

EFFICACY AND SAFETY OF DEFERASIROX WHEN COMPARED TO DEFERIPRONE AS ORAL IRON CHELATING AGENT: A RANDOMIZED CONTROL TRIALSanjeeva G. N¹, Nijaguna N², Mahantesh Matti³, Pooja Gujjal Chebbi⁴**HOW TO CITE THIS ARTICLE:**

Sanjeeva G. N, Nijaguna N, Mahantesh Matti, Pooja Gujjal Chebbi. "Efficacy and Safety of Deferasirox when Compared to Deferiprone as oral iron Chelating Agent: A Randomized Control Trial". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 24, March 23; Page: 4178-4185, DOI: 10.14260/jemds/2015/601

ABSTRACT: BACKGROUND: Thalassemia is one of the most common inherited hemoglobinopathy seen in southern India. With regular blood transfusion, these children live longer but associated morbidity due to iron overload impairs the quality of life. We studied the efficacy and safety of new oral iron chelator, deferasirox, compared with deferiprone which was used for long time. **MATERIAL AND METHODS:** We conducted a prospective randomised control study, between January 2011 to June 2012 at thalassemia day care centre of Indira Gandhi Institute of Child Health, Bengaluru. The children who were diagnosed as Thalassemia and receiving regular blood transfusion with serum ferritin levels more than 1000ng/ml and not receiving any chelation therapy were included in the study. These children were randomly divided into two groups as group 1 and group 2 by computer generated randomization. The children included in group 1 received Deferasirox and group 2 received Deferiprone as chelation therapy. The dosage of deferasirox was 20mg/kg/day once daily and that of deferiprone 75 mg/kg/day in three divided daily doses. The primary study outcome was to measure and compare the decrease in serum ferritin levels between the two study groups. The secondary outcome measures were to compare the side effect profiles among the two groups. **RESULTS:** We included 41 thalassemic children and 19 of them were included in group 1 (Deferasirox) and 22 children in Group 2 (Deferiprone). At the end of study period of 18 months three children in group II discontinued therapy due to side effects, hence the remaining 19 were available for final analysis in group 2 whereas no drop outs in the group 1. During the study period, the serum ferritin decreased from 3261±2613ng/dl to 1586±766 ng/dl in group 1 as compared in group 2 from 4109±3153ng/dl to 1743±1138ng/dl (fig 2). This was also not statistically significant. In group 2, 68% of the children experienced adverse effect as compared to 36.8% in group 1 children. In group 2 children 9 had arthralgia out of which 3 children were discontinued their treatment as compared to one child in group who had arthralgia but none discontinued the treatment. **CONCLUSION:** Both deferasirox and deferiprone are equally efficacious in reducing the serum ferritin levels in thalassemic children receiving chronic blood transfusion therapy. However the side effects profile including severe adverse effects like arthralgia and arthritis requiring discontinuation of therapy was higher in children receiving deferiprone as compared to deferasirox.

KEYWORDS: Deferasirox, Deferiprone.

INTRODUCTION: "Thalassemia" inherited as autosomal recessive pattern, is the most common hemoglobinopathy seen throughout the world. With carrier frequency of 3 – 17%, thalassemia is major health burden in India. With the regular blood transfusion thalassemia has become chronic manageable disease. Though transfusions are life-saving, are associated with burden of iron overload.

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This excess iron causes iron mediated free radical damage causing liver fibrosis, endocrine failure and myocardial damage leading to morbidity and mortality. Cardiomyopathy due to iron overload is most common cause of death in well transfused children. Hence iron chelation therapy becomes very important to prolong the lives of thalassemic children.

Oral iron chelators presently available are –Deferiprone and Deferasirox. Deferiprone is oral iron chelator, dosage being 75 mg/kg/day (range 50-120 mg/kg/day) in 2-4 divided doses. Incidences of side effects such as neutropenia, agranulocytosis, arthropathy are higher. Thus there is a constant search for an ideal chelator which is oral, effective with less side effects.

Deferasirox is a new oral chelator now available. It is approved by the US Food and Drug Administration. Adverse effects are gastrointestinal disturbances, diffuse rash, fever, headache and cough, mild to moderate elevation of the S.creatinine level, Elevations of liver enzyme levels. Deferasirox is the most recommended chelator by the thalassemia international federation.¹

There is need to study and compare these two oral iron chelators with respect to their efficacy in reducing iron overload and adverse effects. Most of the studies compared Deferoxamine which is a parental iron chelator either with Deferasirox or with Deferiprone. This study was to compare these two oral drugs, to help physician to choose better among them.

