Comparative analysis of deferasirox and deferiprone iron chelator on the growth pattern of Bengali β-thalassemia major children of West Bengal, India

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ABSTRACT

Background: Ineffective erythropoiesis and excessive red blood cell transfusions are the major source of iron overload in case of thalassemia major patients. It is mainly accountable for the growth retardation, morbidity, and mortality in patients with beta thalassemia major. The availability of effective iron chelators and proper knowledge regarding the iron toxicity can significantly improve the rate of survival in thalassemia patients. **Aims and Objectives:** The study was done to compare the efficacy and safety of the deferiprone (DFP) with deferasirox (DFX) in regulating the growth pattern among the thalassemia major patients. **Materials and Methods:** The height and weight were plotted on the World Health Organization recommended growth charts for 0–5 years and 5–19 years old boys and girls during the follow-up visits. Comparison between the role of DFP versus DFX was evaluated by t-test. **Results:** There is no statistically significant (P = 0.11 in males and P = 0.06 in females) difference between DFP versus DFX while considering height velocity. A similar observation was obtained in case of weight velocity (P = 0.78 in males and P = 0.56 in females) and basal metabolic index (BMI) index (P = 0.44 in males and P = 0.53 in females). **Conclusion:** Both DFX and DFP have no significant correlation in regulating the height, weight, and BMI of thalassemia children.

Key words: β-Thalassemia major; Deferasirox; Deferiprone; Height; Weight velocity

INTRODUCTION

Thalassemia is characterized by unbalanced globin-chain synthesis, ineffective erythropoiesis, chronic anemia, increased intestinal iron absorption, and subsequent multi-mortality.[1] Iron overload is foreseeable in case of thalassemia major patients where regular transfusion is foremost requirement for saving life. 100–200 ml of pure red blood cell/kg body weight/year transfusion gathers approximately 0.32–0.64 mg of iron/kg/day.[2-6] In majority of cases, the chronic growth retardation of thalassemia major patients resulted by tissue hypoxia and iron toxicity.

The child with thalassemia major has a particular growth pattern, which is relatively normal until age of 9–10 years; after this age, a slowing down of growth velocity and a reduced or absent pubertal growth spurt are observed.[7-9] Normal growth pattern of β-thalassemia children during the first 10 years of life depends on the Hb levels above 8.5 g/dl. Hypoxia condition may lead to growth retardation and adequate transfusion along with iron chelation therapy makes the thalassemia patients indistinguished from their non-thalassemia peers.[10] Short stature is a common factor in thalassemia children within the age group of 18–36 years and it covers nearly 18% of the patients.[11-16] Although there

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is an advancement in medical therapy, growth and weight retardation continue to be problems found in transfusion-dependent thalassemia major patients. Anomalous growth hormone (GH) secretion may be found in some of the patients but interestingly, the majority of cases with short height do not have deficiency of GH. The reduced serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) concentrations in short thalassemic patients with normal GH reserve and serum GH binding protein levels suggest a secondary GH insensitivity condition. Although iron chelating drug is the essential requirement for overall survival and complication-free endurance, they carry considerable side effects.[17,18]

Among the iron chelators, deferiprone (DFP) and deferasirox (DFX) are most well recognized and widely acceptable drugs.[19] DFP (Ferriprox; Apotex Inc., Toronto, ON, Canada) is a synthetic and bidentate iron chelator. It is orally administered at 75 mg/kg/day in three divided doses. Compliance rates with DFP are generally higher than those associated with subcutaneous infusions of desferrioxamine (DFO; Desferal; Novartis Pharma AG, Basel, Switzerland).[20] On other hand, DFX (ICL670; Exjade; Novartis) is a N-substituted bis-hydroxyphenyltriazoles compound, related to a new class of tridentate iron chelators which is orally bioavailable.[21] In 2005, Food and Drug Administration, and subsequently the European Medicine Agency (EMEA) approved its use in thalassemia major patients (aged ≥6 years), transfused with ≥7 ml/kg/month of packed red blood cells.[22]

So far, few studies have been reported complications related to growth delay and underweight in transfusion-dependent beta thalassemia major patients. Although, the effects of iron chelators on development pattern in terms of height, weight, and basal metabolic index (BMI) in thalassemia children have not been evaluated so far.

Aims and objectives

The aim of the study was to enlighten the efficacy of two well-known iron chelators, DFX, and DFP on the growth pattern in Bengali beta thalassemia major children in a comparative manner.

