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Original Article

Comparative Effects of Iron Chelators on the Transfusion-Dependent Beta-Thalassemia Patients

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Abstract

This prospective study assessed the quality of life of patients with transfusion-dependent beta-thalassemia receiving three different iron chelation treatments. Patients enrolled were receiving one of the following chelation therapies: Group-I: deferoxamine (n=21), Group-II: deferasirox (n=75) and Group-III: deferoxamine in combination with deferiprone (n=39).

The three groups were compared in terms of their quality of life, satisfaction and adherence to treatment, control of their health, and self-esteem through the completion of five questionnaires. A higher percentage of patients receiving deferoxamine felt that their treatment negatively influenced their body and skin appearance and limited their ability to work, attend school, and perform daily tasks (P=.0.0066). The adherence to treatment rate and self-esteem were the lowest in the deferoxamine group (P<0.05). The deferoxamine group also had the lowest physical component summary score in the SF-36 questionnaire (P=0.014).

This study suggests that the quality of life of beta-thalassemia patients receiving chelation therapy is dependent on the type of iron chelation treatment they receive. The study provides insight into important factors associated with the quality of life of these patients, which are essential for developing a more suitable clinical support team and counseling in order to maximize the treatment benefits for these patients in daily clinical practice.

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Introduction

Beta-thalassemia is a genetically inherited disorder characterized by reduced synthesis of the beta-hemoglobin chain which in turn results in reduced synthesis of hemoglobin A (HbA). To date more than 1,000 mutations are known that influence the structure or synthesis of the alpha- and beta-globin chains that make up HbA and which are listed in the HbVar database (HbVar), a database of all the mutations related to thalassemia and the variations of hemoglobin[1,2,3].

Treatment of patients with thalassemia major consists of regular blood transfusions and iron chelation therapy, which is vital to prevent excess iron buildup in the body. In Bangladesh there are three iron chelating agents available: deferoxamine (DFO, Desferal), an iron chelator given by infusion, and two oral chelators deferiprone (DFP, Ferriprox) and deferasirox

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(DFX, Exjade). Treatment with iron chelators has significantly increased the life expectancy of affected individuals into the third to fifth decade[4], while simultaneously decreasing the comorbidities of the disease[5].

Despite advancements in care, patients with transfusion-dependent beta-thalassemia still present complications and often suffer from psychological problems due to their lifestyle[6]. While the effectiveness of iron chelation therapies has been thoroughly investigated, there is limited comparative information about the benefits of the therapies on the quality of life and self-esteem of the patients. Furthermore, the quality of life of patients presenting with this disease and the effect of the type of iron chelation treatment on the patient's quality of life have not been evaluated. Thus, the objective of the present study was to compare the quality of life, self-esteem, and satisfaction and adherence to treatment of patients with transfusion-dependent beta-thalassemia in Bangladeshi population receiving three different chelation treatments and to identify parameters affecting their quality of life. The SF-36 questionnaire was used in order to evaluate the quality of life in the 135 patients of the study. Three other questionnaires were administered which provided important information on factors varying among patients receiving different types of iron chelation therapy.

Methods

Patients: A total of 135 transfusion-dependent beta-thalassemia Patients attending in the Bangladesh Thalassemia Centre and Haematology department of BSMMU (Bangabandhu Sheikh Mujib Medical University) Dhaka between February 2012 and February 2013 were enrolled in the study. During this time period, 174 beta-thalassemia patients were attending the aforementioned two-three units; 39 did not return their questionnaires and did not provide reasons for dropping out of the study. Diagnosis with transfusion-dependent beta-thalassemia was the only criterion used for inclusion in the study. There were no exclusion criteria. The scientific committee of the study and the local ethics committees of the participating hospitals approved the study. All patients provided written informed consent for their participation.

