Section: Pediatrics

Original Research Article

A STUDY TO ASSESS THE SAFETY AND EFFICACY OF ORAL IRON CHELATORS EITHER ALONE OR IN COMBINATION IN PATIENTS WITH THALASSEMIA

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Received *: 10/05/2024*
Received in revised form *: 14/07/2024*
Accepted *: 30/07/2024*

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DOI: 10.70034/ijmedph.2024.3.39

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2024; 14 (3); 221-225

ABSTRACT

Background: Thalassemia is a genetic blood disorder in children that results in the production of abnormal hemoglobin, leading to severe anemia and the need for frequent blood transfusions. Without proper management, these transfusions can cause iron overload in the body, which can damage vital organs such as the heart and liver. Therapy with oral iron chelators is crucial for these children, as it helps to remove the excess iron and prevent potential complications. The aim of this study was to assess and compare the effectiveness and safety of oral iron chelators, both when administered alone and in combination, in children with thalassemia who receive several blood transfusions.

Materials and Methods: The study was carried out in the Department of Pediatrics, Sri Balaji Medical College and Hospital, over a period of ¬¬¬¬24 months. The study included 75 children with thalassemia who had undergone several transfusions and were receiving daily treatment with iron chelation.

Results: The current study included 75 children with thalassemia who had received multiple blood transfusions. For duration of 12 months, they received daily iron chelation therapy with either deferiprone alone (Group 1), deferasirox alone (Group 2), or a combination of the two (Group 3). The serum ferritin levels were found to be reduced in all 3 groups, however the difference was not significant. The hepatic T2- MRI values had increased from baseline to follo-up, however the difference was significant only in Group 3. The reduction of cardiac T2* MRI value was significantly reduced in Group 3 from baseline to follow-up.

Conclusion: This study concluded that deferiprone and deferasirox were effective and safe when administered alone in children with thalassemia who had received several transfusions.

Keywords: Children, thalassemia, safety, innovative combination, and comparative efficacy.

INTRODUCTION

The advent of chelation therapy in the 1960s revolutionized treatment for patients needing regular blood transfusions. Deferoxamine, introduced in the 1970s with six iron-binding sites, significantly improved thalassemia patient survival rates but faced challenges due to its administration method and cost, affecting adherence. Deferiprone, a two-site chelator used since 1987, proved particularly effective in removing iron from heart muscles, but required close patient monitoring due to side effects like erosive arthritis (5-20% of cases), neutropenia (up to 5%), and severe agranulocytosis (up to 0.5%).[1-3]

An ideal iron-chelating drug should have high oral bioavailability and a manageable dosage schedule. Deferasirox, a new oral chelator developed through focused research, meets these criteria with its once-daily administration ensuring continuous drug availability due to its 8-16-hour half-life. Clinical trials showed that a minimum dosage of 30 mg/kg/day is necessary to reduce serum ferritin

levels, and the effectiveness of deferasirox is influenced by the extent of transfusional iron load.[4-6]

Deferasirox has proven to be tolerable in most patients, with common side effects including gastrointestinal issues, rash, slight creatinine increases, and raised liver enzymes. These trials showed lower iron burdens in patients compared to average Indian patients, where cost, compliance, and toxicity of earlier chelators like deferoxamine and deferiprone hindered adequate therapy. Deferasirox received FDA approval in 2005 and entered the Indian market in -April 2008.[7-10]

T2 star MRI (T2* MRI) can assess iron concentrations in the heart and liver, aiding in the early detection of myocardial hemosiderosis before clinical symptoms appear.[11]

This study was conducted with an aim to evaluate safety and efficacy of deferasirox in children with thalassemia major, with major focus on patient adherence. The study aims to assess the benefits of oral iron chelators used alone or in combination in children undergoing frequent blood transfusions.

MATERIAL AND METHODS

This prospective observational study was conducted in the OPD of Department of Pediatrics, Sri Balaji Medical College and Hospital, over a period of 24 months, i.e. from June 2022 to May 2024. All patients with thalassemia major who underwent several blood transfusions and are on daily oral iron chelator therapy were included in the study. Patients with history of anaphylactic reaction to oral iron chelators, or with deranged renal function tests or presence of other concurrent systemic conditions or with neutropenia (ANC <1.5 X 109/ mL) or thrombocytopenia (< 50,000/ mm3) were excluded from the study.

