Section: Pediatrics

Original Research Article

EFFICACY AND SAFETY OF SINGLE-DOSE AND DIVIDED-DOSE DEFERASIROX IN CHILDREN WITH TRANSFUSION-DEPENDENT BETA THALASSEMIA

Sabeel Abdulla PR[1], Gireeshan VK[2], Aslam PK[3] Ajithkumar VT[4]

[1]*Assistant Professor, Department of Pediatrics, Government Medical College, Kozhikode, Kerala, India.*
[2]*Professor, Department of Pediatrics, Dr. Moopen's Medical College, Wayanad, Kerala, India.*
[3]*Associate Professor, Department of Pediatrics, Government Medical College, Kozhikode, Kerala, India.*
[4]*Professor and head, Department of Pediatrics, Government Medical College, Thrissur, Kerala, India.*

Received *: 05/07/2025*
Received in revised form *: 22/08/2025*
Accepted *: 11/09/2025*

Corresponding Author:
Dr. Sabeel Abdulla P R,
Assistant Professor, Department of Pediatrics, Government Medical College, Kozhikode, Kerala, India,
Email: sabeelabdulla@gmail.com

DOI: 10.70034/ijmedph.2025.3.500

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

Int J Med Pub Health
2025; 15 (3); 2722-2726

ABSTRACT

Background: Transfusion-dependent beta-thalassemia results in chronic iron overload, potentially leading to considerable morbidity and mortality from organ damage. Deferasirox has significantly improved chelation therapy; however, a divided-dose regimen may be advantageous due to its plasma half-life of 8-16 hours. **Objectives**: Its primary objective was to see how well once-daily and twice-daily divided-dose deferasirox worked on serum ferritin levels in children with beta-thalassemia major. A secondary objective was to assess and compare the safety and tolerability of both regimens.

Materials and Methods: This prospective cohort study was conducted at the Division of Hemato-oncology, Department of Pediatrics, Govt Medical College, Kozhikode, from March 2014 to August 2015. Forty-seven children with beta-thalassemia major on a stable deferasirox regimen of at least 30 mg/kg/day were enrolled. They were grouped into a once-daily cohort (n=25) and a twice-daily divided-dose cohort (n=22). Serum ferritin was measured at baseline and every three months for a year. Adverse events, serum creatinine, and SGPT levels were monitored for safety.

Results: Both regimens demonstrated a reduction in mean serum ferritin levels over the one-year study period. The once-daily group showed a mean decrease of 437.2 (SD 1168) µg/L, while the twice-daily group showed a mean decrease of 610.8 (SD 985.58) µg/L. An independent sample t-test revealed no statistically significant difference in the mean serum ferritin reduction between the two cohorts (p=0.857). Both regimens were generally well-tolerated, with comparable incidence of adverse events like vomiting, nausea, abdominal pain, and elevated SGPT levels.

Conclusion: Once-daily and twice-daily divided-dose deferasirox regimens are equally effective in reducing serum ferritin levels in children with transfusion-dependent beta-thalassemia. The study supports using deferasirox as a safe and effective oral chelator. It indicates that the more convenient once-daily schedule is a legitimate and equally effective alternative for patients on high-dose regimens.

Keywords: Deferasirox, Beta-Thalassemia, Iron Overload, Pediatric, Serum Ferritin, Divided Dose.

INTRODUCTION

Beta-thalassemia major is a severe genetic blood disorder that makes it hard for the body to make enough beta-globin chains. This leads to severe anemia.[1] People with this condition need to get red blood cell transfusions for the rest of their lives. These transfusions keep them alive and build iron in the body over time.[2] Transfusional iron overload can lead to severe health complications and mortality, as iron accumulates in vital organs such as the heart,

liver, and endocrine glands, impairing their function and causing damage.[3]

Iron chelation therapy has been a big step forward in treating beta-thalassemia. It has dramatically improved the patients' long-term survival and quality of life.[4] Deferoxamine, the first widely used chelator, is a potent drug, but it needs uncomfortable and inconvenient intravenous or subcutaneous infusions, which often make patients less likely to follow the instructions.[5] Creating oral iron chelators has fixed this problem, and deferasirox is a big step forward. The US FDA approved deferasirox in 2005, making taking the drug daily by mouth much easier, significantly improving adherence to therapy.[6]

The first suggested dose of deferasirox was 20 mg/kg/day. However, more recent studies have shown that higher doses, up to 40 mg/kg/day, are often needed to get a negative iron balance and keep the drug's effects going, especially in people with a lot of iron in their bodies.[7] The plasma half-life of deferasirox is between 8 and 16 hours. This pharmacokinetic profile supports a once-daily regimen; however, a theoretical argument persists that splitting the daily dose into two administrations may sustain more stable therapeutic drug levels, potentially enhance clinical efficacy, and diminish dose-dependent side effects.[8] Nonetheless, a deficiency of comprehensive clinical data exists evaluating the efficacy and safety of once-daily versus twice-daily divided-dose regimens, especially in the pediatric demographic. This study was designed to fill this vital gap in knowledge by directly comparing these two dosing schedules in a group of children with transfusion-dependent beta-thalassemia major.