Evaluation Questionnaires: All patients were asked to answer the following four questionnaires: (i) the SF-36 questionnaire [10]; (ii) a Wallston's health locus of control scale, in which the patients answered 18 questions using a 6-point Likert-type scale response format [11] with 1 and 2 = strongly and moderately disagree, respectively, 3 = neither agree nor disagree, and 4, 5, and 6 = slightly, moderately, and strongly agree, respectively; (iii) a self-esteem questionnaire with 13 questions using a 5-point Likert-type scale (with 1 = very well and 5 = very poorly); (iv) a questionnaire about patient satisfaction from their current therapeutic chelator with 41 questions with responses varying from never to always. In addition, personal data and the hematological profile of the patients were obtained in order to be able to better evaluate the quality of life of the patients enrolled in our study.

Statistical Analysis: All continuous variables are expressed as the mean ± standard deviation (SD). The categorical (nominal) variables are expressed as percentages of the total population. Comparisons of the categorical variables between the three therapies were performed by the chi square test. Differences were considered significant when the *P* value was <0.05.

In order to investigate if chelation treatment is associated with patients' quality of life, univariate regression analysis was performed in which the eight scales and the two components of the SF-36 were set as dependent variables and chelation treatment was set as the independent variable.

Statistical analyses were performed with SPSS version 18.0 for Windows 7.

Results

Patient Characteristics: Of the 135 adult patients with transfusion-dependent beta-thalassemia that were recruited in this study, 59 were males and 76 were females. The patients were divided into three groups based on the therapy they were receiving: the first group was receiving deferoxamine (DFO; Desferal, Novartis), the second group deferasirox (DFX; Exjade, Novartis), and the third group

deferoxamine + deferiprone (DFP; Ferriprox, Demo S.A.) combination therapy.

The mean age of the patients was 37.3±10.1 for the DFO group, 34.3±7.4 for the DFX group, and 37.8±8.3 for the DFO + DFP group. The differences among the groups were not statistically significant. The demographic characteristics of the patients are shown in Table 1. More than half of the patients (75/135) were receiving DFX, while 39 and 21 were receiving combination therapy and DFO alone, respectively. The majority of the patients receiving DFO (19/21) and DFO + DFP (33/39) were not involved in sports, while 34/70 of DFX patients were, a statistically significant difference (P<0.0001) (Table 1)

Table 1: Demographic characteristics and physical activity of the patients.

	DFO		DFX		DFO + DFP		*P* value
	(n=21)		(n=75)		(n=39)		
	n	%	n	%	n	%	
Gender							
Male	15	71.4	40	53.3	21	53.8	NS
Female	06	28.6	35	46.7	18	46.2	
Marital Status							
Single	12	57.1	48	64.0	26	66.7	NS
Married	08	38.1	20	26.7	11	28.2	
Divorce	00	00.0	04	05.3	00	00.0	
Parent hood							
Yes	05	23.8	12	16.0	10	25.6	NS
No	15	71.4	60	80.0	28	71.8	
Physical activity	08	38.1	17	22.7	03	07.7	NS
None/Low	13	61.9	54	72.0	36	92.3	
Moderate/high							
Sports							
Yes	02	09.5	34	45.3	06	15.4	<0.0001
No	19	90.5	36	48.0	33	84.6	
Smoking status	03	14.3	15	20.0	10	25.6	NS
Smoker	16	28.6	36	48.0	10	25.6	
Non-smoker	12	57.1	24	32.0	39	48.7	
Did not answer							
Employment status							
Employed	16	76.2	60	80.0	28	71.8	NS
Unemployed	05	23.8	12	16.0	11	28.2	

Disease Characteristics: The disease characteristics of patients of the three groups are presented in Table 2. There were no significant differences among the three groups between their age at the time of diagnosis and their age when DFO treatment began. When examining the comorbidities, the patients receiving DFO had significantly higher percentages of myocardial dysfunction (33.3%) and hepatic dysfunction (38.1%), while 71.4% had undergone splenectomy and 14.3% suffered from allergies (Table 3)

Table 2: Disease characteristics.

