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Comparison of Deferasirox and Desferrioxamine in Term of Mean Serum Ferritin Levels in Patients of β-Thalassemia Major with Iron Overload

Khadeeja Iram[1*], Zulfiqar Ali[1], Fauzia Aamer[2], Aslam Shiekh[1] and Maria Hassan[1]

[1]Department of Pediatric Hematology Oncology, The Children's Hospital and Institute of Child Health, Multan, Pakistan
[2]Department of Pediatric Hematology, The Children's Hospital and the Institute of Child Health, Lahore, Pakistan

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***Corresponding Author:**
Khadeeja Iram
Department of Pediatric Hematology Oncology, The Children's Hospital and Institute of Child Health, Multan, Pakistan
iram.khadeeja@yahoo.com

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ABSTRACT

Iron chelation treatments as adjuvant therapy can reduce iron stores to minimize the related morbidity and mortality in patients with thalassemia major. **Objective:** To compare Deferasirox (DFX) and Desferrioxamine (DFO) in terms of mean serum ferritin levels in patients of β-thalassemia major having Iron overload. **Methods:** This randomized controlled trial was conducted at the Thalassemia Center of Hematology Department, "The Children's Hospital and The Institute of Child Health", Multan, Pakistan from January 2023 to September 2023. After randomization, children in DFO group were given DFO in a dose of 50mg/kg, through subcutaneous route by infusion pump five days a week. Children in DFX group were given DFX in a dose of 30mg/kg, orally in tablet form once daily. Baseline serum ferritin levels were measured and the change in mean serum ferritin level for each group was calculated and compared for both groups after 6-months of treatment. **Results:** In a total of 142 children, 87 (61.3%) children were male. The mean age was 7.08 ± 2.41 years. The mean number of blood transfusions at the time of enrollment were 13.4 ± 4.2. After 6 months of treatment in DFO versus DFX groups, the net change in mean serum ferritin levels from baseline to post-treatment was 947.2 ± 454.0 µg/L for DFO and 1053.5 ± 389.8 µg/L for DFX, with no statistically significant difference between the groups (p=0.1367). **Conclusions:** Once-daily oral deferasirox has good compliance, acceptable tolerability and appears to have similar efficacy to desferrioxamine in reducing iron burden of transfused patients with beta thalassemia major.

INTRODUCTION

Thalassemia is a frequently occurring genetic blood condition brought on by a mutation in the globin gene that causes a high level of red blood cell lysis [1]. The global scenario surrounding inherited substantial hemoglobinopathies reveal staggering numbers, with approximately 400,000 children born annually with these conditions, while around 80 million individuals carry β-thalassemia [2, 3]. These conditions manifest across three clinical states of increasing disease intensity; the asymptomatic β-thalassemia carrier state, thalassemia intermedia, and the severe thalassemia major (TM) [4]. The β-thalassemia carrier state, stemming from heterozygosity for β-thalassemia, exhibits no clinical symptoms but presents distinct hematological characteristics [5]. Chronic transfusion therapy leads to iron overload, which creates a need for iron chelation treatments as adjuvant therapy so that iron stores in the body can be reduced to minimize the related morbidity and mortality in TM [6, 7]. Right now, Deferasirox (DFX), Deferiprone (DFP), and Desferrioxamine (DFO) are the most commonly adopted iron chelators accessible for therapeutic usage. DFO has nevertheless been regarded as a standard treatment approach managing iron overload in the last several decades, despite its short half-life, poor compliance, and requirement for regular subcutaneous or intravenous injections five to seven days a week [8]. The first iron chelator, DFP, had good compliance but was associated with several major adverse effects, including arthropathy, neutropenia, agranulocytosis, and gastrointestinal disorders [9]. On the other hand, DFO and

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DFP together have a synergistic effect on patient compliance and iron elimination [10]. While there are a few moderate side effects associated with DFX, certain researchers have suggested that it lowers liver iron levels and increases patient compliance. A study from Iraq reported that DFO exhibited notably higher serum ferritin levels (8160 ± 234 ng/dL) compared to DFX (3001 ± 188 ng/dL; p<0.001), highlighting a distinct impact of these iron-chelating medications on iron status [11]. DFX is considered the latest oral chelator to be utilized in the treatment of chronic iron overload. In contrast DFP, DFX underwent more thorough scientific investigation during development. Numerous investigations have addressed the efficacy and safety of DFX, even though there is still scarcity of long-term outcome data. This study was planned to compare deferasirox and desferrioxamine in terms of mean serum ferritin levels in patients of β-TM having Iron overload. Choosing an effective iron chelator is crucial to increasing iron chelation therapy compliance. Not much local data exists in Pakistan comparing the effectiveness of DFX and DFO.