Previous research has yielded significant insights into the pharmacology and clinical application of deferasirox, although the majority have predominantly concentrated on once-daily administration. Some small-scale reports and observational data indicate that divided dosing may enhance gastrointestinal tolerability and sustain more stable serum drug concentrations; however, the findings have been inconsistent and frequently constrained by methodological limitations. Moreover, pediatric patients constitute a distinct demographic in which growth, development, and long-term organ preservation are essential factors. As a result, there is a particular need for meticulously structured comparative studies within this cohort to elucidate optimal dosing strategies and ensure both efficacy and safety in the extended management of iron overload.

MATERIALS AND METHODS

Study Design and Setting: This prospective cohort study was conducted in the Division of Hemato-Oncology, Department of Pediatrics, Government Medical College, Kozhikode, Kerala, India. The hospital is a tertiary care referral center with a thalassemia unit that regularly transfuses and follows up with a large group of children with beta-thalassemia major.

Study Population: 47 children in total had been diagnosed with beta-thalassemia major. Blood tests, clinical signs, and hemoglobin electrophoresis were used to analyze. Eligible participants were transfusion-dependent, having received a minimum of 15 red blood cell transfusions, and were on a stable oral deferasirox regimen of ≥30 mg/kg/day for at least one year before study entry. The average age of the people in the study was 10.15 years (SD 3.25), and there were 27 males and 20 females.

Inclusion and Exclusion Criteria

Children were eligible if they:

- had a confirmed diagnosis of beta-thalassemia major,
- were on regular blood transfusions and oral deferasirox therapy,
- and had a baseline serum ferritin >1000 µg/L.

Exclusion criteria included

- presence of chronic systemic illness such as hepatitis B, hepatitis C, or HIV under active treatment,
- co-existing cardiovascular, renal, or hepatic disease that could affect drug metabolism or safety outcomes,
- concurrent use of alternative or traditional medications for thalassemia,
- and noncompliance with prescribed therapy or study follow-up.

Study Cohorts and Intervention: Participants were categorized into two treatment cohorts based on the mode of deferasirox administration:

- **Cohort 1 (Once-Daily Regimen):** 25 patients receive the full daily dose in one administration.
- **Cohort 2 (Twice-Daily Regimen):** 22 patients receiving the same daily dose, divided equally into two administrations.

The dosing schedule was determined according to existing clinical practice patterns, and no randomization was performed. All patients continued to receive standard supportive care, including regular transfusions to maintain pre-transfusion hemoglobin levels between 9 and 10 g/dL.

Efficacy Assessment: The primary efficacy endpoint was the change in serum ferritin levels over the one-year follow-up period. Serum ferritin was measured at baseline and subsequently every three months (total of five assessments: baseline, 3, 6, 9, and 12 months). All ferritin measurements were performed in an accredited laboratory to minimize inter-assay variability.

Secondary efficacy assessments included

- **Cardiac function:** Left ventricular ejection fraction was assessed at baseline and at the end of the study using echocardiography (T2* MRI was not feasible in this resource-limited setting).
- **Growth parameters:** Height and weight were recorded at baseline and every three months, and

expressed as standard deviation (SD) scores relative to age and sex.

Safety Assessment: Safety was monitored throughout the study by recording clinical adverse events and laboratory parameters. Clinical monitoring focused on common drug-related effects, including gastrointestinal intolerance (nausea, vomiting, abdominal pain, diarrhoea), skin rash, and musculoskeletal symptoms (arthralgia). Laboratory monitoring included serum creatinine (with estimated glomerular filtration rate [eGFR] calculated using the Schwartz formula) and liver function tests (SGPT/ALT). All abnormal results were rechecked and documented.

Sample Size Considerations: The sample size was established using data from prior clinical studies assessing the efficacy of deferasirox in individuals with transfusion-dependent thalassemia. The variability in serum ferritin reduction documented in previous studies was a benchmark to guarantee sufficient statistical power for identifying a clinically significant difference between once-daily and twice-daily dosing regimens. According to these estimates, each group needed at least 23 patients. In the current study, 25 children were assigned to the once-daily cohort and 22 to the twice-daily cohort, meeting the requisite sample size.

