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Effect of Combined versus Monotherapy with Deferoxamine and Deferiprone in Iron Overloaded Thalassemia Patients: a Randomized Clinical Trial

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Abstract

Background: Patients with transfusional iron overload have depended on iron chelation therapy and improving chelation regimens have been of the highest priority. The aim of this study was to compare effect of combined versus monotherapy with Deferoxamine (DFO) and Deferiprone (DFP) in iron overloaded beta thalassemia (BT) major patients

Materials and Methods

We studied 36 BT major patients (mean age 7.6±4.6; range 3–16 years) attending the Ormieh Motahari hospital for regular transfusional support. Patients were randomly allocated to receive one of the following two treatments: DFO in combination with DFP (n=12), DFO alone (n=12) and DFP alone (n=12). Serum ferritin level, liver enzymes, blood urea nitrogen, and creatinine and side effects were monitored over a 12 months period.

Results: After one year, serum ferritin decreased more significantly in patients on DFO+DFP therapy compared to patients who only received DFO or DFP alone ($P<0.01$). Side effects of DFP, including gastrointestinal upset (nausea, vomiting and abdominal pain) and mild agranulocytosis occurred in five (41.7%) and two (8.3%) patients, respectively but none led to discontinuation of the treatment.

Conclusion: In comparison to the standard chelation monotherapy of DFO, combination treatment with additional DFP reduced serum ferritin and is effective procedure in clinical management of iron overload in patients with BT major.

Key Words: Beta thalassemia, Deferoxamine, Deferiprone, Iron overload.

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1- INTRODUCTION

Beta-thalassemias (BT) are a group of inherited disorders that are caused by altered or absent hemoglobin chain synthesis resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. Some patients, like those with the carrier genotypes, have no clinically obvious symptoms. Others, like BT major patients, depend on lifelong transfusions for survival (1-5). Recent surveys estimated that 5.2% of the world population are carriers of such disorders and over 330,000 affected infants are born annually 80% of which occurs in developing countries (6). Moreover, an estimated number of 18,000 deaths occurred due to thalassemia in 2010 (7).

Findings in untreated or poorly transfused individuals with thalassemia major, as seen in some developing countries, are growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, development of mass from extramedullary hematopoiesis, and skeletal changes that result from expansion of the bone marrow. Regular transfusion therapy leads to iron overload-related complications including endocrine complication (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and less commonly, adrenal glands), dilated cardiomyopathy (DCM), liver fibrosis and cirrhosis)(9,10). Compliance with iron chelation therapy (see later) mainly influences frequency and severity of the iron overload-related complications. Individuals who have not been regularly transfused usually die before the second-third decade. Survival of individuals who have been regularly transfused and treated with appropriate chelation extends beyond age of 40 years (11). Chelation therapy with Deferoxamine (DFO), the most widely used iron chelator, has been associated with a significant decrease in the rate of iron-induced complications (12). DFO has also been associated with a variety toxicological side effects such as visual and auditory neurotoxicity, growth retardation and bone abnormalities. Due to these complications, many patients are non-compliant with DFO therapy and fail to achieve adequate chelation, increasing the risk iron-induced complications and early death (13, 14). Deferiprone (DFP) as an oral chelator first synthesized in 1982. The most serious DFO side effects are agranulocytosis, transient gastrointestinal symptoms, arthropathy and a transient rise in serum transaminases (15-18).

The combined use of both DFO and DFP has been suggested to increase iron chelation effectiveness (19). Wonke et al. first reported that combined therapy of DFO and DFP significantly reduce serum ferritin concentrations (20). Another studies observed statistically significant reduction of ferritin serum values associated with a higher mean urinary iron excretion (21-23).

The present study aims to compare the efficacy of DFO, DFP and them combination on serum ferritin value in BT patients who have been receiving regular blood transfusion.

