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Comparison of deferasirox and deferoxamine effects on iron overload in patients with blood transfusion-dependent β-thalassemia

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Introduction: Beta-thalassemias is an autosomal recessive hematological disorder prevalent in the Mediterranean area due to defects in the synthesis of β chains of hemoglobin. The present study aimed to compare the effects of deferasirox and deferoxamine on iron overload in patients with blood transfusion-dependent β-thalassemia major and intermedia.

Methods: This prospective cross sectional study was done in Dhaka Shishu Hospital and Institute, involved 100 patients with known cases of β-thalassemia major or intermedia who have been treated with blood transfusion and iron chelators from January 2020 to December 2023. Serum ferritin, serum iron, and serum total iron binding capacity were assessed in deferoxamine and deferasirox-treated patients.

Results: In deferoxamine-treated patients, serum ferritin levels were high (4600.56 + 119.2ng/dL) compared to deferasirox-treated patients (3000.261 ± 121.2 ng/dL; P< 0.0001), also there were significant differences in serum iron and total iron-binding capacity (P< 0.0001) in deferasirox-treated patients compared to deferoxamine-treated patients.

Conclusion: This study indicated that deferasirox is more effective than deferoxamine regarding iron overload in patients with blood transfusion-dependent β-thalassemia.

Keywords: Deferasirox, Deferoxamine, Serum Ferritin, B-Thalassemia

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Introduction

Beta-thalassemia is an autosomal recessive hematological disorder prevalent in the Mediterranean area due to defects in the synthesis of β chains of hemoglobin, caused by a mutation in the HBB gene on chromosome 11 leading from asymptomatic to clinically severe hypochromic microcytic anemia [1].

The types of beta-thalassemia are major, intermedia, and minor depending on hemoglobin type and clinical presentations that include splenomegaly, hemolytic anemia, jaundice, and gallstones, those only seen in major and intermedia types, while in beta-thalassemia minor the clinical presentation is mainly misdiagnosed as iron deficiency anemia that was refractory to iron therapy [2].

Beta-thalassemia minor is treated with folic acid only and rarely needs a blood transfusion, while beta-thalassemia major and intermedia are blood transfusion-dependent types since untreated beta-thalassemia leads to congestive heart failure and eventually death [3]. Repeated blood transfusions lead to iron overload and toxicity causing cardiac siderosis, pulmonary hypertension, and endocrinopathy [4].

Therefore, iron chelating therapy is mandatory to prevent iron overload-induced complications accordingly, iron chelators such as deferoxamine, deferiprone, and deferasirox are used with repeated blood transfusion in the management of anemia in beta-thalassemia major and intermedia [5]. The first iron chelator was deferoxamine derived from *Streptomyces pilosus* which was introduced in 1960, administrated parenterally (intravenous [IV] or subcutaneous [SC] but not intramuscular) with a short half-life and dose-dependent effect [6].

SC administration of deferoxamine leads to severe pain at the site of injection, while prolonged IV administration leads to noncompliance; also, frequent deferoxamine administration causes growth retardation [7], thus, the necessity for oral iron chelator is required like deferiprone and deferasirox. Deferiprone is the first oral iron chelator, and it is a bidentate hydroxypyridone introduced in the year 1980 for the management of iron overload through binding with iron and the complex will excreted in the urine [8];

Deferiprone has a relatively short half-life due to rapid hepatic metabolism and given in a dose of 75 mg/kg/day with significant lowering of intracellular iron overload [9]. Deferiprone leads to many adverse effects such as agranulocytosis due to myelotoxicity, gastric upsets, liver damage, and arthralgia [10].

Deferasirox is a new oral iron chelator introduced in 2005 for the management of iron overload in beta-thalassemia major and intermedia. Deferasirox has high plasma protein binding with a long half-life and is metabolized by the liver with subsequent faecal excretion [11].

It is more effective than deferiprone in the treatment of iron overload even in sickle cell anemia with relatively fewer adverse effects compared to deferiprone, but it causes transient acute renal insufficiency [12].

Therefore, the present study aimed to compare the effects of deferasirox and deferoxamine on iron overload in patients with blood transfusion-dependent beta-thalassemia major and intermedia.

