RESEARCH PAPER

# Comparative Efficacy and Safety of Oral Iron Chelators and their Novel Combination in Children with Thalassemia

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**Objective:** To compare the efficacy and safety of oral iron chelators (Deferiprone and Deferasirox) when used singly and in combination in multi-transfused children with thalassemia.

**Design:** Prospective comparative study.

**Setting:** Thalassemia Center of a medical college affiliated hospital

**Participants and Intervention:** 49 multi-transfused children with thalassemia with a mean (SD) age 11.6 (6.21) y received daily chelation therapy with either deferiprone alone (75 mg/kg/day in 3 divided doses), deferasirox alone (30 mg/kg/day single dose) or their daily combination (same dose as monotherapy) for 12 months.

**Outcome measures:** Serum ferritin levels at the start of study, after 6 months and after 12 months. MRI T2* of liver and heart initially and after 6 months of follow up. 24-hour urinary iron excretion values at the outset and after 12 months of chelation therapy. At every visit for blood transfusion, all patients were clinically assessed for any adverse effects; liver and renal functions were monitored 6-monthly.

**Results:** After 12 months of respective chelation therapy, serum ferritin values decreased from a mean of 3140.5 ng/mL to 2910.0 ng/mL in deferiprone alone group, 3859.2 ng/mL to 3417.4 ng/mL in deferasirox alone group and from 3696.5 ng/mL to 2572.1 ng/mL in the combination group. The combination therapy was more efficacious in causing fall in serum ferritin levels compared to deferiprone and deferasirox monotherapy (*P*=0.035 and 0.040, respectively). Results of MRI T2* were equivocal. Combined drug usage produced maximum negative iron balance in the body by maximally increasing the iron excretion in urine from 61.1 µmol/day to 343.3 µmol/day (*P*=0.002). No significant adverse reactions were noticed in either the monotherapy or the combination group.

**Conclusion:** Oral combination therapy of deferiprone and deferasirox appears to be an efficacious and safe modality to reduce serum ferritin in multi-transfused children with thalassemia.

**Key words:** *Blood transfusion, Thalassemia, Deferiprone, Deferasirox, Combination Iron Chelation therapy.*

Iron overload causes significant complications in patients with transfusion-dependent thalassemia major. These complications can be managed effectively by iron chelation therapy. The three iron chelators presently in use: Desferoxamine, Deferiprone and Deferasirox when used as monotherapy can prevent some of these complications. Combination of parentral desferoxamine with oral deferiprone [1] or deferasirox [2] has been successfully used in some studies but at the cost of multiple painful injections and decreased compliance [3]. A few studies have also used oral chelators deferiprone and deferasirox in combination [4-6] in some "difficult to treat thalassemics", but there is paucity of studies evaluating combined use of oral iron chelation drugs in children with thalassemia. The present study aimed to evaluate the efficacy and safety of oral iron chelators alone and in combination.

## METHODS

This prospective comparative study was conducted at the Thalassemia day care unit of a tertiary care hospital. Forty-nine patients of thalassemia major having serum ferritin levels >1500 ng/mL were included in the study. Those patients who had a history of anaphylaxis due to deferiprone and/or deferasirox, or those with serum creatinine value above the upper limit of normal for that age were excluded. An informed written consent was taken from the parents/guardians of these patients. Ethical clearance was obtained from the institutional ethical committee before starting the study.

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From the patients fulfilling the inclusion criteria, 44 were already on either deferiprone (23 patients) or deferasirox (21 patients) monotherapy. By computer generated random number table, we selected 6 children each from those already receiving deferiprone monotherapy and deferasirox monotherapy to from a third group to be given combination of two oral iron

chelators. Five new patients who were not on any chelating agent and fulfilling the inclusion criteria were also included in the study (2 in group 2 and 3 in group 3). Thus, Group 1 (Deferiprone alone): consisted of 17 patients (23–6=17), who received deferiprone monotherapy in the dose of 75 mg/kg/day in 3 divided doses daily. Group 2 (Deferasirox alone): consisted of 17 patients ([21–6] + 2=17), who received deferasirox monotherapy in the dose of 30 mg/kg/day single dose daily. Group 3 (Deferiprone and Deferasirox Combination): consisted of 15 patients ([6+6] + 3 = 15), who received daily combination of both deferiprone (75 mg/kg/day in 3 divided doses daily) and deferasirox (30 mg/kg/day single dose daily). All patients received packed red blood cell transfusion every 3 weekly to maintain pre-transfusion hemoglobin of 9-9.5 g/dL.