MATERIAL AND METHODS: We conducted a prospective randomised control study, between January 2011 to June 2012 at thalassemia day Care Centre of Indira Gandhi institute of child health, Bengaluru. During this initial 6 months, between January 2011 till June 2011, recruitment of the study subjects were made. The children who were diagnosed as Thalassemia and receiving regular blood transfusion with serum ferritin levels more than 1000ng/ml and not receiving any chelation therapy were included in the study. The thalassemic children who were already on chelation therapy or having chronic liver or renal disease were excluded from the study.

These children were randomly divided into two groups as group 1 and group 2 by computer generated randomization. The children included in group 1 received Deferasirox and group 2 received Deferiprone as chelation therapy. The dosage of deferasirox was 20mg/kg/day once daily and that of deferiprone 75 mg/kg/day in three divided daily doses.

Children from both the group were followed up monthly to assess for side effect profile. S. ferritin levels, WBC, platelet count, blood urea, serum creatinine and serum enzymes (SGOT and SGPT) were recorded before starting chelation therapy and the same were repeated every 3 months. The blood transfusions, drugs and investigations were provided free of cost and were continued even after completion of Serum ferritin was measured by ELISA method.

OUTCOME MEASURE: The primary study outcome was to measure and compare the decrease in serum ferritin levels between the two study groups. The secondary outcome measures were to compare the side effect profiles among the two groups.

STATISTICAL METHODS: Results of continuous variables are presented as mean±SD and results of categorical variables are presented in number(%). Significance is assessed at 5% level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis). P value of less than 0.05 was considered as statistically significant. The statistical software SPSS 19.0 and Med Calc 9.0.1 were used for the analysis of the data and microsoft word and excel have been used to generate graphs, tables etc.

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RESULTS: We included 41 thalassemic children and 19 of them were included in group I (Deferasirox) and 22 children in Group II (Deferiprone). At the end of study period of 18 months all 19 children remained in group I and three children in group II discontinued therapy due to side effects, hence the remaining 19 were available for final analysis. (Fig. 1)

Among the study groups, 68% of the children in group 1 were under 5 years of age and 63% of children in group 2 were between 6-10years of age. There is no gender difference between two groups. (Table 2)

