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Dr. Pagadala Koteswar
Associate Professor, Department of Paediatrics, Madha Medical College, Chennai, Tamil Nadu, India

Dr. Madhur Nivrutti Raimule
Assistant Professor, Department of Community Medicine, Tagore Medical College, Chennai, Tamil Nadu, India

Correspondence
Dr. Pagadala Koteswar
Associate Professor, Department of Paediatrics, Madha Medical College, Chennai, Tamil Nadu, India

To study safety and effectiveness of oral iron chelators and a new combination in thalassemia patients in rural area

Dr. Pagadala Koteswar and Dr. Madhur Nivrutti Raimule

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Abstract
Background: Thalassemia is a term used to describe anemias that are caused by genetic abnormalities in the production of hemoglobin. 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.
Methods: An examination that looks ahead and examines parallels. The study was carried out in the Department of Community Medicine, Tagore Medical College, located in Chennai, Tamil Nadu, India. The study was done from January 2017 to December 2017. The current study involved the participation of 50 children with thalassemia who had undergone several transfusions and were receiving daily treatment with iron chelation. The study included children with thalassemia who had undergone several blood transfusions and were undergoing daily iron chelation therapy.
Results: The current study included 50 children with thalassemia who had received multiple blood transfusions. For a duration of 12 months, they received daily iron chelation therapy with either defer prone alone, deferasirox alone, or a combination of the two. The participants received the following daily treatments: Deferiprone alone, Deferasirox alone, and a combination of Deferiprone and Deferasirox constituted the treatment groups.
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 introduction of successful chelation therapy in the 1960s marked a significant breakthrough in the treatment of patients who require regular blood transfusions. Deferoxamine, a chelator with six binding sites, was launched in the 1970s and has been the established treatment until recently. It has significantly improved the survival rates of thalassemia patients. Nevertheless, the method of administering the medication directly into the body and the associated expenses have impeded the achievement of ideal adherence. Deferiprone, a chelator that binds to two sites, has been utilized since 1987. Its effectiveness, particularly in eliminating iron from the heart muscle, has been well demonstrated [1-3].
Nevertheless, it is crucial to closely monitor patients due to the occurrence of adverse effects such as erosive arthritis in 5-20% of cases, neutropenia in up to 5% of cases, and severe agranulocytosis in up to 0.5% of cases. An optimal iron-chelating drug should possess several characteristics in addition to its iron-binding capability, such as high oral bioavailability and a once-daily dosage schedule. Deferasirox is a member of a novel group of oral chelators called N-substituted bis-hydroxyphenyltriazoles. It was developed through a focused research effort. The effectiveness and safety of this treatment has been proven in numerous preclinical, phase I, and phase II trials involving both adult and pediatric patients with thalassemia. Due to its plasma half-life of 8 to 16 hours, administering the drug once daily ensures that there is always circulating drug available to remove non-transferrin-bound labile plasma iron [4-6].
Significantly, it was evident that the reaction exhibited a direct correlation with the dosage, and in order to obtain a decrease in serum ferritin levels, a minimum dosage of 30 mg/kg/day was necessary. Both phase 2 and phase 3 clinical trials provide compelling evidence that the amount of continuing transfusional iron load significantly impacts the effectiveness of deferasirox dosages in maintaining or reducing hepatic iron levels [7, 8].

Deferasirox has demonstrated a high level of tolerability in the majority of patients, with the most commonly observed adverse effects include gastrointestinal problems, rash, a slight and non-progressive increase in creatinine levels, and raised liver enzymes. In all of the aforementioned trials, the patients exhibited a lower iron burden compared to what is typically observed in Indian patients [7-9].

This is due to the challenges posed by cost, compliance, and toxicity associated with the use of DFO and deferiprone, which have impeded the achievement of adequate chelation therapy. The medicine received FDA approval in 2005 and was subsequently introduced to the Indian market in April 2008. We made the decision to conduct a prospective research on the initial 50 patients who started taking this medication at our center [8-10]. The current study was undertaken to assess the effectiveness and safety of deferasirox in patients diagnosed with thalassemia major, as well as to monitor the adherence of patients to deferasirox treatment. The objective of this study is to assess 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 & Methods

Looking ahead, we can compare things. Tagore Medical College in Chennai, Tamil Nadu, India, was the site of the research. In this study, fifty children with thalassemia who were receiving daily iron chelation treatment and had a history of numerous transfusions were included. The trial ran from January 2017 to December 2017 and included children with thalassemia who have undergone several blood transfusions and are receiving daily iron chelation treatment.