MATERIALS AND METHODS

Subject selection

A cross-sectional study was conducted among the Bengali children who were ≥2–≤15 years old (31 males and 29 females) with transfusion-dependent thalassemia diagnosed on the basis of hemoglobin electrophoresis or high performance liquid chromatography over a time period of 12 months from January to December 2012. All

the studied subjects were attending the Department of Paediatric Medicine in collaboration with the Department of Haematology, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India. Detailed clinical history was evaluated after getting consent. The following information was collected from medical records of the patients: Demographics (age, gender, and age at the time of diagnosis and at first transfusion), anthropometric parameters (weight, height, and BMI), and clinical details (blood transfusion history, last pre-transfusion hemoglobin, and serum ferritin level).

All were fulfilling the inclusion criteria, which were age between 2 and 15 years, not suffering any serious hepatic, renal, or cardiac disease and not having diabetes mellitus or any other serious infections. The included subjects had already received >10 blood transfusions and had serum ferritin levels >1000 ng/ml and without history of any chelation therapy before the study started was included in the study. The exclusion criteria were patients with any form of anemia other than BTM, short stature due to other chronic systemic disease, or hereditary bone dysplasia.

Sample size

A sum total of 60 thalassemia children with Bengali ethnicity and multiple transfusion history were recruited for the present study. Out of them, 30 children (16 females and 14 males) were treated with DFX and rest of the 30 children (13 females and 17 males) with DFP. The study was conducted over a period of 1 year in between these two groups.

Ethical permission and study design

Due ethical clearance from IEC was obtained in advance and written informed consent was taken from patients/guardians before include them as study population after explaining the aim of the study. The study was conducted in compliance with the Declaration of Helsinki. A questionnaire was framed covering the key points of clinical history of illness and treatment with family background. Relevant clinical examination and investigations were carried out to establish the diagnosis of growth retardation.

Estimation of serum ferritin

About 3 ml of EDTA blood sample was collected by a clean venepuncture from each subject. The blood was allowed to clot. Serum was separated and stored at −80°C. Ferritin levels were performed by enzyme-linked immunoassay (ELISA; Human Ferritin Simple Step ELISA Cat# ab200018; Abcam, Cambridge, MA, USA), in batches of ten each, along with control and patient sample. At first, the serum ferritin level was measured at the beginning of therapy, then at every 3-month interval.

Measurement of height and weight

The World Health Organization (WHO) growth chart was used for boys and girls to assess their weight and height. Short stature is defined as a height more than two standard deviations below the mean for age (less than the 3rd percentile). Tall stature is defined as a height more than two standard deviations above the mean for age (greater than the 97th percentile).[23] Underweight is demarcated as BMI <5th percentile, whereas overweight between 85th and 95th percentile and obese more than 95th percentile.[24]

The measurement of height was done with the help of Stadiometer (Seca; Cat #213 Deutschland, Hamburg, Germany). The height of the children was measured at the start of the therapy and then plotted in the WHO growth chart according to the age and sex of the child. Then, every 3 month, the height was measured and plotted on the respective growth chart. Similarly, weight of the child was measured with the help of electronic digital weighing scale and it was measured at the beginning of the therapy as well as plotted in the WHO growth chart according to the age and sex of the child. It was repeated intermittently throughout the study period.

Drug administration

Thirty children were prescribed with DFX (30 mg/kg/day) single daily dose in the morning on an empty stomach with fruit juices and advised not to take heavy meal for 1 h after consuming the drug. Another 30 children were instructed to give DFP (75 mg/kg/day). It has a shorter half-life, requiring administration 3 times a day and they were observed for a period of 1 year. The parents were advised to report the details about the physical condition including hepatic, renal, and cardiac complication in the interval of 3 months. They were also informed to report directly if the child had any types of hostile effects after drug therapy. At the same time, hematological parameters including total blood count, hemoglobin, and serum ferritin were evaluated every month specially before transfusion regimen.

Statistical analysis

Data were collected and registered accordingly. All the clinical records were managed, edited, and analyzed by the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Inc., Armonk, NY, USA) for Windows. A descriptive analysis of all patients in the study was performed. Male: female ratio was also considered. The mean, median, and range were calculated for clinical variables. Short stature and weight were computed as per different study characteristics. The level of significance taken for all the statistical test was $P<0.05$.

RESULTS

Subject information

Out of the 60 patients, the mean ($\pm$SD) age was found 4.59 ($\pm$0.85) years in DFX-therapy group and 4.66 ($\pm$0.88) years in case of DFP-therapy group. The overall male and female proportion within the studied group was 0.94:1. Therefore, there was no sexual biasness in the included subjects. The mean frequency of blood transfusion per year was 14.61$\pm$3.5 and mean hemoglobin level before transfusion 6.43$\pm$0.72 (g/dL).