Ethical committee approval was taken from the ethics committee of our institution. Written informed consent was collected from the parents or guardians of the patients. Those who were unwilling to participate in the study were excluded.

A detailed history was taken with special emphasis on birth history, past medical history, treatment history, any history of transfusion reactions or anaphylaxis to iron chelating agents. General and systemic clinical examination was done. All patients were subjected to routine haematological investigations such as complete blood count, liver function tests, kidney function tests and viral markers were done. Complete iron profile was done which included serum iron, serum ferritin, transferrin saturation and total iron binding capacity. Patients with serum ferritin levels >1500ng/mL were considered to be having iron overload. Investigations were repeated 6 months after follow-up.

A total of 75 patients were included in the study. All patients were equally divided into ones on therapy with deferasirox (DFX) alone (n = 25) or deferiprone (DFP) alone (n = 25) or on a combination of DFP+DFX (n = 25). Doses used were DFX-30 mg/kg, DFP- 75 mg/kg/day and DFP+DFX-50 +30 mg/kg/day daily.

All patients were subjected to T2* MRI to assess the amount of iron present in cardiac and hepatic tissue. Each scan lasted about 30 minutes and included the measurement of hepatic and cardiac T2*. The cut off points are as follows: Hepatic: normal > 6.3ms, mild: 2.8-6.3ms, moderate: 1.4-2.7ms, severe <1.4ms. Cardiac: normal >20ms, mild: 14-20ms, moderate: 10-14ms, severe <10ms.

Data was entered into MS Excel and analysed using SPSS 23.0 software. Categorical variables were evaluated using analysis of variance, Chi-square test, or Fischer's exact test. P value of 0.05 was considered as statistically significant.

RESULTS

F75 children with thalassemia who were receiving daily iron chelation therapy were included in this study. The medication consisted of either deferiprone alone, deferasirox alone, or a combination of both, and was administered for a duration of 12 months. The participants were categorized into three groups, each getting daily treatment according to the following protocol: Group 1 consists of participants who received just Deferiprone (n = 25), Group 2 consists of participants who received only Deferasirox (n = 25), and Group 3 consists of participants who received a combination of Deferiprone and Deferasirox (n = 25).

Serum Ferritin

Measurements of serum ferritin were taken at the beginning of the study, at 6 months, and at 12 months following chelation therapy. The baseline mean serum ferritin levels in Group 1 were 3324.05 + 562.98 ng/mL, in Group 2 were 2879.89 + 512.54 ng/mL and in Group 3 were 3514.74 + 665.24 ng/mL. The average serum ferritin levels were reduced after initiation of chelation therapy as observed at 6 months and 12 months. However, there was no statistically significant difference in the baseline and follow-up mean serum ferritin concentrations among all three study groups, indicating that the groups were equivalent. [Table 1]

T2* MRI hepatic values at baseline and follow up:

The baseline mean values of T2* MRI in the Deferiprone group (Group 1) was 4.62 $\pm$ 0.84 m sec, 6.24 $\pm$ 0.42 m sec in Group 2, and 6.64 $\pm$ 0.54 m sec in Group 3. The T2* MRI values of hepatic tissue at 6 months of follow-up are - 6.60 $\pm$ 0.58 m sec in Group 1; 6.74 $\pm$ 0.43 m sec in Group 2; 6.85 $\pm$ 0.23 m sec in Group 3. The values were found to be elevated in all three groups during the subsequent MRI conducted after six months of their individual treatments, suggesting a decrease in the amount of iron accumulated in the liver. Despite a decrease in iron accumulation, the findings were still found to indicate a mild level of iron excess in the liver. The

difference is not significant in Group 1 and Group 2, but is statistically significant in Group 3. [Table 2]

MRI T2* cardiac, Baseline and Follow up:

The baseline mean values of T2* MRI cardiac in the Deferiprone group (Group 1) was 34.81 m sec, 33.24 m sec in Group 2, and 31.47 m sec in Group 3. The T2* MRI values of hepatic tissue at 6 months of follow-up are as - 30.24 m sec in Group 1; 31.52 m sec in Group 2; 31.02 m sec in Group 3. There was reduction of values from baseline to follow-up visit. The difference was statistically significant in patients of Group 3. [Table 3]

During the clinical assessment of all patients included in the trial, two patients in group 3, who were receiving a combination of deferiprone and deferasirox, developed arthropathy in their major joints within 5 weeks after starting the medication. The administration of Deferiprone was halted and further observation revealed a reduction in arthropathy symptoms among patients. A patient undergoing treatment with deferasirox experienced modest abdominal pain, which was found to decrease after using oral proton pump inhibitors for a duration of 10 days. No negative effects of the medications being examined justified stopping chelation therapy during the entire trial period. Furthermore, there were no instances of death recorded throughout the duration of the study. The complete blood counts and renal function tests were within the normal range. None of the patients had proteinuria throughout the whole research period. Elevated liver enzymes were detected without any apparent clinical symptoms. [Table 4]

Table 1: Study Groups

	Group 1 (Deferiprone) (n = 25)	Group 2 (Deferasirox) (n = 25)	Group 3 (Combination Therapy) (n = 25)
Mean Age (+-SD)	12.74 (+-2.64)	12.80 (+-2.84)	12.84 (+-2.45)
Gender (M/F)	(15/10)	(18/7)	(13/12)

Table 2: Serum Ferritin Values

Serum Ferritin	Group 1 (Deferiprone)	Group 2 (Deferasirox)	Group 3 (Combination Therapy)
Baseline	3324.05 ± 562.98 ng/mL	2879.89 ± 512.54 ng/mL	3514.74 ± 665.24 ng/mL
At 6 months	2994.78 ± 589.65	2587.26 ± 557.95	3098.99 ± 684.99
At 12 months	2457.99 ± 579.71	2124.49 ± 525.23	25410.54 ± 632.65
P value	0.08	0.06	0.08

Table 3: Mean Values of Liver at Baseline and Follow-Up

MRI T2* Liver (msec) (+-SD)	Group 1 (Deferiprone)	Group 2 (Deferasirox)	Group 3 (Combination Therapy)
Baseline	4.62 ± 0.84 m sec	6.24 ± 0.42 m sec	6.64 ± 0.54 m sec
Follow up	6.60 ± 0.58 m sec	6.74 ± 0.43 m sec	6.85 ± 0.23 m sec
P value	P>0.05	P>0.05	P<0.05

Table 4: Mean Values of MRI T2* Heart at Baseline and Follow-Up

MRI T2* Heart (msec) Mean (+-SD)	Group 1 (Deferiprone)	Group 2 (Deferasirox)	Group 3 (Combination Therapy)
Baseline	34.81 m sec	33.24 m sec	31.47 m sec
Follow up	30.24 m sec	31.52 m sec	31.02 m sec
P value	P>0.05	P>0.05	P<0.04

DISCUSSION

Packed red blood cell transfusion is crucial for treating refractory anemias, including transfusion-dependent thalassemia. However, iron overload from frequent transfusions can lead to severe complications such as hepatic dysfunction, endocrinopathies, and cardiac issues, making iron chelation therapy necessary to manage iron levels. Macrophages play a key role in recycling iron from old red blood cells, but the body cannot excrete excess iron from transfusions, leading to potential iron-related health issues.[12-14]