This study would be helpful in providing baseline data and formulating new protocols for iron chelation therapy, in which DFX may be a useful oral alternative to parenteral DFO.

METHODS

This randomized controlled trial was conducted at the Thalassemia Center Hematology Department, "The Children's Hospital, and the Institute of Child Health," Multan, Pakistan, from 1st January 2023 to 30th September 2023. The inclusion criteria were transfusion-dependent patients of either gender, aged 2-15 years, diagnosed with β-TM by hemoglobin electrophoresis, and iron overloaded. The exclusion criteria were patients with other transfusion-dependent anemias, TM with cardiomyopathy or arrhythmia, chronic renal failure, chronic liver disease (ALT >200 IU), hypersensitivity to either DFX or DFO, or those who were already on combined chelation therapy. Iron overload in "transfusion-dependent β-TM" was defined as "serum ferritin level above 1000 µg/L" [12]. After explaining details in terms of the benefits and risks of the study, informed and written consents were acquired from parents/guardians. Approval from the "Institutional Ethical Committee" was obtained (reference number: 1870). Sample size of 122 (61 in each group) was calculated using G*Power software considering effect size (d) as 6%, alpha error probability as 5% with 95% confidence level and allocation ratio of 1:1. For this trial 142 (71 in each group) children were considered. This clinical trial was registered at clinicaltrials.gov, with trial numbered as NCT06468423. All of the necessary information, like age, gender, weight, height, date of chelation, and number of blood transfusions, were noted at the time of presentation. Baseline serum ferritin levels were measured for all patients in both groups through the institutional laboratory using Vitros Immunodiagnostics employing chemiluminescence methodology, and ferritin reagent kit was used. Then, using the lottery method, 142 children were allocated randomly to both study groups. DFO group (n=71) included children who were given DFO at a dose of 50 mg/kg through the subcutaneous route by infusion pump five days a week. DFX group (n=71) included children who used oral (tablet) DFX at a dose of 30 mg/kg once daily. Monthly follow-up was done for the children in both groups, ensuring compliance as assessed viewing the empty medicine containers. Blood samples for serum ferritin were analyzed at the end of 6 months. The change in mean serum ferritin levels from the baseline to after 6 months of treatment was calculated. A special pre-designed proforma was used to record all of the relevant study information. Data analysis was performed using "IBM-SPSS Statistics" version 26.0. Age, weight, baseline serum ferritin levels, and the mean serum ferritin level at the end of 6 months were shown as mean and standard deviation (SD). Frequency and percentage were calculated for gender. The comparison of serum ferritin levels in two groups was done by applying independent sample t-test. P-value below 0.05 was taken as significant.

RESULTS

In a total of 142 children, 87 (61.3%) children were male and 55 (38.7%) female. The mean age was 7.08 ± 2.41 years. The mean number of blood transfusions at the time of enrollment was 13.4 ± 4.2. Table 1 shows comparison of baseline characteristics between children of study groups.

Table 1: Baseline Characteristics (n=142)

Variables		DFO Group N (%) / (Mean ± SD)	DFX Group N (%) / (Mean ± SD)	p-Value
Gender	Male	47 (66.2%)	40 (56.3%)	0.2279
	Female	24 (33.8%)	31 (43.7%)	
Age (Years)		7.3 ± 2.9	6.7 ± 2.1	0.1602
Weight (Kg)		24.42 ± 8.9	22.8 ± 6.7	0.2282
Height in (cm)		109.88 ± 12.2	107.9 ± 10.7	0.3008
Number of Blood Transfusions		13.6 ± 5.9	12.9 ± 2.4	0.3560

After 6 months of treatment, both DFO, and DFX groups experienced a reduction in mean serum ferritin levels. However, the observed difference in mean serum ferritin levels between the two groups was not statistically significant (p=0.2298). When examining the net change in mean serum ferritin levels from baseline to post-treatment, it was found to be 947.2 ± 454.0 µg/L for the DFO group and 1053.5 ± 389.8 µg/L for the DFX group (0.1367), as shown in table 2.