In the present study, the beta thalassemia major subjects within the age group of ≥ 2–≤ 15 years were only considered. Therefore, pubertal development and growth were not determined further. The mean height of our patients was significantly lower. Regarding short stature, 56.67% patients were recorded to be short stature whereas 16.67% patients were underweighting before initiation of chelation therapy. The details of the height and weight of the studied subjects were plotted on the WHO recommended growth chart before initiating the chelation therapy and depicted in supplementary figures (Figures S1 and S2). The demographic characters of the studied subjects are described in Table 1. In the studied subjects treated with DFP, there is a significant correlation ($P=0.001$) between short stature and number of transfusions. Likewise, underweight is also significantly ($P=0.002$) related with number of transfusions. Serum ferritin level also plays a predominant role for short stature ($P=0.005$) and underweight ($P=0.008$) among the studied

Table 1: Demographic characteristics of studied thalassemia subjects

Characteristics	No (%), mean ± SD
Age (years)	5.43 ± 6.3
Gender	
Male	51.66%
Female	48.33%
Female: male	0.94:1
Mean hemoglobin level before transfusion (g/dL)	6.43 ± 0.72
Mean height (cm)	98.49 ± 11.61
Mean weight (kg)	15.46 ± 1.3
Mean BMI (kg/m²)	15.39 ± 1.48
Short Stature (no. of patients)	34 (56.67%)
Under weight (no. of patients)	10 (16.67%)
Initial serum Ferritin (ng/ml)	3554.55 ± 784.38
Initial LVEF	69.28 ± 2.18
Initial age of starting iron chelation (years)	
Deferasirox	4.59 ± 0.85
Deferiprone	4.66 ± 0.88
Splenectomy	3 (5%)
Number of blood transfusion/year	14.61 ± 3.5

BMI: Basal metabolic index, LVEF: Left ventricular ejaculatory factor

thalassemia major patients (Table 2). Similar findings were obtained in case of DFX treated group.

Comparative efficacy of DFX and DFP on the height gain

The physical growth rate among the studied thalassemia patients was detected by calculating the height velocity among both males and females. We have classified the studied subjects into two groups; Group-I contains male thalassemia patients whereas Group-II includes female only. In Group-I, the mean (±SD) height was 107.26 (±4.15) cm at the beginning of study and it became 113.06±3.61 cm at the end of study period in DFX-treated group. Similarly, in case of DFP group, the mean (±SD) height was 107.75 (±5.83) cm at the beginning and height became 113.19±5.69 cm at the end of the study period (Table 3). The height of the boys increases in both the groups. The mean relative change of height was 5.8 (±0.79) cm in case of DFX whereas it is 5.43 (±0.44) in case of DFP-treated group. Although, the relative change in height in between DFX and DFP is not statistically significant (P=0.110).

Consequently, in Group-II, the mean height at the beginning of the study was 106.08 (±5.08) cm and at the end of the therapy, it was 112.29 (±4.64) cm in DFX-treated girls. Similarly, the value was 107.75 (±5.83) cm and 112.00 (±5.88) cm in case of DFX and DFP, respectively. While considering the mean relative change of height in between DFX and DFP -treated group, it was not statistically significant (P=0.06), which reflects there is no substantial difference between DFX and DFP in regulating the growth velocity in both gender (Table 3).

While plotting these values in the WHO growth chart according to the age and sex of the child, the height remains between −2 and +2 Z score (Figure 1). The male subjects trail their normal height velocity while getting chelation therapy either with DFX or DFP (Figure 1a and b). Likewise, females also follow the same pattern of growth rate without getting influenced by the individual chelating drug (Figure 2a and b).

Comparative efficacy of DFX and DFP on the weight gain

In Group-I, the mean weight at the beginning of the study was 15.89 (±1.25) kg whereas at the end of the therapy, it was 18.09 (±1.25) kg while treating with DFX. Likewise, within the same group, DFP-treated males had initial weight 16.02 (±1.33) kg and it was 18.27 (±1.02) kg after 1 year of therapy. In case of Group -II, the mean weight at the beginning of the therapy was 15.9 (±1.28) kg in DFX-treated females while 16.10 (±1.23) kg in case of DFP-treated group. Although the relative change of weight

Table 2: Clinical variables including the height and weight of the studied patients before starting DFP and DFX-treated group

