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Original Research Article

INCIDENCE OF DILATED CARDIOMYOPATHY IN PATIENTS OF THALASSEMIA MAJOR RECEIVING DEFERASIROX AND DEFEROXAMINE AS CHELATORS

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Abstract: *The objective of this study was to determine the frequency of dilated cardiomyopathy in patients with β-thalassemia major who received treatment with deferasirox and deferoxamine. A descriptive cross-sectional study was conducted in the Department of Paediatrics, Combined Military Hospital, Rawalpindi, from May 2022 to January 2023. All 746 paediatric patients aged between 4 to 18 years, of both genders, who had been diagnosed with β-thalassemia major and had received chelation with either deferasirox or deferoxamine for at least one continuous year were included. Patients who were non-compliant with treatment based on history or suffered from concurrent chronic cardiopulmonary, renal (including proteinuria), hepatic, or neoplastic disease, those who suffered from malabsorption syndromes, or those who had undergone gastrointestinal surgery were excluded. All patients underwent a 2D echocardiographic study to document cardiac dilatation and measurement of ejection fraction. Dilated cardiomyopathy was defined as dilating one or both heart ventricles with an ejection fraction of less than 40%. Patients were divided into two groups: those who had received deferasirox and those who had received deferoxamine. Data was analyzed using SPSS 26.0. The study population had a median age of 8.00 (IQR: 5.00) years, with a male majority of 384 (51.5%). The median time on chelation therapy was 23.00 (IQR: 10.00) months, while the median age at first transfusion was 12.00 (IQR: 7.00) months. The median number of lifetime transfusions was 60.50 (IQR: 33.00), while only 431 (57.8%) patients had received chelator therapy previously. Out of the total sample population, 36 (4.8%) patients had dilated cardiomyopathy, of whom 22 (5.9%) occurred with deferasirox while 14 (3.8%) were seen with deferoxamine (p=0.172). The study concluded that the frequency of dilated cardiomyopathy secondary to iron deposition in the myocardium of patients with β-thalassemia major on deferasirox for at least one year was similar to those using deferoxamine for the same minimum period.*

Keywords: Deferasirox, Deferoxamine, Dilated Cardiomyopathy, Iron Overload, Thalassemia Major

Introduction

Every year, approximately 5,000 children are born in Pakistan with β-thalassemia major, a country with a β-thalassemia trait carrier rate estimated at 5% to 8% of the total population (Ghafoor et al., 2021). While options such as hematopoietic stem cell transplantation and gene therapy are potentially curative in the management of this disorder, they are not readily or cheaply available to the population at large. As a result, most patients are managed with drugs that stimulate the production foetal haemoglobin and frequent blood transfusions, the requirement for which steadily increases with age (Ali et al., 2021; Rattananon et al., 2021). Regular transfusions increase total body iron, which begins to deposit in different body tissues when the total level crosses the binding ability of carrier proteins and the threshold of solubility in plasma.[4,5] Common sites for deposition include the liver, pancreas, pituitary, and heart (Brissot et al., 2019; Ding et al., 2023).

Cardiac disease remains a major cause of mortality in patients with β-thalassemia major. Organ dysfunction within this system may manifest as pump dysfunction, development of arrhythmias, and pulmonary hypertension (Paul et al., 2019). Iron deposition within the cardiac tissue results in electrophysiological disorders within the heart's conduction system and affects cardiac myocyte contractility, compromising heart function (Sukardi et al., 2023). Iron chelators are a class of drugs used to remove excess iron from the body, bypassing the human body's shortcoming of being unable to actively excrete iron (Pinto and Forni, 2020). Deferoxamine, an intravenous preparation, is one of the first chelators to manage iron overload. However, studies have shown that oral preparations such as deferiprone are more effective in reducing myocardial iron load and may be associated with improved compliance (Kontoghiorghe and Kontoghiorghes, 2016; Pennell et al., 2006). However, whether this benefit is also evident with deferasirox, another oral iron chelator, is unclear.

This study was conducted to determine whether patients who had received chelation with deferasirox had a lower incidence of dilated cardiomyopathy as compared to patients on deferoxamine while suffering from β-thalassemia major. If proven to be effective, deferasirox, by its nature of being an oral iron chelator that is readily available, can be potentially incorporated into existing guidelines as first-line therapy, which can result in a significant decrease in the morbidity and mortality due to iron overload seen in patients in β-thalassemia major.