Serum ferritin levels were measured at the start of study, at 6 months and at 12 months of respective chelation therapy. C-reactive protein (CRP) was also measured along with all measured values of serum ferritin in all the patients to rule out any acute infection which could cause a factitious rise of serum ferritin values. MRI T2* of liver and heart was done in five patients of each group (due to financial constraints) at the time of enrolment and at 6 months of respective chelation therapy. This was performed with an iron quantification T2*-weighted multi-slice multi-echo (8) sequence 1.5 Tesla MRI scanner using a phased-array surface coil. Iron content in the liver and heart was then calculated using GE Healthcare software. These values were measured in milliseconds (msec). A higher reading meant a lower iron loading for both liver and heart. Iron overload in liver was graded as None if MRI T2* values were >6.3 msec, Mild (6.3-2.7 msec), Moderate (2.7-1.4 msec) and Severe (<1.4 msec) while that in heart was graded as None if MRI T2* valves were >20 msec, Mild (12-20 msec), Moderate (8-12msec) and Severe <8 msec [7,8]. 24-hour urinary iron excretion was measured in all patients at the beginning of the study and after 12 months of treatment with equal number of age- and sex-matched controls.

Safety measures were assessed clinically at each visit for blood transfusion, for any adverse events like joint pains, rashes, pain abdomen, nausea or vomiting. Complete blood counts were carried out during each visit for blood transfusion. Liver and kidney function tests with urinary protein detection using uristix were done along with viral markers and HIV status at the start of study and at 6 monthly intervals.

Statistical analysis was carried out using SPSS 20.0 version. Repeated measure two way ANOVA was used for comparing serum ferritin values with fixed factor as group and repeated factor as time. As serum ferritin levels are not normally distributed and have high variances, the log base 10 transformation was used to stabilize the variances across the groups. Analysis of covariance (ANCOVA) was carried out taking baseline serum ferritin values as covariate and marginal means were estimated. Paired T-test was used for analysing MRI T2* values of liver and heart and 24-hour urinary iron excretion values. Pearson correlations were used to find correlations between values of MRI T2* of liver, heart and serum ferritin levels.

## RESULTS

A total of 49 children (30 males) with a mean (SD) age of 11.6 (6.21) years fulfilled the criteria and were included in the study. The mean values of serum ferritin measured at the start of study, at 6 months and at 12 months of chelation therapy are depicted in ***Fig.* 1**. The baseline serum ferritin values were similar in all of the three groups (***Table* I**). A decrease was noticed in serum ferritin values in all the three groups after 6 months and 12 months of chelation therapy. The decrease in serum ferritin observed in group 3 was significantly higher than that observed in group 1 ($P$=0.035) and group 2 ($P$=0.04). Both the drugs when used alone had almost similar efficacy. CRP was negative in all patients at all time points.

All the patients in whom MRI T2* of liver was

**TABLE I** SERUM FERRITIN VALUES AT THE START, AT 6 MONTHS AND AT 12 MONTHS IN STUDY PARTICIPANTS

| | *Serum Ferritin levels Geometric Mean (95% CI of GM) (ng/mL)* | | |
|---|---|---|---|
| *Time Points* | *Deferiprone monotherapy (n=17)* | *Deferasirox monotherapy (n=17)* | *Combination therapy* (n=15)* |
| At start | 3140.5 (2617.5-3767.9) | 3859.2 (3168.8-4700.0) | 3696.5 (3079.6-4438.1) |
| At 6 months | 3010.9 (2548.5-3557.1) | 3671.1 (3098.1-4350.1) | 2977.1 (2384.5-3717.1) |
| At 12 months | 2910.0 (2220.7-3812.4) | 3417.4 (2734.6-4270.7) | 2572.1 (2138.9-3093.1) |

*P=0.008 for comparison by ANOVA; Multiple comparison (using Tukey's Test) found no pairs of two time points to be significant in both monotheraphy groups; however, baseline S. ferritin was significantly different with 6 month and 12 month S. ferritin value.*