Variables	DFP-treated group						DFX-treated group					
	Short stature	Normal	P-value	Under weight	Normal	P-value	Short stature	Normal	P-value	Under weight	Normal	P-value
Sex	Male: 8 Female: 7 Male:Female=1.14	Male: 9 Female: 6 Male:Female=1.5	-	Male: 3 Female: 1 Male:Female=3	Male: 14 Female: 12 Male:Female=1.16	-	Male: 8 Female: 11 Male:Female=0.727	Male: 6 Female: 5 Male:Female=1.2	-	Male: 3 Female: 3 Male:Female=1.0	Male: 13 Female: 11 Male:Female=1.18	-
Age of first diagnosis (years)	1.30 ± 0.47	1.11 ± 0.48	0.28	1.65 ± 0.37	1.35 ± 0.41	0.18	1.45 ± 0.52	1.59 ± 0.36	0.43	1.75 ± 0.58	1.40 ± 0.50	0.14
Hb before transfusion (g/dl)	6.42 ± 0.6	6.38 ± 0.42	0.85	6.42 ± 0.43	6.41 ± 0.48	0.96	6.14 ± 0.61	5.94 ± 0.49	0.36	6.46 ± 0.61	6.38 ± 0.61	0.78
No. of transfusion before therapy	31.87 ± 2.39	28.27 ± 3.17	*0.001**	38.50 ± 3.00	28.27 ± 5.95	*0.002**	32.11 ± 2.69	27.27 ± 6.08	*0.005**	39.00 ± 2.83	31.46 ± 6.04	*0.006**
Ferritin (ng/ml)	3386.53 ± 220.27	2891.93 ± 582.34	*0.005**	4284.50 ± 258.29	3298.38 ± 674.39	*0.008**	3441.95 ± 208.86	3000.67 ± 602.06	*0.007**	4255.33 ± 535.96	3357.71 ± 595.79	*0.002**

Variables are in mean ± SD; statistically significant (p<0.05) values are in bold italics with*. DFX: Deferasirox, DFP: Deferiprone

Table 3: Effect of DFX and DFP in height and weight velocity of the studied thalassemia subjects

Group	Iron chelating drugs	Sex	Mean (± SD) age at the beginning of therapy (years)	Height (mean ± SD) (cm)			P-value	Weight (mean ± SD) (kg)			P-value
				At the beginning of therapy	At the end of therapy	Relative change of height		At the beginning of therapy	At the end of therapy	Relative change of weight	
I	DFX	Male	4.63 ± 0.79	107.26 ± 4.15	113.06 ± 3.61	5.8 ± 0.79	0.110	15.89 ± 1.25	18.09 ± 0.95	2.2 ± 0.35	0.78
	DFP		4.53 ± 0.90	107.75 ± 5.83	113.19 ± 5.69	5.43 ± 0.44		16.02 ± 1.33	18.27 ± 1.02	2.24 ± 0.45	
II	DFX	Female	4.54 ± 0.92	106.08 ± 5.08	112.29 ± 4.64	6.21 ± 0.75	0.06	15.9 ± 1.28	18.21 ± 1.16	2.31 ± 0.41	0.56
	DFP		4.76 ± 0.84	107.75 ± 5.83	112 ± 5.88	5.6 ± 0.98		16.10 ± 1.23	18.32 ± 0.89	2.21 ± 0.52	

DFX: Deferasirox, DFP: Deferiprone; $P<0.05$ is considered as statistically significant

irrespective to the gender (male $P=0.78$ and female $P=0.56$) is not statistically significant, while treating with DFX or DFP (Table 3).

In both the treatment groups, the studied patients were gaining weight in a normal trend while on chelation therapy over the period of 1 year. After plotting these values in the WHO growth chart according to the age and sex of the child, the weight remains between the −2 and +2 Z score throughout the study period (Figure 2a-d). The studied children follow their normal weight velocity while getting chelation therapy either with DFX or DFP and no significant difference was observed between these two groups.

Comparative efficacy of DFX and DFP on BMI

In case of Group-I, the male subjects treated with DFX and DFP do not show a significant mean relative change of BMI ($P=0.44$). Likewise, in Group-II, the increment of relative change in BMI rate is not statistically substantial ($P=0.53$) (Table S1). Therefore, the BMI of the studied subjects was not influenced by DFX and DFP chelation therapy.

The BMI values of the studied subjects before initiating the chelation therapy are described in supplementary figure (Figure S3).

