Comparative effects of iron chelators on the transfusion-dependent Beta-Thalassemia Patients

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Abstract

Background: 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 (DFX, Exjade). **Objective:** To compare the disease characteristics, comorbidities and quality of life of the patients with transfusion-dependent beta-thalassemia receiving three different chelation treatments. **Methods:** This was a cross-sectional descriptive type of study conducted at the Bangladesh Thalassemia Centre and Haematology department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. A total of 175 attending transfusion-dependent beta-thalassemia patients between February 2012 and February 2013 were enrolled in this study, among them 135 (77.1%) patients were responded. Data were collected by self-administered questionnaires: SF-36 questionnaire and a personal questionnaire. Statistical analyses were performed with SPSS version 18.0 for Windows 7. Chi square test and univariate regression analysis were performed. **Results:** A total of 135 patients, 75(55.6%) patients were receiving DFX, 39(28.9%) were receiving combination therapy of DFO + DFP and the rest 21(15.5%) patients were receiving DFO alone. Mean hemoglobin level prior to transfusion (gm/dl) in DFX therapy recipients was significantly higher than the other two groups (p=0.0208). Highest percentage (92.3%) of the patients in DFO+DFP therapy garoup were moderately or highly physically active than the patients in DFO and DFX therapy groups. The patients receiving DFO had significantly higher percentages of myocardial dysfunction (33.3%), hepatic dysfunction (38.1%), splenectomy (71.4%) and allergies (14.3%) than the other two groups. A higher percentage of patients receiving DFO 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). **Conclusion:** DFX or DFO + DFP therapy is more suitable choice for iron chelation treatment in transfusion-dependent beta-thalassemia patients than DFO therapy in term of comorbidities and quality of life in Bangladesh.

Key Words: Iron Chelators, Beta Thalassemia, Blood Transfusion

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 5(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 (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

This was a cross-sectional descriptive type of study conducted at the Bangladesh Thalassemia Centre and Haematology department of BSMMU (Bangabandhu Sheikh Mujib Medical University) Dhaka. All the transfusion-dependent beta-thalassemia patients attending at the aforementioned centre and department constituted the study population. A total of 175 attending patients between February 2012 and February 2013 were briefly informed about the study and invited them to participate in this study providing the self administered questionnaire and written informed consent. Among them 135 patients returned the questionnaires with their answers and written consent. The scientific committee of the study and the local ethics committees of the participating hospitals approved the study.

Data were collected by self-administered questionnaires, SF-36 questionnaire and a personal questionnaire. 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). Scores for all dimensions are expressed on a scale 0-100, where higher scores indicate better health and well-being. The scores were calculated for respondents completing 50% or more of the items within a scale. The personal questionnaire was designed to record the personal and disease characteristics of the patients. The personal characteristics included age, gender, marital status, parent hood, physical activity, sports, smoking status and employment status. The disease characteristics include age of onset of disease, age of starting the treatment, frequency of transmission per month, hemoglobin level gm/dl prior to transfusion, ferritin level ng/ml upon enrollment, myocardial dysfunction, hepatic dysfunction, thyroid diseases, hypogonadism, slenectomy and allergies. Patients took help from the attending data collectors and doctors if needed to give the answers of these questionnaires.

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

Results

A total of 135 patients, 75(55.6%) patients were receiving deferasirox (DFX; Exjade,

Novartis), 39(28.9%) were receiving combination therapy of deferoxamine (DFO; Desferal, Novartis) + deferiprone (DFP; Ferriprox, Demo S.A.) and the rest 21(15.5%) patients were receiving DFO alone.

The mean age of the patients was 37.3(±10.1) years for the DFO group, 34.3 (±7.4) years for the DFX group, and 37.8 (±8.3) years for the DFO + DFP group. The differences of mean ages among the groups were not statistically significant. Males were predominant in all therapy groups, but not statistically significant. In DFO group, 57.1% patients were single. It was 66.7% in DFX and 71.8% in combination (DFO+DFP) therapy group. More than 61% of the patients receiving DFO were moderately or highly physically active.

The percentages of moderately or highly physically active patients in DFX and DFO+DFP therapy group were 74.7% and 92.3% respectively The majority of the patients receiving DFO (90.5%, 19/21) and DFO + DFP (84.6%, 33/39) were not involved in sports, while 48.0% (36/75) of DFX patients were involved in sports (P<0.0001). In DFO therapy group, 14.3% of the patients were smokers. The percentages of smokers in DFX and DFO + DFP therapy groups were 20.0% and 25.6% respectively. But in DFO group, more than 57.0% of of the respondents did not mentioned about their smoking/tobacco consumption status, More than 71.0% of the patients in all the groups were employed (Table 1).

Table 1: Patient characteristics and category of therapy received.

	DFO (n=21)		DFX (n=75)		DFO + DFP (n=39)		*P* value
	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	50	66.7	28	71.8	NS
Married	08	38.1	21	28.0	11	28.2	
Divorce	01	04.8	04	05.3	00	00.0	
Parent hood							
Yes	06	28.6	15	20.0	11	28.2	NS
No	15	71.4	60	80.0	28	71.8	
Physical activity							
None/Low	08	38.1	19	25.3	03	07.7	NS
Moderate/high	13	61.9	56	74.7	36	92.3	
Sports							
Yes	02	09.5	36	48.0	06	15.4	<0.0001
No	19	90.5	39	52.0	33	84.6	
Smoking/tobacco consumption 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	19	48.8	
Did not answer							
Employment status							
Employed	16	76.2	60	80.0	28	71.8	NS
Unemployed	05	23.8	15	20.0	11	28.2	

NS: not significant

Table 2: Disease characteristics and category of therapy received.

	DFO Mean±SD	DFX Mean±SD	DFO + DFP Mean±SD	*P* value
Age of diagnosis (years)	2.1 ± 2.4	2.8 ± 4.5	2.3 ± 4.1	NS
Starting age of DFO treatment (years)	13.1 ± 11.1	9.0 ± 9.6	11.1 ± 11.6	NS
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

NS: not significant

Table 3: Frequency of comorbidities or prior splenectomy in different drug recipient groups.

Comorbidity/splenectomy	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

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

Components of SF-36 scale	Chelation treatment	Number N	Estimated mean score	95% CI 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 – 50.3	
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	

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.

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/tobacco consumption 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 this 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].

This study possesses a number of methodological limitations that must be taken into consideration. First, sample size was small. Second, data were collected retrospectively. Third, study subjects in different groups were unequal. A well designed cohort study with large sample size would be needed to ascertain the cause and effect relationship between quality of life and type of iron chelation therapy.

The results of this study have certain implication in clinical practice however. The study findings suggest that DFX or DFO + DFP combination therapy is the drug of choice for iron chelation of the transfusion-dependent beta-thalassemia patients rather than DFO therapy in Bangladesh.

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