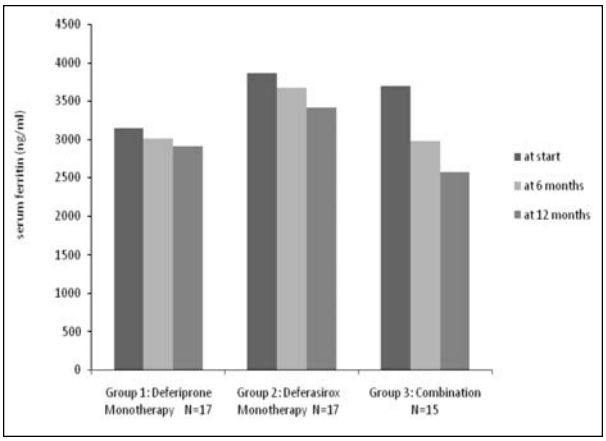


***Fig.* 1** *Geometric Mean S. Ferritin (ng/mL) in all groups at start, 6 months and 12 months of chelation therapy.*

performed showed values indicating mild hepatic iron overload, ranging from 5.1 – 5.4 msec. These values were higher in all the three groups in the follow up MRI performed after 6 month of respective therapy which meant a reduced iron load on liver (***Table* II**), but the values still remained in the category of mild hepatic iron overload (5.4 -5.6 msec). There was no statistically significant increase in values in any of the groups. The individual and the mean values of MRI T2* of heart were almost similar at the baseline (29.5–33.3 msec) and at follow up (31.2-32.3 msec). No correlation could be established in MRI T2* values of heart or liver with serum ferritin values. 24-hour urinary iron excretion showed an increase at 12 months from a mean value of 200.2 µmol/day to 381.9 µmol/day in group 1, 28.8 µmol/day to 30.6 µmol/day in group 2 and 61.1 µmol/day to 343.3 µmol/day in the combination group. Clinical evaluation revealed arthropathy of large joints in one patient within 4 weeks of administration of combination of deferiprone and deferasirox. Arthropathy subsided after discontinuation of deferiprone. Two patients on deferasirox developed mild abdominal pain which subsided with oral proton pumps inhibitors given for 7-10 days. None required discontinuation of chelation therapy. No other side effects were observed in any of the patients. No mortality was noticed during the study period. None of the patients developed neutropenia, thrombocytopenia, or derangements of kidney function tests. There was no detectable protein excretion in urine (as measured by uristix) in any of the patient at any time during the study. Mild derangements in liver enzymes (less than twice the upper limit of normal) was present which did not manifest clinically.

## DISCUSSION

The combination of deferiprone and deferasirox was found to be the most efficacious in the present study which produced a significant fall in mean serum ferritin values. These results are in agreement with those of Farmaki, *et al*. [6] and a few other case reports [4,5]. As the serum ferritin values mainly indicate a trend of iron overload over a period of time and not the actual iron overload in various tissues, we tried analyzing other parameters of iron overload like MRI T2* of liver and heart and 24-hour urinary iron excretion. MRI T2* provides a rapid, non-invasive, reproducible means for hepatic and myocardial iron overload which cannot be predicted from serum ferritin [9-12]. The present study did not reveal any cardiac iron overload and only minimal iron overload of liver tissue. The insignificant difference in the follow-up MRI values of liver and heart may be due to the lesser time interval between these values [7,13]. The maximum increase in excretion of iron in urine observed in group 3 in our study signifies the synergistic effect of both the oral iron chelators in reducing the iron overload.

The study has the limitations of a non-randomized design, small sample size and short follow-up. We also could not perform MRI studies in majority of the included patients.

The present study highlights the efficacy of oral iron chelators, deferiprone and deferasirox, both as single agent therapy or when used in combination. The combination therapy appears to be more efficacious than each of these agent in isolation. We recommend larger studies with well-controlled design to substantiate the efficacy and safety of combination of oral iron chelators in children with thalassemia.

**TABLE II** MEAN (SD) VALUES OF MRI T2* LIVER AND HEART AT THE BASELINE AND FOLLOW-UP

| *Groups* | | *Deferiprone (N= 5)* | *Deferasirox (N= 5)* | *Combination therapy (N= 5)* |
|---|---|---|---|---|
| MRI T2* Liver (msec) | Baseline | 5.4 (0.20) | 5.1 (0.52) | 5.3 (0.26) |
| | Follow up | 5.6 (0.26) | 5.4 (0.58) | 5.5 (0.40) |
| MRI T2* Heart (msec) | Baseline | 33.3 (1.44) | 32.0 (2.00) | 29.5 (1.99) |
| | Follow up | 32.3 (1.66) | 31.7 (2.65) | 31.2 (2.57) |

**WHAT IS ALREADY KNOWN?**

- Iron overload and its complications in patients with thalassemia have been managed with iron chelators used singly or in combination with parentral chelator.

**WHAT THIS STUDY ADDS?**

- Combination of oral iron chelators is efficacious and safe for use in children with thalassemia.

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