Safety profile of DFX and DFP

Iron chelation is the keystone and standard of care in the current treatment strategy of thalassemia major patient. Ideally, since transfusions are initiated early in life, it is judicious to emphasize the importance of chelation and compliance to achieve success. Therefore, in the present study, the patients were regularly monitored for iron toxicity and other effects caused by their underlying condition. The side effects of these two iron chelating agents are demonstrated in the supplementary figure (Figure S4).

DISCUSSION

Thalassemia poses a major challenge to health and it considerably declines the quality of life. However, with optimal treatment including blood transfusion and iron chelation therapy, life expectancy of these patients can be enhanced.[25]

In total, 60 children of transfusion dependent thalassemia were enrolled in this study, of which 51.66% were male and 48.33% female. The anthropometric data from the present study demonstrated growth failure in transfusion dependent beta thalassemia secondary to iron overload. As age advances, growth impairment also increases. As per the
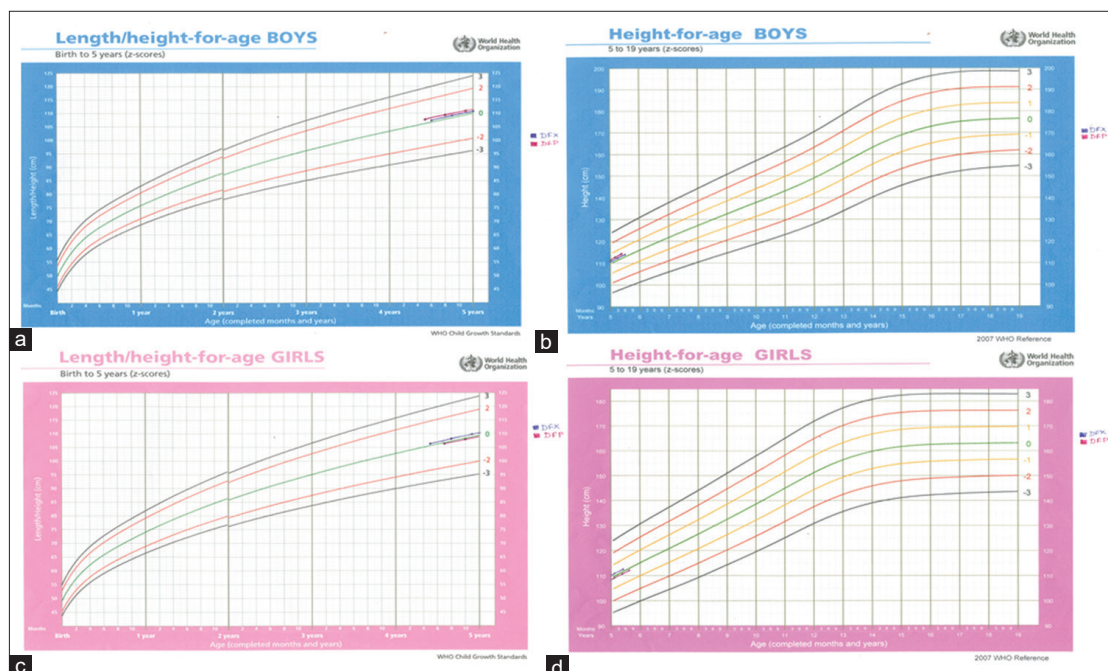
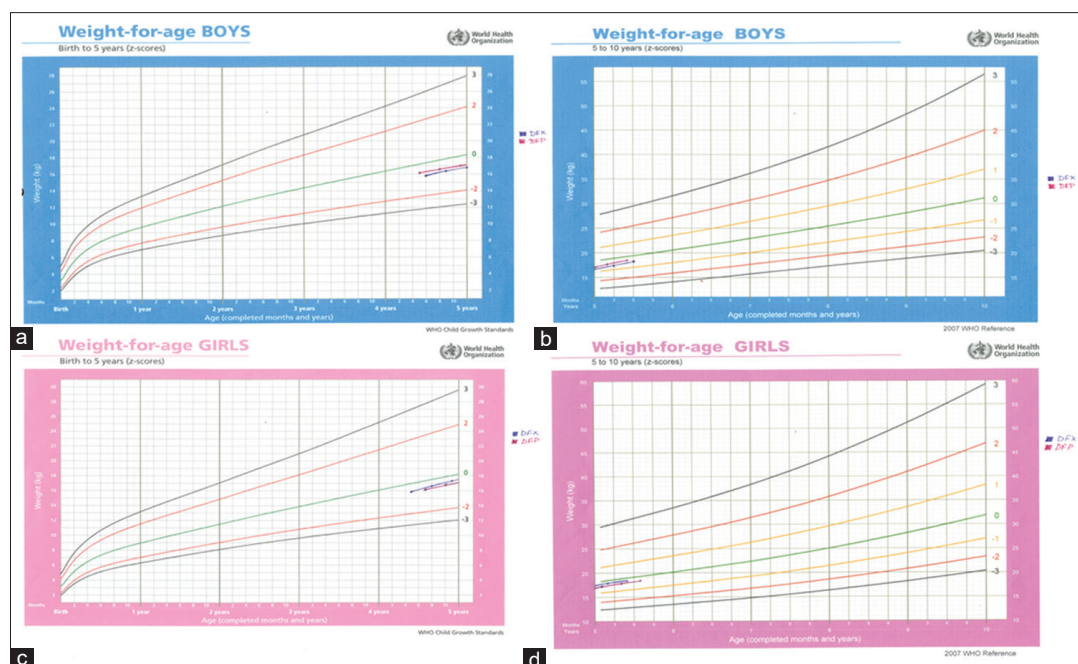**Figure 1:** Height percentiles of studied thalassemia patients of both sexes aged ≥2–≤15 years after 1 year of iron chelation therapy with deferasirox (DFX) and deferiprone (DFP). Height for males (a) birth to 5 years; (b) 5–19 years and females; (c) birth to 5 years; and (d) 5–19 years have been plotted in the WHO guided growth chart. The 3rd, 15th, 50th, 85th, and 97th percentiles are represented with lines of different colors in the graphs. The blue and red colors indicate DFX and DFP, respectively. The height of the studied subjects lies between −2–+2 Z score in the WHO growth chart according to the age and sex of the individuals over the period of 1 year

