Comparative Efficacy of Desferrioxamine, Deferiprone and in Combination on Iron Chelation in Thalassemic Children

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Objective: *Ascertainment of an appropriate strategy of iron chelation for multi-transfused thalassemic children in developing countries.* ***Design:*** *Prospective study from May 2000 to April 2001.* ***Setting:*** *Urban tertiary care center.* ***Methods:*** *Thirty thalassemic children having received more than 20 blood transfusions and a serum ferritin greater than 1500 ng/ml were enrolled and randomized into three groups. Group I received desferrioxamine (DFX) at a dose of 40 mg/kg subcutaneously, 5 days/week. Children in group II received oral deferiprone (L_1) at a dose of 75 mg/kg/day daily and group III received a combination of daily L_1 at a dose of 75 mg/kg/day and DFX at a dose of 40 mg/kg/day two times per week. The assessment of chelation was done by 24-hr urinary iron excretion (UIE) and measurement of serum ferritin levels at start and after 6 months of follow up. Statistical difference of serum ferritin levels between the three groups was assessed by applying analysis of variance. Analysis of covariance was applied to find out the urinary iron excretion keeping serum ferritin values same in each groups.* ***Results:*** *Ferritin levels after 6 months of intervention were maximally decreased in group I. There was a significant difference between groups I and II however, no difference was noted between groups I and group III. There was no statistically significant difference in mean urinary iron excretion by keeping the initial serum ferritin levels equal though it was found to be more in group III as compared to other groups.* ***Conclusions:*** *DFX is the most effective chelating drug in iron overloaded multi-transfused thalassemic patients. In view of cost and unacceptability of daily DFX injections, combination therapy is an effective method of chelation thus increasing the compliance and cost effectiveness. Deferiprone (L_1) alone is not an effective mode of chelation when used for a short period.*

Key words: *Iron chelation, Thalassemia.*

THALASSEMIA syndromes are a heterogenous group of Mendelian disorders characterized by a lack or decreased synthesis of either a or b globin chain of haemoglobin (Hb). It results in ineffective erythropoiesis as well as lysis of mature red cells in spleen(1). These patients require regular blood transfusions to maintain Hb level of around 12 g/dL, which results in transfusional iron overload. The treatment of iron overload is carried out by the use of well established parenteral desferrioxamine (DFX) therapy or by recently introduced deferiprone (L_1), an oral iron chelator(2-4). The parenteral administration of DFX is painful, cumbersome and costly. Many patients find difficulty in complying with daily DFX therapy. The oral iron chelator even on prolonged use has not been effective to reduce serum ferritin values. Moreover it is associated with increased adverse effects especially arthropathy and neutropenia(2,3). Hence, a novel method of treating these patients with combination of DFX and L_1 has been used by few workers with encouraging results(5,6). However, there is paucity of reports of its safety and effectivity

among Indian children who mostly present with high levels of stored iron in the body. The present study was planned to find out the efficacy and safety of combination of DFX and L_1 in comparison to their use singly, in multitransfused thalassemic children.

Subjects & Methods

The study was conducted in Thalassemia Day Care Center in the Department of Pediatrics, of a tertiary care hospital over a period of 12 months. Thirty patients were included and were randomized intro three groups. Their baseline anthropometric data was taken comprising of age, weight and height. The inclusion criteria were (*i*) the patients should have received more than twenty blood transfusions and (*ii*) serum ferritin levels greater than 1500 ng/mL. Children who had a poor compliance and follow-up were excluded from the study.

Chelation Groups

Group I

This group included children receiving subcutaneous DFX at the dose of 40 mg/kg/day over a period of 8-10 hours, five days a week. A total of 10 children were enrolled in this group, of which one opted out and chose group II, and two were excluded. Seven children could be regularly followed up.

Group II

This group included children receiving oral L_1 at the dose of 75 mg/kg/day in 2-3 divided doses daily. A total of 10 children were enrolled into this group; one child later shifted from group I.

Group III

This group included 10 children receiving both oral L_1 at the dose of 75 mg/kg/day in 2-3 divided doses daily and sub-cutaneous desferrioxamine in the dose of 40 mg/kg/day over a period of 8-10 hours two days a week.

The children were followed up for a period of six months. The primary outcome variable was serum ferritin at the start and at the end of the study. At the onset, 24 hr urinary iron excretion, hemogram, liver and kidney function tests and serologic tests for HIV, HBsAg and HCV antibodies were done.

The children were followed up monthly for estimation of blood counts, three monthly for monitoring liver and kidney functions and six monthly for estimating serum ferritin values and hepatic markers (HBsAg and HCV antibodies). They were also clinically monitored for development of any adverse effects.

Six healthy children receiving no chelation therapy acted as controls for measuring 24-hr urinary iron excretion.