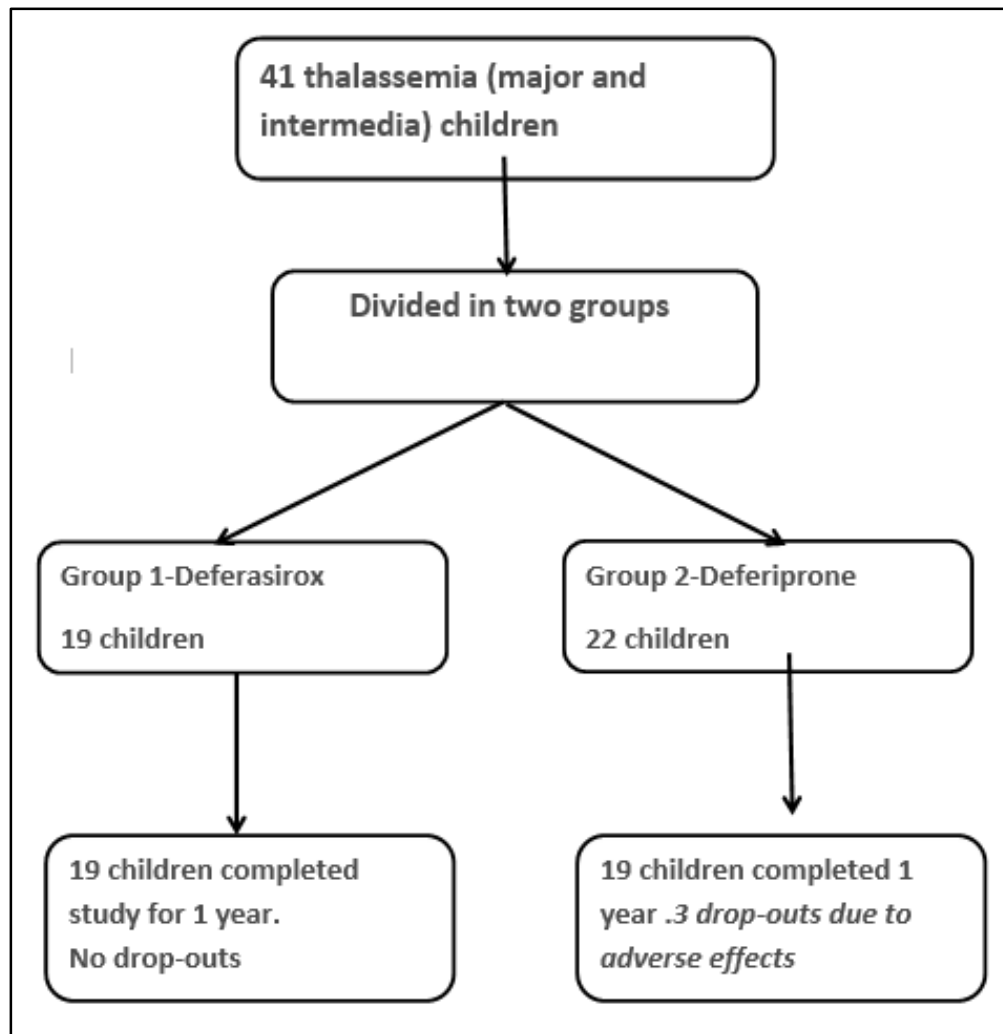


Fig 1: Study profile

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| Age in years | Group I | | Group II | |
|---------------|-----------------|--------------|-----------------|--------------|
| | No | % | No | % |
| 1-5 | 13 | 68.42 | 04 | 21.05 |
| 6-10 | 05 | 26.31 | 12 | 63.12 |
| >10 | 01 | 5.27 | 03 | 15.83 |
| Total | 19 | 100 | 19 | 100 |
| Mean \pm SD | 5.23 \pm 2.76 | | 7.26 \pm 2.42 | |
| Median | 4 | | 7 | |
| Gender | | | | |
| Male | 11 | 57.89 | 11 | 57.89 |
| Female | 08 | 42.11 | 08 | 42.11 |
| Total | 19 | 100.0 | 19 | 100.0 |

Table 1: Baseline parameters

The group 2 children has received more number of blood transfusions (mean= 29) before they were included in the study as compared to group 1 who have received mean 21 number of blood transfusions. The mean volume of blood received before enrolment was 3600 \pm 2010 ml in group 1 as compared to 4787 \pm 1793 ml in group 2 which was not statically significant. The base line serum ferritin level was 3261 \pm 2613ng/dl in group 1 as compared to 4109 \pm 3153 ng/dl in group 2 children. This was not statistically significant.

| | Group I | Group II | P value |
|--|-----------------|------------------|---------|
| Variables before chelation therapy | | | |
| No. of transfusion before chelation (median) | 21 | 29 | NA |
| Volume of blood before chelation in ml | 3600 \pm 2010 | 4787 \pm 1793 | 0.0627 |
| Ferritin before chelation | 3261 \pm 2613 | 4109 \pm 3153 | 0.3727 |
| Variables after one year of study period | | | |
| No. of transfusions during chelation | 10.68 \pm 2.1 | 11.42 \pm 2.11 | 0.2858 |
| Volume of blood during chelation (ml) | 2163 \pm 645 | 2560 \pm 646 | 0.0661 |
| S. ferritin at 1 year | 1586 \pm 766 | 1743 \pm 1138 | 0.6209 |

Table 2: Variables before and after study period

During the study period group 1 children received mean 10.68 \pm 2.1 times blood transfusions as compared to group 2 children who received mean 11.42 \pm 2.11 times blood transfusions. The mean volume of blood received during study period was 2163 \pm 645 ml in group 1 as compared to 2560 \pm 646 ml in group 2 which was not statically significant. The serum ferritin level at the end of one year was 1586 \pm 766 ng/dl in group 1 as compared to 1743 \pm 1138 ng/dl in group 2 children. This was not statistically significant (Table 2).

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During the study period, the serum ferritin decreased from 3261 ± 2613 ng/dl to 1586 ± 766 ng/dl in group 1 as compared in group 2 from 4109 ± 3153 ng/dl to 1743 ± 1138 ng/dl (fig 2). This was also not statistically significant.