Figure 2: Weight percentiles of studied thalassemia patients of both sexes aged ≥2–≤15 years after 1 year of iron chelation therapy with deferasirox (DFX) and deferiprone (DFP). Weight for males (a) birth to 5 years; (b) 5–19 years and females; (c) birth to 5 years; and (d) 5–19 years have been plotted in the WHO guided growth chart. The 3rd, 15th, 50th, 85th, and 97th percentiles are represented with lines of different colors in the graphs. The blue and red colors indicate DFX and DFP, respectively. The weight of the thalassemia subjects lies between −2 and +2 Z score in the WHO growth chart according to the age and sex of the individuals over the period of 1 year

growth pattern, we found that 56.67% were short stature and rest had normal height. The proportion of short stature in our study was comparable to the previous findings of

Jana et al.,[26] Fadlyana et al.,[27] and Das and Majumdar,[28] which revealed the incidence of short stature were 65.8%, 62%, and 67%, respectively.[26-28]

The pathogenesis of growth failure in thalassemia is multifactorial[29-32] and one of the most common factors is iron overload.[33,34] Frequent blood transfusion is essential to acquire the baseline hemoglobin level, but if serum ferritin levels are greater than the anticipated level, patient's physical growth can be retarded in terms. In our study, there was a significant correlation observed between serum ferritin level and short stature as well as underweight in both DFX and DFP treated group (Table 2). The findings of the present study also support the previous ones.[35-39] In addition, the average age of the studied subject was 5.43±6.3 years. Here, we did not get any significant association between age of onset and short stature (P=0.287) or underweight (P=0.18) in both the DFP and DFX treated (P=0.43 and P=0.14, respectively) groups (Table 2).

We have observed the physical growth pattern and development proceeded normally while plotting the values on the WHO growth chart for all pediatric patients after 1 year of continuous treatment with DFX and DFP. The values were under normal range, that is, Z score in between −2 and +2 (Figures 1 and 2). The findings of the present study were supported by the Tanner stage by Piga et al.,[40] and ESCALATOR study of Taher et al.,[41] which shows that the body growth progressed normally in all pediatric patients with DFX therapy.[40,41] Consequently, the present study shows that both male and female follow their normal growth velocity with respect to height, weight, and BMI during therapy with either DFX or DFP (Table 3 and Table S1).

The growth pattern of thalassemic children depends mostly on hemoglobin level which should be maintained at above 10–11 g/dL for maintaining proper physiological function and regular activity. Hypoxia is one of the major factors that have a key role in growth and development of thalassemia major patients.[35] Here, the studied subjects showed average hemoglobin levels before transfusion was 6.43±0.72 g/dL and there was no association between hemoglobin levels before transfusion and the incidence of short stature (P>0.05). In contrast to that, previously another study was conducted in Malaysia revealed hemoglobin level <9 g/dl before transfusion was statistically upsurge the incidence of short stature and underweight.[42]

Limitation of the study

The limitation of this study was that the thalassemia subjects were not inspected for some other factors including hormonal status, endocrinopathies on growth, and their exact association with iron chelating drug such as DFX and DFP. Hormonal assay for T3, T4 and TSH, and IGF-1 and IGFBP-3 could not be assessed due to the expensive cost of hormonal testing.