Methodology

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Our research was conducted as a descriptive cross-sectional study from May 2022 to Jan 2023 in the Department of Paediatrics, Combined Military Hospital, Rawalpindi, on 746 paediatric patients diagnosed as suffering from β-thalassemia major, after receiving written, informed consent from their parents/guardians. The participants were selected via non-probability, consecutive sampling. The World Health Organization (WHO) sample size calculator was used to calculate the sample size keeping the level of significance (α) at 5%, power of the test (1-β) at 90%, anticipated population proportion (P_1) of 8.3%, and an anticipated population proportion (P_2) of 3.3%, which were the percentage of patients of β-thalassemia major who suffered from cardiomyopathy after one year of treatment with deferasirox and deferoxamine, respectively, from Pepe et al (Pepe et al., 2011).

All paediatric patients aged between 4 and 18 years, of both genders, who were diagnosed as cases of β-thalassemia major and had received chelation with either deferasirox or deferoxamine for at least one continuous year, were included.

Patients who were non-compliant with treatment based on history or suffered from concurrent chronic cardiopulmonary, renal (including proteinuria), hepatic, or neoplastic disease, those who suffered from malabsorption syndromes, or those who had undergone gastrointestinal surgery were excluded.

All patients were documented for demographics and family history and underwent a physical examination at enrollment. This was followed by a 2D echocardiographic study to document cardiac dilatation and measurement of ejection fraction. A consultant pediatric cardiologist performed all echocardiograms with at least five years of post-fellowship experience. Dilated cardiomyopathy was defined as dilatation of one or both heart ventricles with an ejection fraction of less than 40% (Gherli et al., 2022).

Data was analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows version 26, IBM Corp; Armonk, USA). Mean and standard deviation were calculated for quantitative variables, specifically patient age, duration of chelation therapy, time since RCC transfusions were started, total number of lifetime transfusions received, and serum ferritin levels. Qualitative variables like gender, type of chelation received, whether a different form of chelation was received previously, infection with hepatitis B, hepatitis C, or both, and whether dilated cardiomyopathy occurred were recorded in frequency and percentage. Patients were divided into two groups: those who received deferasirox and those who received deferoxamine. Quantitative variables were compared across groups using the independent samples *t*-test/Matt Whitney U test, while the Chi-square test/Fischer exact test was used for qualitative variables, and a *p*-value of ≤0.05 was considered significant.

Results

This study was conducted on 746 pediatric patients diagnosed with β-thalassemia major, with a median age of 8.00 (IQR: 5.00) years. Males and females were roughly equal proportions: males were in a marginal majority in the sample, i.e., 384 (51.5%). The median time on chelation therapy was 23.00 (IQR: 10.00) months, while the median age at first transfusion was 12.00 (IQR: 7.00) months. The median number of lifetime transfusions was 60.50 (IQR: 33.00), with a mean time between transfusions of 6.14 weeks. The median ferritin level of the sample was 926.50 (IQR: 1144) ng/mL, while only 431 (57.8%) patients had received chelator therapy previously. A total of 234 (31.4%) patients were infected with hepatitis C, 50 (6.7%) suffered from hepatitis B, while 12 (1.6%) suffered from both the C and B viral infections. A negative serology for both hepatitis B and C was seen in 450 (60.3%). A total of 36 (4.8%) had dilated cardiomyopathy, of whom 22 (5.9%) occurred with deferasirox while 14 (3.8%) were seen with deferoxamine. Table I shows the patient characteristics and study results distributed according to the chelator received.

Table-I. Patient Characteristics/Study Results According to Chelator (n=746)

Variable	Deferasirox (n=373)	Deferoxamine (n=373)	*p*-value
Age (years)	8.00 (IQR: 5.00)	8.00 (IQR: 4.00)	0.402
Gender			
Males	209 (56.0%)	175 (46.9%)	0.013
Females	164 (44.0%)	198 (53.1%)	
Duration of Chelation (months)	22.00 (IQR: 11.00)	23.00 (IQR: 10.00)	0.065
Age at First Transfusion (months)	12.00 (IQR: 8.00)	12.00 (IQR: 7.00)	0.645
Total Number of Lifetime Transfusions	60.00 (IQR: 34.00)	61.00 (IQR: 33.00)	0.672
Ferritin Level (ng/mL)	895.00 (IQR: 1166)	967.00 (IQR: 1143)	0.087
Previous Chelation Received			
Yes	186 (49.9%)	245 (65.6%)	<0.001
No	187 (50.1%)	128 (34.4%)	
Hepatitis B/C Status			
None	225 (60.3%)	225 (60.3%)	0.256
Hepatitis B only	31 (8.3%)	19 (5.1%)	
Hepatitis C only	110 (29.5%)	124 (33.2%)	
Both Hepatitis B and C	7 (1.9%)	5 (1.4%)	
Cardiomyopathy Present?			
Yes	22 (5.9%)	14 (3.8%)	0.172
No	351 (94.1%)	359 (96.2%)	