Inclusion Criteria

Patients with significant Thalassemia who have serum ferritin levels greater than 1500ng/ml.

Exclusion Criteria

- Individuals with a history of deferiprone anaphylaxis
- Individuals whose serum creatinine level is higher than the maximum limit of normal
- Kids suffering from any other persistent systemic disease.

Data Analysis

The data underwent statistical analysis using MS Excel and SPSS 23.0. Categorical variables were evaluated using analysis of variance, Chi-square test, or Fischer's exact test. At each visit, safety measures were clinically evaluated for blood transfusion, including for any adverse events such as joint pains, rashes, abdominal pain, nausea, or vomiting. Complete blood counts were conducted at each visit to assess the need for blood transfusion. At the beginning of the trial and every 6 months thereafter, liver and kidney function tests were conducted, along with the detection of urine protein using uristix. Additionally, viral indicators and HIV status were assessed.

Results

The current investigation involved a cohort of 50 children with thalassemia who were receiving daily iron chelation therapy. 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, Group 2 consists of participants who received only Deferasirox, and Group 3 consists of participants who received a combination of Deferiprone and Deferasirox.

Table 1: Study Groups

	Group 1 (Deferiprone)	Group 2 (Deferasirox)	Group 3 (Combination Therapy)
Mean Age (+-SD)	11.64 (+-2.54)	11.70 (+-2.74)	11.74 (+-2.33)
Gender (M/F)	(9/8)	(8/6)	(10/8)

Serum Ferritin

Measurements of serum ferritin were taken at the beginning of the trial, at 6 months, and at 12 months following chelation therapy. The initial average serum ferritin levels in the Deferiprone group were measured at 3277.01ng/mL. In the Deferasirox group, the initial average serum ferritin levels were measured at 2977.79ng/mL. In the group receiving both Deferiprone and Deferasirox, the initial average serum ferritin levels were measured at 3405.94ng/mL. There was no statistically significant difference in the baseline mean serum ferritin concentrations among all three study groups, indicating that the groups were equivalent.

Table 2: Serum Ferritin Values

Serum Ferritin	Group 1 (Deferiprone)	Group 2 (Deferasirox)	Group 3 (Combination Therapy)
Baseline	3277.01 (+-560.95)	2977.79 (+-506.94)	3405.94 (+-660.54)
At 6 months	3044.88 (+-588.75)	2759.66 (+-547.55)	3021.89 (+-664.96)
At 12 months	2844.89 (+-574.81)	2533.79 (+-532.55)	2640.70 (+-640.24)
P value	0.08	0.04	0.008

Follow up

The range of results in the Deferiprone group was 4.01-5.81 sec, with a mean value of 5.04. The Deferasirox group had a range of values between 4.95 and 5.55, with a mean value of 5.24. The range of values in the Deferiprone and Deferasirox group was discovered to be between 5.03 and 5.75, with the mean value yet to be determined. Consequently, 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. A statistically significant difference was seen between the mean baseline and follow-up values.

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	4.21 (+-0.44)	6.12 (+-0.21)	6.32 (+-0.33)
Follow up	6.32 (+-0.49)	6.47 (+-0.33)	6.58 (+-0.32)
P value	p>0.04	p>0.04	P<0.04

MRI T2*Heart, Baseline and Follow up

The baseline values in the Deferiprone group ranged from 31.02 to 34.05 msec, with a mean value of 32.84. The Deferasirox group had a range of values between 30.36 and 34.06, with a mean value of 31.93. The range of results in the Deferiprone and Deferasirox group was between 30.25 and 32.98, with a mean value of 29.76. The range of values in the Deferiprone group at follow-up ranged from 30.02 to 32.65 msec, with a mean value of 32.28. The Deferasirox group exhibited a range of values between 28.8 and 31.1, with a mean value of 31.63. The range of values in the Deferiprone and Deferasirox group ranged from 28.99 to 31.19, with a mean value of 30.38. A statistically significant difference was seen in the mean values of MRI T2* of the heart between the baseline and follow-up measurements. There was no discernible association between the MRI T2* values of the heart or liver and the serum ferritin values.

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	33.18	32.88	30.88
Follow up	31.32	32.55	30.47
P value	p>0.04	p>0.04	*p*<0.05

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.