CONCLUSION

Poor socioeconomic condition and low educational background compounds ameliorate the quality of life in case of thalassemia major patients. Growth retardation can be overcome by early detection, sufficient transfusion, and proper chelation therapy. Consequently, new strategies, planning, and guidelines seem to be required to minimize the complications. All the patients should investigate in terms of growth by measuring height and weight every 6 months alteration. The findings of the present study emphasized the importance of preservation of normalized hemoglobin level by maintaining blood transfusion, good monitoring of growth parameter, and iron over load with optimal iron chelation therapy.

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SUPPLEMENTARY

Table S1: Effect of DFX and DFP in BMI of the studied thalassemia subjects

Group	Iron Chelating Drug	Sex	Mean (± SD) age at the beginning of therapy (years)	BMI Mean (± SD) (Kg/m²)			P-value
				At the beginning of therapy	At the end of therapy	Relative change of BMI (kg/m²)	
I	DFX	Male	4.63 ± 0.82	13.85 ± 0.71	14.18 ± 0.63	0.55 ± 0.56	0.44
	DFP		4.56 ± 0.93	13.99 ± 1.05	14.40 ± 1.01	0.7 ± 0.49	
II	DFX	Female	4.54 ± 0.92	14.12 ± 0.75	14.33 ± 1.10	0.77 ± 0.78	0.53
	DFP		4.76 ± 0.84	14.23 ± 0.98	14.60 ± 1.01	0.61 ± 0.52	

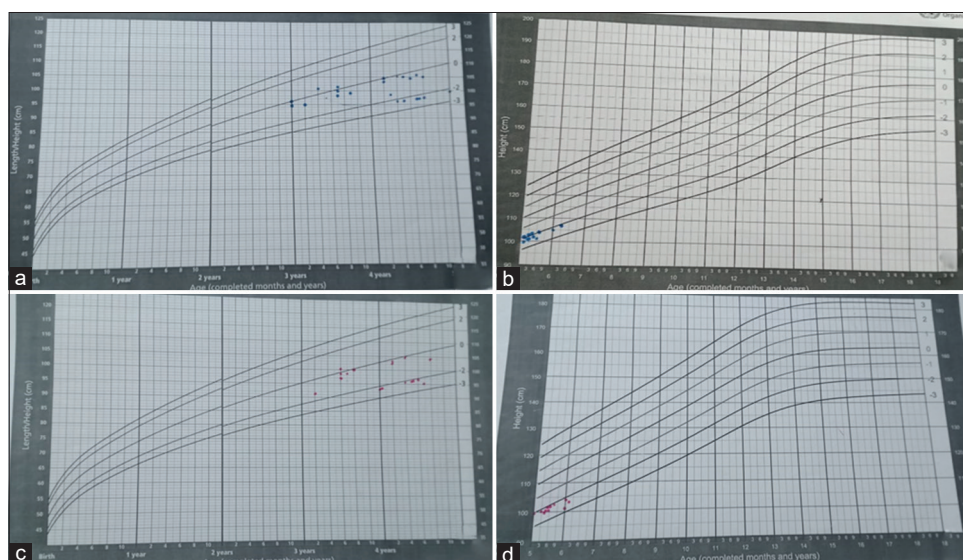DFX: Deferasirox, DFP: Deferiprone; *P*<0.05 is considered as statistically significant