24 hr urinary iron excretion (UIE)

The parents/guardians were instructed to collect 24 hr urinary samples soon after starting the first dose of iron chelation therapy. Iron free glass containers were given to them with strict instruction to prevent any contamination by dust or spillage of urine during or after collection. The method of estimating UIE was based on the recommendations of the International Committee for Standardization in Hematology for determination of serum iron but these were standardized for urine(7).

Serum ferritin was carried out by microparticle enzyme linked immunoassay by kit manufactured by Abbott laboratories (USA).

ELISA antibody kit methods were used in detection of HIV (Lab systems, Finland), hepatitis B (Biokit, SA, Spain) and hepatitis C (J. Mitra, India) infections.

TABLE I–*Serum Ferritin Levels (ng/ml) (mean ± SD)*

Group	Number	Before therapy (*i*)	After therapy (*f*)	Difference (*i* – *f*)
I	7	5077.18 ± 1714.99	3718.30 ± 738.39	1358.87 ± 1374.14
II	11	2672.90 ± 886.44	3422.65 ± 1581.01	–749.75 ± 1155.77
III	10	3347.78 ± 1526.46	3376.57 ± 1222.41	–28.79 ± 915.86

f value = 7.40, *p* = 0.00253 (power92%). Turkey at 5% level: Group I was significantly different from group II.

The side effects and the drug therapy were monitored during the follow up period.

Statistical Methods

Statistical difference between serum ferritin levels was assessed by applying analysis of variance (ANOVA). Analysis of covariance (ANCOVA) was applied to find out the urinary iron excretion keeping the serum ferritin value same in each group. Intention to treat analysis was the basis for assessing the efficacy of each chelating regimen.

Results

The comparison of the anthropometric data showed no statistically significant difference between various groups (P >0.05). The amount of blood transfusion to each patient was uniformly given as 15 ml/kg of red cells. Moreover the frequency of blood transfusion in each patient was around 3 weeks in the study period of six months, thus not affecting disproportionately the serum ferritin values in each group.

Serum ferritin

The final and initial mean values of serum ferritin along with their difference are shown in *Table I*. The values showed that group I was significantly different from group II. The mean final and initial serum ferritin values were log transformed to normalize the non-Gaussian distribution of values, and serum ferritin difference calculated in each group. ANOVA applied on these values revealed that group I was significantly different from group II (*Tables II and III*).

Urinary iron excretion

The effect of chelation was assessed by measuring the 24-hr UIE after giving required drugs in each group. The mean value of UIE along with the control values is shown in *Table IV*. The UIE was correlated with levels of serum ferritin.

To find out the UIE keeping the initial serum ferritin levels equal, analysis of covariance was applied. It was found that the homogenicity of regression slopes was not significantly different. However, the UIE was higher in group III (7.37 ± 1.89 mg/day) followed by group II (5.93 ± 1.22 mg/day) and group I (5.83 ± 1.65 mg/day) *Table IV*, though the difference was not significant (P = 0.2).

TABLE II–*Difference in Ferritin Values after Log Transformation*

Group	No. of patients	Serum ferritin difference* (mean ± SD)
I	7	0.123 ± 0.099
II	11	–0.085 ± 0.1677
III	10	–0.018 ± 0.1388

*Serum ferritin difference = log (serum ferritin initial) – log (serum ferritin final).

f value: 4.574; P value: 0.020. Turkey at 5% level: Group I significantly different from group II (P = 0.016),

TABLE III–*Difference in Serum Ferritin Levels after Log Transformation (Intention to treat analysis)*

Group	No. of patients	Serum ferritin difference (initial - final)
I	10	0.0935 ± 0.0966
II	10	–0.1010 ± 0.1682
III	10	–0.0180 ± 0.1388

P = 0.014; f = 5.031; Tukey test at 5% level: Group I statistically different from Group II (P = 0.010).

TABLE IV: *Mean Urinary Iron Excretion (UIE) after Chelation Therapy*

Group	24 hr UIE in each group at different ferritin levels mg/day(μmol/day)	24-hr UIE keeping the initial serum ferritin values equal. mg/day(μmol/day)
I	7.96 ± 5.05 (142.5)	5.83 ± 1.65 (104.4)
II	4.78 ± 2.12 (85.6)	5.93 ± 1.22 (106.2)
III	7.14 ± 4.99 (127.8)	7.37 ± 1.89 (132.0)
	P > 0.05	P > 0.05

Mean control value of UIE = 0.175 mg/day.

Adverse effects

No adverse effects were noted in group receiving DFX. However, 2 patients out of 21 patients (9.52%) receiving L_1 alone or in combination with DFX had arthropathy of large joints. The medication in these children, was stopped and after resolution of symptoms, was restarted after 10 days in each child. There were no reactions, noticed after restarting the therapy. No hematological abnormality (agranulocytosis, thrombocytopenia) or renal function derangement was detected in any of the patients. Most (85.7%) patients showed raised blood levels of SGPT. All these patients had elevated serum ferritin and 9/28 patients (32.41%) also had associated HCV infection. Hence the causal effect of the drugs or increased iron load on liver toxicity could not be ascertained. None of the children in the study group were HbsAg positive.