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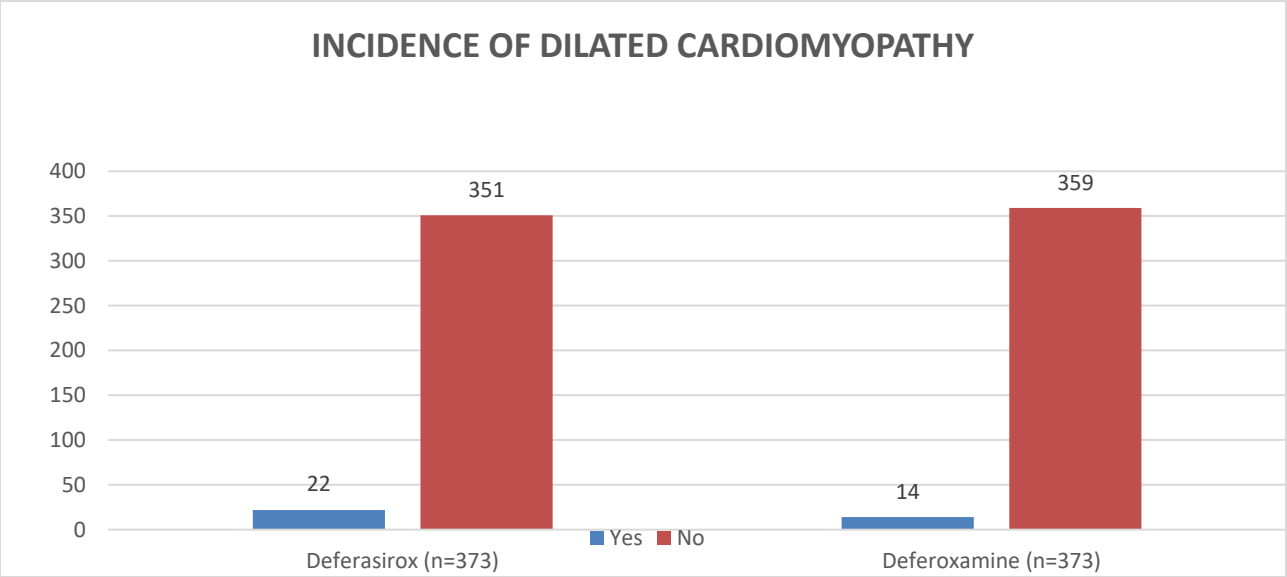

Figure 1: Incidence of dilated cardiomyopathy in both groups

Discussion

Monitoring for iron overload and iron chelation has dramatically improved the life expectancy of patients suffering from β-thalassemia major (Baird et al., 2022). Older chelators such as deferoxamine require parenteral subcutaneous administration over long periods, which can result in poor compliance with treatment (Jones et al., 2022). Deferasirox bypasses these issues as it is an oral iron chelator; however, it was unclear whether it was as efficacious as deferoxamine in preventing myocardial iron toxicity (Shirley and Plosker, 2014): our study showed that there was no difference in the frequency of dilated cardiomyopathy in patients suffering from β-thalassemia major when treated with deferasirox when compared to those on deferoxamine.

In the current study, males and females were almost equal in the sample: males accounted for 51.5% of cases. This is in keeping with other studies on the subject, such as Uddin et al., who reported 44.5% of patients of β-thalassemia major in their study were male, as well with Al-Suliman et al. reported that 53.4% of patients found positive for anomalies of the β-chain related hemoglobinopathies were male (Al-Suliman, 2006; Uddin et al., 2012). Thus, it can be safely concluded that β-thalassemia major does not appear to have any gender predilection.

The median time on chelation therapy in the current study was 23.00 (IQR: 10.00) months, which resulted in a median ferritin level of 926.50 (IQR: 1144) ng/mL; unfortunately, we did not have a baseline ferritin level before the initiation of chelation therapy. Alymara et al. noted that the mean ferritin levels of patients decreased from a baseline mean value of 2637 ± 1292 ng/mL to 1580 ± 1024 ng/mL (p=0.002) after a mean time of 13.5 months on chelation therapy (Alymara et al., 2004). Mishra et al. reported that the mean serum ferritin level remained high (with a mean value of 2767.52 ± 1849.1 ng/mL) despite adequate time on chelation therapy (Mishra and Tiwari, 2013). We believe the variation in serum ferritin levels, despite similar lengths of time on treatment between our study and the ones mentioned above, may be associated with variations in the frequency of blood transfusions and compliance with chelation therapy.