Discussion

Transfusion of packed red blood cells is the foundational treatment for many refractory anemias, including transfusion dependent thalassemia and many congenital and acquired forms of the disease. Patients who have received an excessive amount of iron via transfusions should undergo iron chelation treatment in order to lessen their iron load and avoid or delay complications caused by iron accumulation in tissues [8, 9]. Iron overload from transfusions is a problem that increases with the number, size, and duration of blood transfusions. The consequences of untreated transfusional iron overload include hepatic dysfunction and failure, endocrinopathies, and cardiac dysfunction. In theory, iron chelation is necessary as the body gets all the iron it needs through a balanced process of absorption and excretion, which amounts to about 1 mg daily [8-10].

Iron is essential for erythrocytes to produce heme, and it is also used metabolically by other cells in the body. Hepatocytes and macrophages store excess iron as part of a dynamic cycle that includes both use and recycling of iron. Macrophages are essential in iron recycling because they feed on old red blood cells and release iron from their heme into the blood plasma. However, there is no way for the body to get rid of the additional iron that is in transfusions [11, 12]. In transfusion-dependent thalassemia, for example, the daily iron levels can reach 0.3-0.6 mg/kg if the transfusion rate is 2-4 units per month, with 200-250 mg of iron in each unit. Thalassemia major, thalassemia intermedia, and thalassemia minor are the three most common forms of beta-thalassemia. Iron overload can lead to endocrine problems, liver fibrosis, cirrhosis, and dilated myocardiopathy when transfusion therapy is administered on a regular basis. Treatment for thalassemia major includes regular red blood cell transfusions, iron chelation, and management of secondary effects of iron overload [11-13].

In a related study conducted by Gomber S *et al*., 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 study was conducted by Cappellini MD *et al*. Totaling 237 individuals, the ESCALATOR experiment conducted by Taher A *et al*. 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 individuals with transfusion-dependent thalassemia by Eshghi P *et al*multicentric. In keeping with the present investigation, their mean age 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*. (36 patients, mean age 136.9 years) studied the efficacy and safety of combining deferiprone with deferasirox medicine in the context of -thalassemia major [14-16].

The efficacy of deferasirox as an iron chelator was assessed in a research by Merchant R *et al*. in which 30 patients who underwent several blood transfusions were included. The

mean age of the patients was 15.7±6.8 years. Among the 1,115 thalassemia patients included in the EPIC study by Cappellini MD *et al*., the mean age varied between 2 and 72 years. Red blood cell transfusions are necessary for the treatment of severe anaemia, which is commonly experienced by people with thalassemia major in the first two years of life. With a minimal Hb concentration of 9.5 to 10.5 g/dL, a regular transfusion program can keep growth and development typical until the age of 10 to 12 years [17-19]. 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 the Deferiprone group, 2977.79 ng/mL for the Deferasirox group, and 3405.94 ng/mL for the Deferiprone and Deferasirox combined group. All three groups had similar serum ferritin levels at the beginning of the current study [20-22].

According to the meta-analysis conducted by Xia S *et al*., which included two subgroups of four trials, there was no statistically significant difference in SF level 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 [21-23].

Farmaki K *et al*. undertook a two-year evaluation of sixteen individuals. An estimate of the total body iron load based on serum ferritin was shown to be significantly reduced in the effectiveness measures investigation. Gomber S *et al*. 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 [22-24].

Farmaki K *et al*. undertook a two-year evaluation of sixteen individuals. An estimate of the total body iron load based on serum ferritin was shown to be significantly reduced in the effectiveness measures investigation. At baseline, six months, and twelve months after starting chelation treatment, the researchers Gomber S *et al*. measured the average serum ferritin levels. There was no significant difference in serum ferritin levels between the three groups at baseline. All three groups showed a decline in serum ferritin levels after 6 and 12 months of chelation treatment, respectively. Combined, the effects on serum ferritin levels were much more pronounced.

Left ventricular ejection fraction is another important metric associated with cardiac iron, and MRI T2* has lately grown as a major standard for assessing cardiac iron because it is non-invasive in comparison to biopsy [23-25].

All three groups demonstrated a slight excess of hepatic iron in the current investigation's baseline MRI T2*Liver data. All three groups showed increased values in the follow-up MRI performed six months following corresponding treatment, suggesting a reduced iron load on the liver. Mild hepatic iron overload was still diagnosed despite the reduced iron dose. The results of the study by Gomber S *et al*. 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 contrast to serum ferritin, MRI T2* provides a rapid, non-invasive, and repeatable way to diagnose iron overload in the liver and heart [24-26].

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. At no time throughout the experiment did any of the study medications cause an individual to need to discontinue chelation therapy due to side effects. No fatalities occurred over the research period. 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 [27-29].

Conclusion

The combination of deferiprone and deferasirox shown 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

None

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