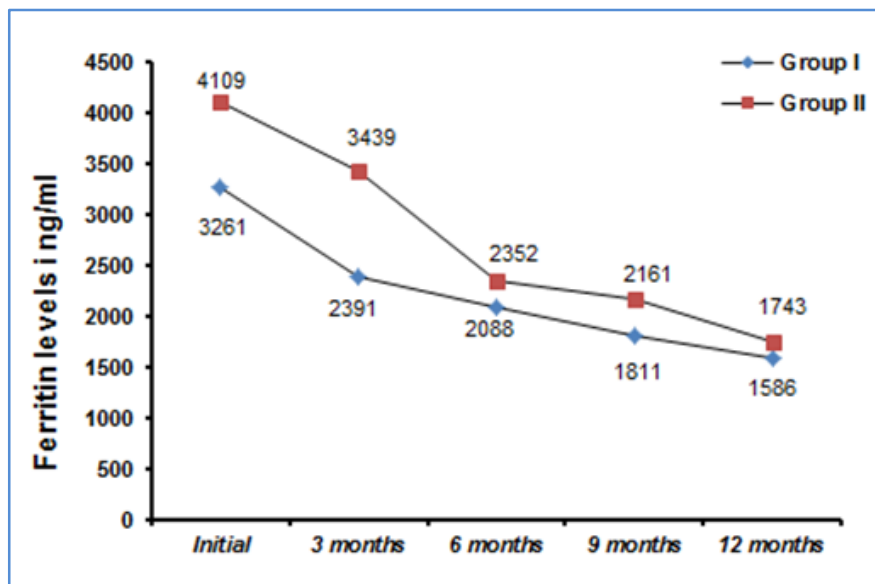


Fig. 2: Response to Chelation therapy

Supplement Decrease in the serm ferritin levels.

| Ferritin levels | Group I | Group II | P value |
|--------------------------------------|-----------------|-----------------|---------|
| Initial | 3261 ± 2613 | 4109 ± 3153 | 0.3727 |
| 3 months | 2391 ± 1589 | 3439 ± 2774 | 0.1616 |
| 6 months | 2088 ± 1536 | 2352 ± 1269 | 0.5671 |
| 9 months | 1811 ± 1155 | 2161 ± 1324 | 0.3910 |
| 12 months | 1586 ± 766 | 1743 ± 1138 | 0.6209 |
| P value (from baseline to end value) | 0.0110 | 0.0040 | |

In group 2, 68% of the children experienced adverse effect as compared to 36.8% in group 1 children. In group 2 children 9 had arthralgia out of which 3 children were discontinued their treatment as compared to one child in group who had arthralgia but none discontinued the treatment.

| Adverse effects | Group I n=19 | | Group II n=22(19+3) | |
|-----------------|-----------------|------|------------------------|------|
| | No | % | No | % |
| Nil | 12 | 63.1 | 7 | 31.8 |
| Present | 7 | 36.8 | 15 | 68.2 |

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| | | | | |
|---|---|------|---|------|
| • P. Arthralgia | 1 | 5.2 | 9 | 40.9 |
| • Pain abdomen | 0 | 0 | 1 | 4.5 |
| • Nausea & vomiting | 6 | 31.5 | 6 | 27.2 |
| • Rash | 0 | 0 | 0 | 0 |
| Table 3: Adverse effects of the chelating agents | | | | |

DISCUSSION: We studied the efficacy and safety of two oral chelating agents' deferasirox and deferiprone in thalassemic children. The efficacy was studied by measuring the reduction in serum ferritin levels during one year study period in both groups. The safety of the chelating agents was measured by the incidence and severity of adverse effects observed during the study period. The children in group 2 were older than children in group 1 because 4 thalassemia intermedia children were included in group 2 had. Largest ever investigation conducted for an iron chelator was EPIC study by Cappellini et al with 1744 patients included patient's aged 2-89 years.²

There was no statistically significant difference in gender, mean volume of blood transfusion before chelation therapy and baseline ferritin levels in both the groups. Similarly, during the study period number of transfusions and volume of blood received was comparable in both the groups after 12 months of therapy. The dosage used in the study was comparable to that used in other studies.

There are no literature available comparing the efficacy and safety of these chelating agents together. Instead many studies were conducted using individual chelating agents separately.