Our study's median age at first transfusion was 12.00 (IQR: 7.00) months. Maaloul et al. reported that the mean age at which patients with β-thalassemia major received their first blood transfusion was 11.5 months, which was similar to our study, as were the results of Ansari et al., who reported a median age of 9 (range: 6-15) months when their study sample received their first transfusion (Ansari et al., 2022; Maaloul et al., 2018). Requirements for transfusions at an early age translate into an early requirement for chelation therapy; patients of β-thalassemia major require adequate monitoring of iron status and chelation from an early age if complications secondary to iron overload are to be prevented.

Our study sample had a median number of lifetime transfusions of 60.50 (IQR: 33.00), with a mean time between transfusions of 6.14 weeks. Mishra et al. noted that the time between transfusions in their study sample ranged from 2 to 8 weeks (Mishra and Tiwari, 2013). Guidelines suggest that patients with β-thalassemia major should be transfused more frequently at an average of 2 to 4 weeks to maintain haemoglobin targets; however, this is not always possible keeping in view the cost of treatment and physicians are compelled to increase the time between transfusions (Ehsan et al., 2020; Farmakis et al., 2022).

In the current study, 31.4% of patients had a positive serology for hepatitis C, 6.7% had a positive hepatitis B serology, and 1.6% suffered from concurrent C and B viral infections. Ehsan et al. reported a similar prevalence of 26.0% positive hepatitis C seroprevalence in their meta-analysis of patients with β-thalassemia major, while hepatitis B seropositivity was seen in 3.13% of their patients (Ehsan et al., 2020). Waheed et al. reported a prevalence of 29.79% for hepatitis C and 4.13% for hepatitis B in their

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study of patients with β-thalassemia major (Waheed et al., 2021). Poor screening of blood products and non-standardized transfusion practices has resulted in an epidemic of cases of viral hepatitis, which has serious long-term complications for these patients, including in conjunction with iron overload as well as with different chelators (Mirzaei et al., 2021).

Lastly, our study showed that patients on deferasirox for at least one year had a frequency of dilated cardiomyopathy of 5.9%, while it was 3.8% with deferoxamine (p=0.172), indicating that there was no difference between the two therapies in terms of myocardial iron clearance. Pepe et al. noted that, after one year of chelator therapy, 8.3% of patients suffered from dilated cardiomyopathy with deferasirox versus 3.3% with deferoxamine (p>0.05) (Pepe et al., 2011). Pennell et al. reported the effects of the two drugs on myocardial T2* improvement. They noted that deferasirox therapy for one year resulted in an improvement from a baseline of 11.2 milliseconds at baseline to 12.6 milliseconds, while these figures with deferoxamine were 11.6 milliseconds at baseline, which improved to 12.3 milliseconds after one year of therapy (p>0.05) (Pennell et al., 2014). Thus, the studies, as mentioned earlier, demonstrated no difference between the two drugs regarding myocardial outcomes at one year.

Our study was limited by the fact that it was not randomized: patients had been receiving chelation according to the preference of their primary physician. Secondly, compliance with therapy in each treatment arm was assessed using hospital and pharmacy records and clinical history, which may not have been completely accurate. Additionally, there was a difference between the two treatments arms regarding the previous chelation received, which may have influenced the results. Lastly, this study was conducted in a single center where the study population was based on the wards of personnel from the armed forces who were entitled to treatment in the study institute and, as such, the study should be performed on a larger, multi-center population so that the result can be more generalizable to the population-at-large.

Conclusion

The frequency of dilated cardiomyopathy in pediatric patients suffering from β-thalassemia major receiving deferasirox for iron chelation for at least one year was similar to that in patients on deferoxamine for the same indication and minimum period. It may be employed as therapy for chelation in children as it carries the added benefit of having an oral formulation while providing similar efficacy regarding myocardial protection. Further research in prospective, randomized trials is needed to establish the efficacy and safety of deferasirox, whether alone or in combination with other chelators, in the Pakistani population.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.
Approved by the department Concerned.

Consent for publication
Approved

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Not applicable

Conflict of interest

The authors declared absence of conflict of interest.

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