Material and Methods

This prospective cross sectional study was done in Dhaka Shishu Hospital and Institute, involved 100 patients with known cases of β-thalassemia major or intermedia who have been treated with blood transfusion and iron chelators from January 2020 to December 2023.

This clinical patients-based study was done according to the World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects [13].

This study was approved by the Ethics Review Board of BICH. A written informed consent was taken from all patient relatives for enrollment in this study.

Study design

This study was a cross-sectional study done in the Thalassemia Centre of DSH involving 100 patients with known cases of β-thalassemia major or intermedia that has been treated with blood transfusion and iron chelators.

The patients were selected randomly regardless of age and gender. Patients with β-thalassemia were divided according to the type of therapy into two groups.

Group (A): 42 patients (22 females + 20 males) were treated with blood transfusion plus IV deferoxamine infusion (8 h/day) 30 mg/kg/every 3 days/week. Group (B): 58 patients (30 females + 28 males) were treated with blood transfusion plus oral deferasirox 30 mg/kg/day. Splenectomy had been achieved in 8 patients (5 males + 3 females) and the duration between splenectomy and participation in this study was 2–3 years.

Exclusion criteria included patients with sepsis, heart failure, renal failure, active liver disease and rheumatologic diseases.

Haematological parameters

A fasting blood sample of 10 mL was taken from an antecubital site from each patient and then centrifuged immediately; sera were stored at −80°C until used. Serum ferritin in ng/dL was assessed by a specific ELISA kit (Human Ferritin ELISA Simple Step ab200018).

Serum iron in µg/dL was estimated by a specific ELISA kit (serum iron ELISA Kit. ABIN2105464). Serum total iron binding in µg/dL was assessed by a specific ELISA kit (MBS2601224 Human Total iron-binding capacity ELISA Kit). All ELISA Kit methods were done according to the manufacturer's instructions.

Unsaturated iron-binding capacity (UIBC) which measures levels of free transferrin (not bound to iron), UIBC = Total iron-binding capacity (TIBC) (µg/Dl) − serum iron (µg/dL) [14]. A complete blood picture was prepared by Automated Touch Screen Hematology Analyzer, Hs Code: 90189090, China (WHY 6480).

Statistical analysis

Data were expressed as mean ± standard deviation, number and percentage. The unpaired Student's *t*-test was used to evaluate the significance of differences between the treated groups in terms of a 95% confidence interval, t value with $P < 0.05$ as statistically significant. Data analysis was done using SPSS (IBM SPSS Statistics for Windows, Version 26.0., 2023 Armonk, NY: IBM Corp).

Results

A total number of 100 patients with β-thalassemia aged 9.3 ± 2.5 years, female to male ratio was 1.08:1.

Regarding types of thalassemia, it has been found that 67.19% of β-thalassemic patients were major type while 32.81% were intermediate type. The duration of starting blood transfusion was 13.12 ± 2.9 years whereas the duration of starting iron chelation was 4.68% for age <5 years, 60.93% for age 5–10 years and 34.37% for age >10 years.

Table 1: Demographic characteristics of thalassemic patients

Characteristics		n(%), mean + SD
Age(years)		9.3+2.5
Number		100
Gender	Male	48(48)
	Female	52(52)
	Male: Female ratio	1:1.08
Type of Thalassemia	Major	45(45)
	Intermedia	55(55)
Duration of blood transfusion(years)		9.2+2.3
Duration of starting iron chelation(years)	<5	23(23)
	5-10	65(65)
	>10	12(12)
Iron chelators	Deferoxamine	42(42)
	Deferasirox	58(58)
Splenectomy		12(12)
Complications	Skeletal malformations	08(8)
	Recurrent infections	12(12)
	Gall stone	06(6)
	Hepatitis C	03(3)
	Hepatitis B	04(4)

Concerning iron chelation treatment, 42% got deferoxamine and 58% got deferasirox. In addition, 8 (8%) patients experienced splenectomy. This study pointed out that complications were recorded in 33% of thalassemic patients which includes recurrent infections 12%, skeletal malformations 8%, hepatitis C 3%, and hepatitis B 4% and gallstone 6%. The demographic characteristics of thalassemic patients are summarized in Table 1. In deferoxamine-treated patients, serum ferritin levels were high (4600.56 ±119.2 ng/dL) compared to deferasirox-treated patients (3000.26 ± 121.2 ng/dL; $P < 0.0001$); also there were significant differences in serum iron, TIBC, and UIBC ($P < 0.0001$) in deferasirox-treated patients compared to deferoxamine-treated patients. There were insignificant differences in hemoglobin and platelet count in deferoxamine and deferasirox-treated patients ($P = 0.5332$ and $P = 0.0233$, respectively) [Table 2].