	DFO	DFX	DFO + DFP	*P* value
Age of disease onset, years	2.1 ± 2.4	2.8 ± 4.5	2.3 ± 4.1	NS
Age at start of DFO treatment, years	13.1 ± 11.1	9.0 ± 9.6	11.1 ± 11.6	NS
Frequency of DFO therapy, times per week	5.2 ± 1.0	-	4.4 ± 1.9	<0.0001
Frequency of transfusion per month	2.2 ± 0.6	1.9 ± 0.5	2.1 ± 0.7	NS
Hemoglobin level prior to transfusion gm/dl	9.5 ± 0.9	10.1 ± 3.4	9.7 ± 0.4	0.0208
Ferritin levels upon enrollment ng/ml	1559.2 ± 1778.1	1738.0 ± 1636.9	1023.1 ± 944.3	NS

DFO: deferoxamine, DFX: deferasirox, DFP: deferiprone, NS: not significant, value < 0.05 indicated statistical differences between three groups. All values are mean ± SD

Table 3: Frequency of comorbidities or prior splenectomy per group.

	DFO	DFX	DFO + DFP	*P* value
Myocardial dysfunction	33.3	6.7	15.4	0.0058
Hepatic dysfunction	38.1	6.7	2.6	<0.0001
Thyroid disease	28.6	58.7	53.8	0.0499
Hypogonadism	14.3	10.7	10.3	NS
Splenectomy	71.4	38.7	48.7	0.0319
Allergies	14.3	9.3	2.6	0.0487

NS: not significant, value < 0.05 indicated statistical differences between three groups.

Results from Questionnaires: The SF-36 questionnaire was used as a measurement of the quality of life of the patients. This questionnaire consists of eight scales (1) physical functioning, (2) role limitations because of physical health problems, (3) bodily pain, (4) general health perceptions, (5) vitality (energy/fatigue), (6) social functioning, (7) role limitations due to emotional problems, and (8) general mental health (psychological distress and psychological wellbeing). The scores were calculated for respondents completing 50% or more of the items within a scale. Higher scores represent better health. The type of chelation treatment was proven to be statistically significantly associated with

physical functioning (P=0.048), role limitations due to physical health problems (P=0.021), bodily pain (P=0.015), vitality (P<0.001), and mental health (P=0.001) (Table 4). Pairwise comparisons performed in the aforementioned scales in order to ascertain differences among the treatments revealed that those who received DFX or DFO + DFP demonstrated significantly higher mean scores (better quality of life) than patients who received DFO alone, in all scales tested, apart from the bodily pain scale. In the bodily pain scale, only treatment with DFX resulted in a significantly higher mean score than treatment with DFO alone

Table 4: Association between SF-36 scales and chelation treatment.

SF-36 scale	Chelation treatment		Estimated mean score	95% Cl for estimated mean score		P value
Physical functioning	DFX	72	80.3	75.7	84.8	
	DFO+DFP	19	80.9	74.2	87.6	0.048
	DFO	33	68.4	59.6	77.3	
Role limitations due to physical health	DFX	71	79.9	71.5	88.3	
	DFO+DFP	17	76.5	64.2	88.8	0.021
	DFO	33	52.9	35.8	70.1	
Bodily pain	DFX	71	80.3	74.4	86.3	
	DFO+DFP	17	73.6	64.9	82.3	0.015
	DFO	33	60.7	48.6	72.8	
General health perceptions	DFX	70	51.6	47.4	55.9	
	DFO+DFP	17	53.1	46.9	59.3	0.111
	DFO	33	42.3	33.6	50.9	
Vitality	DFX	71	61.8	57.6	65.9	
	DFO+DFP	17	68.5	62.4	74.6	<0.001
	DFO	33	46.2	37.7	54.7	
Social functioning	DFX	71	76.4	71.2	81.6	
	DFO+DFP	17	77.3	69.7	85.0	0.845
	DFO	33	73.5	62.9	84.1	
Role limitations due to emotional problems	DFX	71	77.9	69.6	86.3	
	DFO+DFP	17	71.4	59.2	83.6	0.338
	DFO	33	64.7	47.7	81.7	
Mental Health	DFX	71	65.4	61.1	69.6	
	DFO+DFP	17	65.3	59.1	71.6	0.001
	DFO	33	46.8	38.1	55.5	

Association between SF-36 scales and chelation treatment Univariate analysis;
NS: not significant, value< 0.05 indicated statistical differences among the three groups.

