5.9%) of patients no changes were seen. (Table-1)
Mean reduction in serum ferritin level was 493 μg/lit in combination therapy (P- value = 0.007) and mean elevation in serum ferritin level was 637.6 μg/L in desferal group. (P- value = 0.01)

Adverse events
Gastrointestinal symptoms and joint problem: In 2 cases (10.6%) sever symptoms of GI occurred in the first trimester of trial conducted to transient discontinuation of treatment (Table-2). symptoms including dyspepsia and nausea and abdominal pain.
In 2 (10%) patient joint problems occurred, including pain and stiffness without swelling or any sign of inflammation (Table-2). These 2 patients withdrawn from study because of joint problems. In 19 patients who completed this study in 2 patient dyspepsia and in other 2 patients arthralgia were reported but symptoms of these patients subsided during one week spontaneously.
No hepatotoxicity or agranulocytosis developed during the study. So frequency of GI symptoms and joint problem were 18% and 13.6% that cause to withdrawal of study in 13.6% and 9% respectively. 15 patients at the first group that included in combination trial withdrew because at protocol violation.
No patient showed any significant side effect in desferal group.

Discussion
In Balveer et al (2001)(13), Moural et al (2003)(14), Kattamis et al (2002)(15) studies, including patients didn’t have compliance to desferal and serum ferritin level showed sever iron overload state. But in this study the patients used desferal in order and regular program and adequate dosage as same previously.
Baseline ferritin level in Mourad, Balveer and Kattamis s studies was 4153, 6614, 4543 μg/lit Respectively while in our study baseline ferritin level was 2176 μg/lit.
Mean reduction in serum ferritin level in our study was 493 μg/lit in comparision to the other study like Kattamis, Mourad and Balveer that mean reduction in serum ferritin level was 1246, 1348 and 2623 μg/lit respectively. This result in our study can be related to intial ferritin level that was below than other studies.
This study showed that combination therapy was also effective in the lower level of ferritin in spite of pervious concept and can be used as a alternative option in patients whom recived desferal in regular pattern.
Another important finding was elevation in serum ferritin level while patients recived desferal in order. This can explain the cause of organ damage in many of patients who recieved desferal in order for years.
Frequency of side effects in Fadi Mourad et al(15) study were GI symptoms in 45% and join problems in 27.3% of patients and none of them showed agranulocytosis and none of them required discontinuation of deferiprone because of side effects.
In our study GI symptoms in 13.6% and joint problems in 9% of patients conducted to discontinuation of treatment. These side effects were mild to moderate and can be controlled and monitored with supportive care but phobia of drug (know this drug is a choice drug for cardiac disease) was the cause of discontinuation Adverse event in our study is compliant with other studies and show that combination therapy is safe protocol if these advers event monitor carefully.
The result of the study confirm that combination therapy in thalassemia patients is rational option in patients who received desferal in order and decided to change the protocol of treatment.

References