2- MATERIALS AND METHODS

This study was a single-blind randomized clinical trial and was done at Ormieh Motahari hospital (a city in North-west of Iran) during 12 months from February 20th 2011 to February 20th 2012. Thirty six patients with BT major were randomized to receive one of the following two treatments: 12 patients treated with DFO alone (50 mg/kg, 5 days weekly), 12 patients treated with DFP alone (75 mg/kg, daily) and 12 patients treated with DFP given at a daily dose of 75 mg/kg in combination with DFO (50 mg/kg, twice weekly) (20). All patients received regular blood transfusions at 2-4 weekly intervals to maintain hemoglobin levels above 9 g/dl

and all had been treated with DFO prior to the commencement of the study.

Sample size calculation was performed according to Daar and Pathare study (24). This study found that mean [standard deviation (SD)] serum ferritin in monotherapy with DFO and combined therapy with DFO and DFP was 3088 (1299) and 5760 (2047) ng/mL respectively. Considering type I and II error of 0.5 and 0.2 respectively and according to two means comparison formula the estimated sample size was 7 patients and then by multiplying calculated sample size by the square root of the number of groups (3 groups) the estimated sample size was 12 patients in each group. All of them were followed regularly at the Thalassemia center for at least 6 years. All patients were screened for hepatitis C virus (HCV) antibody and hepatitis B surface antigen (HBs Ag) with appropriate standard commercial assay. During the study period, no change was allowed in the dose of DFP while the DFO dose was adjusted according to the ferritin level.

2-1. Inclusion Criteria

- Transfusion-dependent thalassemia
- Age > 3 year
- Serum ferritin level < 5,000 ng/L
- Progressively increasing undergoing chelating therapy with subcutaneous DFO.

2-2. Exclusion Criteria

- Severe liver, kidney or cardiac disease
- Serious adverse events with DFO or DFP
- Neutrophil count < 2000/L during the past 2 years or platelet count < 100,000/L
- History of arthropathy.

Serum ferritin concentrations were measured before intervention and at six monthly intervals prospective to assess the efficacy of therapy. All subjects were evaluated at the same time (at the beginning and at end of 6th and 12th months of study) and we have documented records on all patients retrospectively over periods exceeding 12 months before study enrollment. Full blood count was performed at each monthly visit, while liver and renal function assessment was performed at three monthly intervals and multi-transfusion virological screen was performed at six monthly intervals. Echocardiography was performed before enrollment to the combination treatment and 12 months after therapy.

Informed consent was obtained from all patients and/or their parents according to their age after getting the approval of the medical ethic committee of Urmia University of Medical Sciences and hospital research ethics board and registered in Iranian Registry of Clinical Trials Center (IRCT2016041627412N1).

Continuous variable are presented as mean (SD). Analysis of variance was used to test differences of mean values and the P-value less than 0.05 was considered as statistically significant.

3- RESULTS

Thirty six patients (17 females and 19 males) were enrolled in the study, from which all patients successfully completed the study after 1 year. The mean age of patients at enrollment was 7.6 (4.4) years. Baseline characteristics were not statistically significant between groups (**Table 1**).

At the beginning of the study, the results of ANOVA showed that there was no significant difference between the three groups in ejection fraction and also at 12 months after treatment, there was no significant difference in ejection fraction between groups.

There was a statistically significant reduction of serum ferritin values in all of three groups. After one year, the mean

(SD) serum ferritin in DFO alone group declined from 2328 (985) ng/mL to 2200 (705) ng/mL (P=0.001). In DFP alone group, serum ferritin reduced from 2563 (737) ng/mL to 2337 (765) ng/mL (P=0.001). In group treated with DFO and DFP, a dramatically reduction from 2811 (938) ng/mL to 1873 (613) ng/mL (P=0.001) was noticed. The between group difference was significantly in favor of the combined treatment group (P=0.001). There was no significant difference in serum ferritin in DFO and DFP mono-therapy groups at 12 months (P=0.59). Five patients (41.7%) experienced nausea, most frequently during the first weeks of combination treatment. Nausea was associated with vomiting or abdominal pain in two patients. In DFP mono-therapy group, five patients (41.7%) developed mild nausea that associated with vomiting or abdominal pain in two patients and one patient had mild vomiting and abdominal pain. In DFO group, two patients had nausea that was associated with pain in one case. Out of 36 patients tested, three patient (8.3%) developed mild agranulocytosis and fortunately none of the patients developed neutropenia, and hepatic toxicity and the drug was not interrupted in any of them.