Table 2: Comparison of Desferrioxamine and Deferasirox in Mean Serum Ferritin Levels (n=142)

Mean Serum Ferritin Level	DFO Group (Mean ± SD)	DFX Group (Mean ± SD)	p-Value
Baseline (µg/L)	4128.6 ± 2171.6	3914.2 ± 1828.2	0.5255

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Post-Treatment(µg/L)*	3181.4 ± 1717.6	2860.7 ± 1438.4	0.2298
Net Change (µg/L)	947.2 ± 454.0	1053.5 ± 389.8	0.1367

*after 6 months of treatment

DISCUSSION

The present findings suggested that both DFO and DFX contributed to a decrease in serum ferritin following six months of treatment, although there wasn't a significant difference observed between the two treatments. Some Randomized Controlled Trials (RCTs) have shown that none of the contemporary treatment options are superior in reducing iron overload or preventing end organ damage. Data show that strong evidence is missing advocating the use of combination of DFP and DFO in comparison to monotherapy in terms of reduction in iron stores [13-15]. This lack of clear superiority or consistent benefits highlights the requirement for future research than can aid in better understanding about the comparative efficacy of contemporary treatment options aiming prevention of iron-related organ damage. Taher A *et al.*, evaluated the effectiveness of DFX in heavily iron-overloaded thalassemia patients and found it efficacious when given at 30 mg/kg/day to most of the patients. DFX showed effectiveness in lowering liver iron concentrations and serum ferritin levels to a greater extent [16]. Rasalkar DD *et al.*, revealed that DFX was as effective as DFO for iron chelation among TM patients and these findings stand consistent with what we noted [17]. Arya A *et al.*, from Iran reported that among the iron-chelating agents DFX, DFP, and DFO, there was no discernible difference in their efficacy for reducing ferritin levels in patients with thalassemia [18]. Consequently, the choice of chelating agent can be made considering factors such as cost, availability, the patient's condition, and their preference. This suggests that treatment decisions can be tailored based on individual circumstances and considerations beyond just the comparative efficacy of these agents in reducing ferritin levels. Our findings are also very consistent to a recently published local study where Syed A *et al.*, from Lahore revealed no statistically significant difference in the effectiveness of DFX of DFO as chelation therapy among patients with β-TM [19]. The shift to a once-daily, oral regimen, as seen with DFX, typically enhances patient compliance compared to parenteral treatments. This improved adherence to therapy is anticipated to result in decreased morbidity and mortality associated with iron overload. With adequate laboratory oversight, the availability of DFX as a safe and effective oral option holds promise in averting complications stemming from iron overload, offering a more convenient and potentially impactful approach to chelation therapy [20]. In comparison to the present study, some researchers have documented different observations. A study from Iraq revealed that DFX exhibited greater efficacy in managing iron overload compared to DFO in patients reliant on blood transfusions due to β-TM [11]. However, notably, this superiority was not observed concerning the immunological profile. Despite the effectiveness of DFX in addressing iron overload, DFX did not show a significant advantage over DFP in terms of impacting the patient's immune system parameters. Although, this study has revealed very useful results, a large, long-term, and multicenter local trial is required for the validity of our findings. Single center study design and a relatively small study treatment duration were some of the limitations of this study.

CONCLUSIONS

Once a day oral deferasirox had good tolerability and provided relatively similar effectiveness to desferrioxamine in decreasing the iron overload in transfused patients with beta thalassemia major.

Authors Contribution

Conceptualization: KI, ZA

Methodology: FA, AS

Formal analysis: ZA, FA, AS, MH

Writing, review and editing: FA, AS, MH

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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