Statistical Analysis: We put all the collected data into a secure database and used SPSS software to look at it. We showed continuous variables as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. The Shapiro–Wilk test was used to check for normality in the distribution of continuous variables before any statistical tests were done. The independent samples t-test was used to compare the two groups for data that followed a normal distribution. The Mann–Whitney U test was utilized for data that did not follow a normal distribution. We used repeated measures analysis of variance (ANOVA) to look at changes in serum ferritin over time. When the assumptions of sphericity were unmet, we used the Greenhouse–Geisser correction.

The Chi-square test or Fisher's exact test was used to compare categorical variables, such as the number of adverse effects, between groups. Subgroup analyses were conducted to investigate potential differences based on age group and sex. Any missing data were dealt with using a last observation carried forward (LOCF) method to keep the sample's integrity. A two-tailed p-value of less than 0.05 was considered statistically significant for every test.

Ethical Considerations: The Declaration of Helsinki was followed when conducting the study, which was approved by the Government Medical College's Institutional Ethics Committee in Kozhikode. Before inclusion, written informed consent was obtained from parents or legal guardians. The observational study involved no experimental interventions beyond standard clinical practice, thus reducing participant risk.

RESULTS

A total of 47 children with transfusion-dependent beta-thalassemia major were enrolled, including 27 males and 20 females. The average age of the participants was 10.15 ± 3.25 years, and there was no significant difference between the once-daily and twice-daily groups ($p = 0.457$). The average deferasirox dose for the study group was 40.54 ± 4.39 mg/kg/day. The twice-daily group had a slightly higher average dose (41.6 mg/kg/day) than the once-daily group (39.5 mg/kg/day), which was statistically significant ($p = 0.029$). Other baseline characteristics, such as annual transfusion frequency and initial serum ferritin concentrations, were similar between the two groups. [Table 1]

Table 1: Baseline Characteristics of Study Cohorts

Characteristic	Once-Daily (n=25)	Twice-Daily (n=22)	p-value
Gender (M/F)	14 / 11	13 / 9	0.81
Mean Age (years)	10.45 ± 3.42	9.82 ± 3.10	0.457
Mean Deferasirox Dose (mg/kg/day)	39.5 ± 4.11	41.6 ± 4.54	0.029*
Mean No. of Transfusions/Year	25.4 ± 3.65	25.2 ± 4.14	0.82
Mean Baseline Ferritin (µg/L)	3077.6 ± 1819.9	3113.6 ± 1875.9	0.295

**p < 0.05, statistically significant.*

Efficacy: At baseline, mean serum ferritin levels were similar between groups (3077.6 ± 1819.9 µg/L in the once-daily group vs. 3113.6 ± 1875.9 µg/L in the twice-daily group; $p = 0.295$). Over the one-year follow-up, both regimens produced a progressive decline in serum ferritin (Table 2, Figure 1). By the end of 12 months, the once-daily group demonstrated a mean ferritin reduction of 437.2 µg/L (SD 1168), corresponding to a 17% decrease from baseline. The twice-daily group showed a reduction of 610.8 µg/L (SD 985.6), a 19.5% decrease. Although the twice-daily regimen achieved a numerically greater reduction, the difference between groups was not statistically significant ($t = -0.18$, $p = 0.857$).

Table 2: Mean Serum Ferritin Levels Over One Year

Time Point	Once-Daily (n=25)	Twice-Daily (n=22)
Baseline	3077.6 ± 1819.9	3113.6 ± 1875.9
3 Months	2945.4 ± 1840.4	2981.4 ± 1775.0
6 Months	2898.3 ± 1709.7	2816.4 ± 1802.8
9 Months	2673.8 ± 1675.3	2697.6 ± 1916.3
12 Months	2640.3 ± 1673.7	2502.7 ± 1972.6

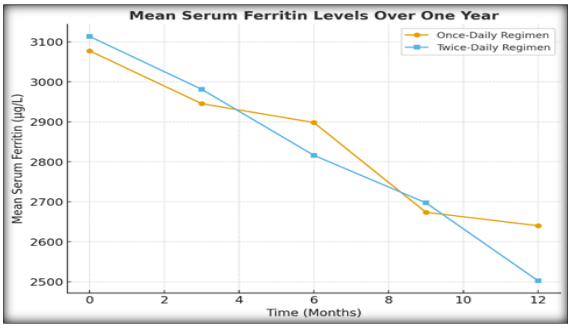

Figure 1: Figure 1: Mean serum ferritin levels over one year in the once-daily and twice-daily cohorts

Safety: Both once-daily and twice-daily regimens were generally well-tolerated, with no serious drug-related adverse events reported. The incidence of common adverse effects is summarized in Table 3. Gastrointestinal symptoms such as nausea and vomiting were mild and self-limiting. Elevated SGPT levels were noted in 52% of patients in the once-daily group and 32% in the twice-daily group; however, this difference was not statistically significant ($p = 0.184$). No significant renal function or echocardiographic parameter changes were observed in either cohort.