Cost of treatment

An attempt was made to find out the relative cost of different modes of chelation therapy (*Table V*). As is evident, the cost of treatment was maximum in the group receiving DFX therapy. The cost is almost double than the group receiving combination therapy and seven times the group on L_1.

The cost increased exponentially with the increasing weight of the child in different groups.

Discussion

The baseline anthropometric data of the patients was similar in all the 3 groups thus ruling out its confounding influence on the observations. The present study clearly demonstrated a direct correlation of UIE with serum ferritin. These results are in conformity with the observations of other workers(8-10).

To ascertain the efficacy of chelating drugs in various groups by following the analysis of covariance it was noticed that the UIE was highest in the group where combination of DFX and L_1 were administered. Wonke, *et al* also noticed an additive effect of combination of drugs on urinary iron excretion(5). The synergistic and additive mechanism in which oral chelator mobilizes tissue iron and then exchanges with the parenteral agent has been proposed(11).

The efficacy of various chelating drugs was assessed by reduction in iron overload as assessed by decrease in serum ferritin values after 6 months of chelation therapy. The DFX was effective in reducing the iron overload whereas serum ferritin levels were almost stationary on the combined regimen. A rise in

TABLE V–*Relative Cost of Treatment of Patient Weighing 10 kg*

Variables	Group I	Group II	Group III
Frequency	Desferrioxamine daily for 5 days a week	Deferiprone daily	Deferiprone daily and desferrioxamine 2 days a week
Dosage	40 mg/kg	75 mg/kg	Deferiprone = 75 mg/kg Desferrioxamine = 40 mg/kg
Dose required per day	400 mg	750 mg	DFX = 400 mg L_1 = 750 mg
Cost of drug	Rs.150 for vial of 500 mg; Rs. 30 for needle and syringe = Rs. 180	Rs. 6 per capsule of 250 mg, 3 capsule daily. Rs. 18	Rs. 198
Cost of treatment per wk	Rs. 900	Rs. 126	Rs. 486
Cost of treatment for 6 mths	Rs. 21600	Rs.3024	Rs. 11664
Cost difference in 6 months with group II as minimum	Rs. 18576	-----	Rs. 8640

ferritin values had been noticed in the group where only deferiprone (L_1) was used.

Therapy with DFX is a well-established effective therapy for iron chelation in thalassemic children (9,12). However it's difficult mode of administration and high cost of treatment are strong impediments to follow this therapy on regular basis, especially in developing countries. The results of combined therapy have been encouraging as also noticed by few other workers(5,6). The combined regimen may be followed in a large group of patients for longer period of time for definitive conclusions.

There was a rise in serum ferritin values after 6 months of chelation with oral L_1 which is in conformity with the results of few earlier workers(13,14). L_1 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(3). 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(14). Recently, there was an interesting study demonstrating increased efficacy of L_1 in reducing myocardial iron as compared to DFX(15). However this effect needs to be studied on a larger number of patients. UIE is an important test to monitor iron overload during treatment. Its measurement helps in assessing the presence or absence of negative iron balance. However the comparative efficacy of chelating agents may not be exactly found out by relying only on urinary excretion as 30-50% of chelatable iron is excreted via feces in children receiving DFX therapy.

The efficacy was further assessed by measuring serum ferritin values. In the present study the changes in serum ferritin values at the end of the study were statistically different in group I as compared to group II. The fall in serum ferritin levels in group I inspite of the

Key Messages

- Desferrioxamine is the most effective chelation therapy for treatment of iron overload in thalassemic children.
- Combination therapy is an effective, acceptable and cheaper mode of chelation therapy, which may be utilized as a method of chelation in developing countries like India.
- Deferiprone alone is not a good chelator of iron, atleast if used for a short period of time.

similar amount of UIE as compared to other groups could be due to the excretion of chelatable iron by DFX into the feces which was not measured in the present study.

The gold standard for measuring and monitoring patients with iron overload, a liver iron concentration was not carried out. Nevertheless, serum ferritin concentration suggests a fairly good assessment of the body iron stores.

Our study did not show any side effects in the daily DFX treated group. No other side effects except arthropathy was noticed in the L_1 treated group either alone or in combination. The lower incidence of arthropathy in the present study, 9.52% vis-a-vis 35.2% reported in another Indian study(3) could be due to increased dose of L_1 (l00mg/kg) used by those workers.

The comparison of the cost incurred by the patients showed a very high cost of the therapy for group I as compared to groups II and group III. Though the efficacy of combined therapy serum ferritin values was less as compared to DFX daily therapy but it succeeded in maintaining the serum ferritin values at almost the same level at a considerable low cost.

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