The drop in the serum ferritin levels in group one children after one year of chelation therapy was significant. The median percentage of fall of ferritin observed is 48.17%. This was comparable with many other studies on Deferasirox. Rashid Merchant et al from Dr. Balabhai Nanavati Hospital, Mumbai studied 30 thalassemia patients who were given Deferasirox at dose of 20-35 mg/kg/day for 18 months. They found statistically significant decrease in serum ferritin values after 18 months of therapy and percentage of fall was 30.2% which was comparable to our study.³ Anil Pathare et al studied 19 heavily iron-overloaded patients with deferasirox therapy for 18-months. They also found significant reduction in median serum ferritin from a baseline. They also reported good cardiac chelation property of Deferasirox.⁴

Cappellini et al in EPIC study studied 1744 patients, who were given Deferasirox at dose of 10-30 mg/kg/day for 52 weeks, showed a significant reduction in serum ferritin from baseline.²

In group 2 children, the reduction in serum ferritin from the baseline after one year of therapy was significant with the percentage fall from the baseline was 55.61%. Panigrahi et al from Post-Graduate Institute of Medical Education & Research (PGIMER), Chandigarh, India studied 110 patients with mean age of 17 years, given the drug for 72 months and observed significant fall in ferritin levels.⁵ El Alfy and colleagues reviewed its use in 100 children (mean age 5.1±2.4 Years) with thalassemia or sickle cell disease. At the end of the 6 month treatment period there was a significant drop in mean serum ferritin levels.⁶

Similar results were reported in another trial by Won Et al who reported that mean serum ferritin levels decreased from the baseline following median treatment duration of 11.4 months.⁷

However, Hoffbrand et al and Cohen et al noted no significant change in overall mean serum ferritin levels achieved in up to 1 year of treatment.^{8,9} The reasons for those study results are not known.

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ANALYSIS OF ADVERSE EFFECTS OF EACH DRUG: Most common side effects observed with chelators are neutropenia, alteration in renal and liver functions as well as GI and musculoskeletal system involvement. In children receiving deferasirox 36.8 % of them developed side effects compared to 68.2% in children who received Deferiprone. Nausea and vomiting was the most common side effect with Deferasirox developed in 6 patients, which did not required any treatment. 1 patient had arthralgia which was managed with short period treatment with analgesics. None of the patients had rashes. These results are comparable with other studies except the incidence of rashes, majority of studies noted rashes as side effect of Deferasirox but we did not have single child developing rash.^(2,10,11,12,13)

In EPIC study the most common adverse events were gastrointestinal disturbances (28%) and skin rash (10%). The most common drug-related adverse events were diarrhoea (14.4%), skin rash (10.0%), and nausea (7.7%) and arthralgia (0.6%).² Ali Taher et al noted vomiting (11%), nausea (8%), skin rash (8%), abdominal pain (6%) and diarrhoea (6%). The side-effects of deferasirox were minimal and easily manageable¹¹. In all these studies adverse effects were predominantly transient and mild to moderate in nature. Their incidence generally decreased after the first year of deferasirox, and tolerance appeared to improve over the long term, because the proportions of patients presenting with the most common drug-related adverse effects decreased considerably after the first year of deferasirox treatment.

Arthralgia, most important side effect of deferiprone, was developed in 9 out of 22 children in our study. Among them 3 children had severe joint pain which could not be relieved with analgesics and temporary stoppage of the drug. In these 3 children drug was stopped permanently and switched over to deferasirox. Joint pain reduced 3 weeks after stopping of drug. In remaining 6 children who had joint pain was mild and was relieved with analgesics. Agarwal et al studied 52 patients on deferiprone and noted 20 patients having arthralgia as major side effect.¹⁴ In another study involving 187 patients Cohen et al noted reddish discoloration of the urine in 74 patients, 20 patients had joint pain, 2 reported joint swelling and 2 reported both symptoms.⁹

The limitation of the study being the small numbers and relatively higher levels of the serum ferritin levels in children who received deferiprone.

To conclude, the chelating agents, deferasirox and deferiprone are equally efficacious in reducing the serum ferritin levels in thalassaemic children receiving chronic blood transfusion therapy. But, the deferiprone is associated with severe adverse effects like arthralgia and arthritis requiring discontinuation of therapy in few children as compared to deferasirox.

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Date of Submission: 09/03/2015.
Date of Peer Review: 10/03/2015.
Date of Acceptance: 13/03/2015.
Date of Publishing: 23/03/2015.