Table 3: Incidence of Adverse Events

Adverse Event	Once-Daily (n=25)	Twice-Daily (n=22)
Vomiting	12%	8%
Nausea	8%	4%
Abdominal Pain	4%	4%
Skin Rash	0%	0%
Joint Pain	4%	4%
Diarrhoea	0%	0%

During the one-year follow-up period, serum ferritin levels were significantly reduced by both once-daily and twice-daily deferasirox regimens, with no discernible difference in efficacy between the two dosing strategies. Only minor and similar side effects were noted in either group, indicating a good safety profile. According to these results, children with transfusion-dependent beta-thalassemia major respond well to either dosage strategy.

DISCUSSION

This study shows that deferasirox divided-dose regimens administered once or twice daily can effectively lower serum ferritin levels in children with transfusion-dependent beta-thalassemia major. The main conclusion is that the more convenient once-daily regimen is equally effective in maintaining iron balance, as there was no statistically significant difference in efficacy between the two dosing schedules. The safety profile of deferasirox in pediatric patients was highlighted by the well-tolerated nature of both regimens and the similar incidence of adverse events.

In our study, the once-daily group experienced a mean percentage decrease in serum ferritin of 17%, while the twice-daily group experienced a mean reduction of 19.5%. These results are mainly in line with previous findings. In a large multicentred trial of once-daily deferasirox, Cappellini et al. (2008) reported a mean reduction of 30%,[9] whereas Taher et al. (2014) reported a decrease of 23%.[10] Our patient population may have a higher baseline iron burden, which could explain the milder reduction we saw in our cohort despite a relatively high mean dose (~40 mg/kg/day). Our findings were corroborated by Cappellin et al. (2011), who reported a 20% decrease with once-daily therapy.[11]

Compared to other published studies, our observed 19.5% reduction in divided dosing was modest. Pongtanakul et al. (2015) showed a significantly higher reduction of 56% than Buaboonnam et al. (2021), who reported reductions of 39.8% and 24%, respectively. [12,13] Heterogeneity in study design, sample size, baseline ferritin levels, adherence patterns, and population characteristics could all account for the disparities. These variations highlight the need for larger, randomized controlled trials to conclusively assess the clinical benefit of divided dosing over once-daily administration.

The strengths of the current study include its prospective design, standardized follow-up, and utilization of a single laboratory for ferritin estimation, which reduced inter-assay variability. The one-year follow-up period also gave us enough time to look at long-term changes in iron burden. Nonetheless, various limitations must be recognized. The non-randomized cohort design may have introduced unmeasured confounding factors despite attempts to match the groups at baseline. The relatively small sample size, especially in the twice-daily group, makes finding minor differences in efficacy and safety outcomes harder. Also, although widely accepted, using serum ferritin as the main sign of iron overload might not give a complete picture of tissue iron burden because infections or inflammation can affect the measurements.

This study shows that both once-daily and twice-daily divided-dose regimens of deferasirox work to lower serum ferritin levels in children with transfusion-dependent beta-thalassemia major. There is no statistically significant difference in how well the two schedules work. These results align with Panachiyil (2022), indicating that once-daily and twice-daily deferasirox regimens effectively and safely address iron overload in pediatric patients with transfusion-dependent beta-thalassemia major.[14] Once-daily dosing is still a valuable and valid option because it works as well and is as easy to take. This is especially true for children who need long-term

treatment.[15] Future extensive randomized controlled trials utilizing more accurate assessments of iron burden, such as MRI-based quantification of hepatic and cardiac iron, are necessary to validate these findings and investigate the potential impact of divided dosing in specific patient subpopulations.

CONCLUSION

The current study demonstrates that in children with transfusion-dependent beta-thalassemia major, deferasirox divided-dose regimens administered once and twice daily can reduce serum ferritin levels. With only minor adverse effects, the two groups reported comparable safety and tolerability. These findings support deferasirox's continued use as a trustworthy oral iron chelator. They also show that a once-daily regimen is a convenient and equally effective choice, especially for patients who need higher doses. Additional extensive, randomized studies utilizing direct assessments of tissue iron burden are necessary to corroborate these findings and inform personalized dosing strategies.

Acknowledgments: We sincerely thank the parents and guardians of the patients who participated in this study. We express our gratitude to the personnel of the Department of Pediatrics and the Division of Hemato-oncology at Government Medical College, Kozhikode, for their invaluable assistance.

Funding: The authors funded this study. No external funding was received.

Conflict of interest: The authors declare no conflicts of interest.

Data availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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