Discussion

One hundred and thirty-five adult beta-thalassemia transfusion-dependent patients took part in this study. The majority of the patients were single without children, in agreement with previous reports[9]. One-fifth of the patients were unemployed, a not very high percentage.

The DFO + DFP combination therapy offers a better control of serum ferritin levels, thus requiring less frequent DFO infusions[10]. It was thus not surprising that we found a decreased frequency of transfusions in the DFO + DFP combination group (P<0.0001; Table 2). A higher percentage of DFO patients had comorbidities compared to the other two groups, except for thyroid disease, which was more prevalent in DFX patients. The presence of hepatic dysfunction in patients with homozygous beta-thalassemia has been correlated with iron overload in the liver as well as to chronic hepatitis[11]. It is also notable that patients receiving DFX had the lowest prevalence of myocardiopathy which is in accordance with reports on the ability of DFX to prevent iron overload in the myocardium[12].

The highest rate of patient adherence to treatment was observed in the DFX patients. Adherence to therapy is the most important parameter for successful therapy. In fact low adherence of patients receiving DFO has been linked to the absence of clinical benefit[5]. In a previous study,

low adherence to DFO was linked to smoking and to difficulties with self-administering the infusion[13].

Our results about satisfaction and ease of receiving their therapy matched those of previous studies, in which DFX was associated with increased satisfaction to treatment. Importantly, it was shown that switching chelators resulted in increased adherence, regardless of whether the patients switched from the oral to the intravenous chelator or vice versa, although the switch from DFO to DFP occurred more often[14].

According to previous studies, patients receiving DFO were more likely to suffer from depression, fatigue, dyspnea, and decreased physical functioning [15]. The majority of patients felt that they could participate in more activities if they were not receiving DFO[16] in accordance with the results of our study indicating that DFO limited the ability of patients to participate in sports and perform daily functions. Furthermore, the results of our study indicate that patients receiving DFO had lower self-esteem and worse PCS scores. These observations are in agreement with the results of the ITHACA study, in which the PCS score was low for patients receiving DFO[17] and with the study of Abetz et al., in which patients with DFO suffered from low self-esteem[15].

Of the specific components of the SF-36 questionnaire, the type of chelation treatment was proven to be statistically significantly associated with physical functioning, role limitations due to physical health problems, bodily pain, vitality, and mental health. Importantly, the results of our multivariate analysis indicate that the dependence of the PCS score on the type of chelation treatment was not confounded by anthropometric variables, such as gender, marital status, level of physical activity, presence of comorbidities, or smoking status. The importance of the SF-36 questionnaire and the results of the individual scales on the multidisciplinary actions that should be taken for patients with beta-thalassemia have been reported[18].

The study is not without limitations. A randomized controlled clinical trial would be needed to ascertain the cause and effect relationship between quality of life and type of iron chelation therapy. Future studies should be of this design. However, its design as a prospective study of patients attending the pediatric, medicine and hematology units of the Rajshahi Medical College Hospital, Pabna Medical College Hospital and Bangladesh Thalassemia Centre is ideal for reflecting daily clinical practice and the impact on the quality of life of these patients in "real-life."

Conclusions

In conclusion, our study provides support for differences in the limitations of daily activities, physical activity, and quality of life among patients with transfusion-dependent beta-thalassemia depending on the type of their chelation therapy. Furthermore, the adherence to treatment, the ease and satisfaction from their therapy, and patient self-esteem differed along the three groups. This study highlights the importance of providing beta-thalassemia patients with the optimal chelation treatment based on their individual needs, in order to decrease the presence of unwanted comorbidities and to increase the quality of life, leading to increased adherence and thus resulting in optimal clinical benefit.

Recommendations

Furthermore, our results highlight the need of the involvement of a multidisciplinary team in the management of patients with this disease.

Ethical Approval

The scientific committee of the study and the local ethics committees of the participating hospitals approved the study. Written informed consent was obtained by all the patients.

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