Table 1: Descriptive Statistics of the Treatment Groups at Baseline

Variables	Deferoxamine	Deferiprone	Combined	P-value
Age, year	8.6±4.8	7.5±4.9	6.7±3.7	0.51
Gender				
Male	8(66.7)	6(50.0)	5(66.7)	
Female	4(33.3)	6(50.0)	7(33.3)	0.65
BMI	16.74±2.86	17.27±5.59	16.87±3.27	0.38
Serum ferritin, µg/L	2328±985	2563±737	2811±938	0.42
LV ejection fraction, %	53.5±3.2	55±3.7	55.8±4.1	0.31

BMI: Body Mass Index; LV: Left Ventricle.

4- DISCUSSION

The results of present study confirm that the combined therapy of DFO and DFP was more effective than DFP or DFO mono-therapy at reducing iron overload. The mean of serum ferritin value in DFP or DFO mono-therapy group, decreased significantly after 12 months but there were no significant differences between two groups. These findings are concordant with previous publish studies (24, 25-29).

Mirbehbahani et al. study showed that combined therapy was effective in reduction of serum ferritin value (25). Karami et al. reported that the two year combination therapy was more effective than mono-therapy with DFO in reducing serum ferritin (27). Kattamis et al. showed that 12 months combination therapy was significantly effective to reduce iron overload in compared to monotherapy with DFP (28). Daar and Pathare study showed that addition of DFP to iron chelator therapy had comparable efficacy to daily DFO mono-therapy in controlling body iron (24). In one recent meta-analysis demonstrated that either DFP only or combined with DFO did not have a significantly different effect on serum ferritin level compared with DFO-only treatment. It suggests that the combination therapy (DFP and DFO) and mono-therapy DFP are as effective as DFO treatment on

the Serum ferritin (SF) levels (30). For transfusion-dependent BT patients, it is important to choose dose of an iron-chelating to reduce iron burden in the body in order to prolong life and improve the quality of life. Although DFO was considered as "gold standard" for the last three decades, clinical experience demonstrated that parenteral DFO treatment was insufficient to reduce cardiac iron burden and had low compliance in patients (31).

The combined therapy was generally well tolerated and safe in our experience. In our study none of the patients stopped treatment. Five patients in each combined therapy and DFP mono-therapy group had gastrointestinal upsets (nausea, abdominal pain and vomiting). Only two patients had nausea in DFO mono-therapy group. This is also a common side effect and could be minimized by dividing the total daily dose into multiple fractions and taking the medication after meals. Three patient (one in DFP and two in combined regimen) developed mild agranulocytosis. Adverse events are increased in patients treated with DFP compared with DFO and in patients treated with combined DFP and DFO compared with DFO alone. In another published study, nausea, vomiting and agranulocytosis was seen in treated patients (25).

In our study, initial left ventricle ejection fraction values were within the normal range in three groups of patients, receiving either DPO or DFP mono-therapy or combination therapy and the mean LVEF values did not change significantly after one year of observation.

This finding was in contrast to Origa et al. study (32). They study revealed that the combined therapy was significantly associated with a change in left ventricular ejection fraction. (32). Daar and Pathare noted that there was a significant improvement in the myocardial function as assessed by the ejection fraction and fractional shortening in those patients receiving combination therapy for a minimum of one year (24). It seem long-term prospective trials are also needed to compare the ability of DFO alone to that of combined therapy in resolving iron-induced heart damage.

4-1. Limitations of the study

Low sample size was main limitation of presents study.

5. CONCLUSION

In conclusion the results of this study showed that combined therapy of DFO and DFP is more efficient than monotherapy in BT major patients with transfusional iron overload. Therefore BT major patients with transfusional iron overload can be successfully treated with a combination of DFO and DFP. However, they may cause some adverse events that were well tolerated with few significant outcomes. Further trials should compare therapeutic effects of DFO and DFP particularly in a long period of time regimen.

6- CONFLICT OF INTEREST: None.

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