Figure S1: Height percentiles of studied thalassemia patients of both sexes aged ≥2–≤15 years before initiating iron chelation therapy with deferasirox (DFX) and deferiprone (DFP). Height for males (a) birth to 5 years; (b) 5–19 years and females; (c) birth to 5 years; and (d) 5–19 years have been plotted in the WHO guided growth chart
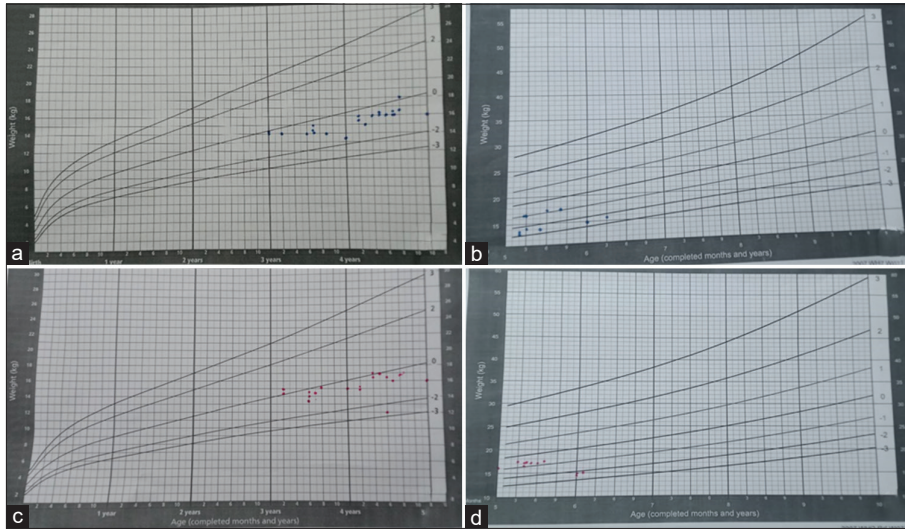
Figure S2: Weight percentiles of studied thalassemia patients of both sexes aged ≥2–≤15 years before initiating iron chelation therapy with deferasirox and deferiprone. Weight for males (a) birth to 5 years; (b) 5–19 years and females; (c) birth to 5 years; and (d) 5–19 years have been plotted in the WHO guided growth chart
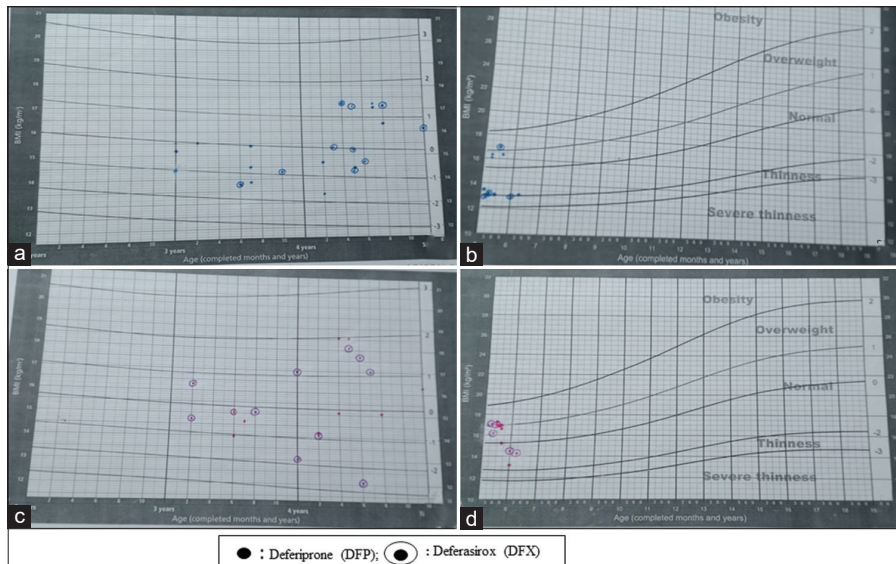

● : Deferiprone (DFP); ⊙ : Deferasirox (DFX)

Figure S3: BMI percentiles of studied thalassemia patients of both sexes aged ≥2–≤15 years before initiating iron chelation therapy with deferasirox and deferiprone. BMI for males (a) birth to 5 years; (b) 5–19 years and females; (c) birth to 5 years; and (d) 5–19 years have been plotted in the WHO guided growth chart.
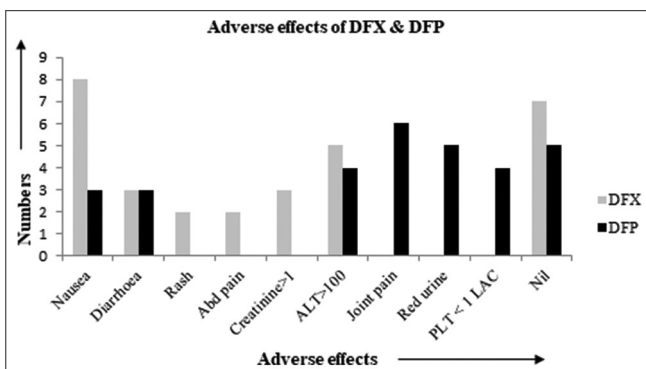

Figure S4: Adverse effects of deferasirox and deferiprone among the studied subjects