The mean age of patients in present study is 12.5 years. In a related study conducted by Gomber S et al,[15] 49 children were involved, and the average age of the patients was determined to be 11.6 years. Many of the patients in a phase 3 study of deferasirox were younger than 16 years old, and the majority of them were treated for one year. The ESCALATOR experiment conducted by Taher A et al,[13] had an age range of 2-42 years, with a mean of 13.2 years. There were 162 pediatric patients, with a mean age of 9.5 years, which is consistent with the results of the present study. The efficacy of DFX was investigated in a research involving 407 patients with transfusion-dependent thalassemia by Eshghi P et al,[16] The mean age in their study was 11.5 + 7.4 years; 108 patients were 17–24 years old, 206 were 6–14 years old, and 93 were 2–5 years old. Totadri S et al,[17] studied the efficacy and safety of combining deferiprone with deferasirox medicine in 36 patients with thalassemia major. The mean age of their study was 13.9 years. The present study's mean age group differs from and is similar to other studies, demonstrating

inconsistencies in research design. Researchers in India typically reported a younger age group when compared to studies conducted in other Asian and Western countries

Baseline serum ferritin values in the present study were 3277.01 ng/mL for Group 1, 2977.79 ng/mL for Group 2, and 3405.94 ng/mL for Group 3. All three groups had similar serum ferritin levels at the beginning of the current study although there was reduction of serum ferritin levels after initation of chelation therapy, the difference was not statistically significant.

According to the meta-analysis conducted by Xia S et al,[3] which included two subgroups of four trials, there was no statistically significant difference in serum ferritin levels between the two iron chelation regimens. There was no statistically significant difference between the control and intervention groups at 12 months, as indicated by the standard mean subgroup difference of -0.16. The results of this meta-analysis show that serum ferritin levels were not significantly changed by the addition of deferiprone to desferrioxamine or by desferrioxamine alone. This finding suggests that, at the SF level, desferrioxamine treatment is just as effective as deferiprone monotherapy or combination therapy.

Gomber S et al,[15] measured the average blood ferritin levels before, six months, and twelve months after chelation treatment began. Serum ferritin levels were similar at baseline in all three groups (Deferiprone, Deferasirox, Deferiprone, and Deferasirox). All three groups showed a decline in serum ferritin levels after 6 and 12 months of chelation treatment, respectively. The serum ferritin reduction rate in the combination group was significantly higher than in groups 1 and 2.

In contrast to serum ferritin, MRI T2* provides a rapid, non-invasive, and repeatable way to diagnose iron overload in the liver and heart. In present study, all 3 groups showed increased levels of hepatic T2* MRI values from baseline to follow-up, the difference was not significant. The results of the study by Gomber S et al,[15] showed that patients exhibited minor hepatic iron excess as shown by liver MRI T2* values. Mild hepatic iron overload was still diagnosed based on the results of the follow-up MRI even after six months of taking the prescribed medicine. Both the baseline and follow-up readings of heart MRI T2* were very similar. The average 24-hour urinary iron excretion value in the combination group was higher at 12 months compared to the baseline value. The seemingly insignificant difference could be explained by the brief lag time between the follow-up MRI scans of the heart and liver.

In present study, five weeks after starting treatment with the combination of deferiprone and deferasirox, two patients in the current inquiry suffered arthropathy of the main joints. It was observed that the arthropathy improved after discontinuing deferiprone. Two of the deferasirox patients had mild stomach pain that resolved after ten days of taking oral proton pump inhibitors. No patient on oral chelation therapy had discontinued the therapy and no fatalities were reported. There were no abnormalities in the renal function tests or full blood counts. Proteinuria was not observed in any of the patients during the trial period. Liver enzyme levels were discovered to be high, despite the absence of any clinical signs.

In present study, there was reduction of cardiac T2* MRI values from baseline to follow-up. However this difference was statistically significant in Group 3 patients.

In study done by Eghbali et al,[11] cardiac T2* MRI is associated with age of patients which is similar to study done by Shamsian et al.[18]

CONCLUSION

The combination of deferiprone and deferasirox proves to be more effective in lowering iron overload compared to the individual drugs. Fifty thalassemia children who had several transfusions had their serum ferritin, hepatic and cardiac MRI*T2 scans, and iron excretion in urine tested. On the other hand, deferiprone and deferasirox were safe and effective when administered alone in thalassemia patients who had undergone several transfusions. Future studies should be conducted with larger sample sizes and longer follow-up periods to determine whether combination therapy can be routinely used to treat children with beta thalassemia major who have undergone several transfusions.

Funding: None

Conflict of Interest: No conflicts of interest were declared.

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