Table 2: The differences between the effect of deferoxamine and deferasirox on haematological parameters of blood transfusion-dependent β-thalassemia major or intermedia

Parameters	Deferoxamine	Deferasirox	t	95%CI	P
Serum ferritin(ng/ml)	4600.56+119.2	3000.26+121.2	90.65	5033.22-5344.33	<0.0001
Serum iron(ug/dl)	334.71+59.2	277.9+44.2	13.8	177.42-223.44	<0.0001
TIBC(ug/dl)	112.4+39.5	154.4+33.2	-3.47	-56.13-19.22	<0.0001
Hemoglobin(g/dl)	10.55	10.46	0.325	-1.33-1.442	0.5332
Platelet count(n/microl)	200017.76+78.2	200009.76+55.2	-1.44	-104.47-3.652	0.0233

*P<0.01, Data expressed as means± SD, TIBC: Total iron binding capacity, SD: Standard deviation, CI: Confidence interval.

Discussion

This study revealed significant effects of deferasirox in reduction of iron overload in β-thalassemia compared to deferoxamine. In deferasirox-treated patients, serum ferritin levels were low compared to deferoxamine-treated patients due to higher efficacy and compliance of deferasirox [15], since; deferoxamine parenteral administration led to poor compliance and efficacy [16].

These findings correspond with the Vichinskyet al. study that showed higher efficacy of deferasirox compared to deferoxamine in the reduction of iron overload in hemolytic anemia [17]. In addition, animal model studies demonstrated the effectiveness of deferasirox in the reduction of liver and heart iron overloads more than deferiprone and deferoxamine [18].

Regarding patients that are treated with deferasirox, TIBC is improved through the reduction of serum iron and iron burden in transfusion-dependent β-thalassemia, since circulating iron is normally bound to transferrin but in a state of iron overload, the capacity for iron binding will be reduced leading to increase in the nontransferrin bound iron.

Consequently, this will lead to the induction of oxidative stress and reduction in the antioxidant capacity, so a high free iron can be taken by cardiac and hepatic parenchyma independent of transferrin receptors causing parenchymal damage [19].

Moreover, Wood et al.'s experimental study demonstrated that deferasirox has cardioprotective and hepatoprotective effects through the reduction of intracellular irons; it decreases cardiac iron by 20.5% as deferiprone and both of these drugs are more effective than deferoxamine [20].

These findings are in agreement with our results. Thus, favourable and potential effects of deferasirox were attributed to the long biological half-life which gave 24-hour protection from the effect of iron overload, unlike the deferoxamine effect which gave protection only limited to the time of drug exposure which was about 8 hours [11].

In general, sustained serum ferritin levels >2500 ng/dL are associated with organ toxicity, thus the goal of chelation therapy is lowering serum ferritin below 2500 ng/Dl [21] but in this study, serum ferritin level in deferoxamine-treated patients was 4600.56 ± 119.2 due to poor compliance while in deferasirox-treated patients serum ferritin level was 3000.26 ± 121.2 due to unavailability and cost of this drug, but clinically none of our enrolled patients observed signs and symptoms of heart or hepatic dysfunctions despite high serum ferritin levels.

Indeed, 8% of our patients developed skeletal and growth retardation due to extramedullary erythropoiesis or endocrinopathy as supported by Saffariet al.'s study, which revealed a wide range of metabolic and endocrine disorders in β-thalassemia major [22].

Conclusion

This study indicated that deferasirox is more effective than deferoxamine regarding iron overload in patients with blood transfusion-dependent β-thalassemia.

What does the study add to existing Knowledge: deferasirox is more effective than deferoxamine regarding iron overload in patients who need frequent transfusions.

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