Adherence to deferasirox among beta-thalassemia major children - A cross-sectional study in a tertiary care hospital

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ABSTRACT

Introduction: Deferasirox, an oral iron chelator has been proved to be very safe and effective in beta-thalassemia major children on chronic blood transfusion (CBT); however, adherence to this medication has always been a challenge. **Objectives**: The aim of this study is to assess the adherence to oral iron chelator- deferasirox among beta-thalassemia major children receiving CBT by using self-reporting questionnaire and the factors associated with poor adherence to deferasirox. **Materials and Methods**: A cross- sectional study was conducted enrolling 91 beta-thalassemia major children (aged between 2 and 14 years, transfused with at least 20 units of packed red blood cell, on deferasirox therapy and serum ferritin greater than 1000 ng/ml) by simple consecutive sampling. Pretested interview schedule was used to collect information on sociodemographic status. Morisky Medication Adherence Scale was used to measure adherence. Data were entered in Microsoft Excel student 2017 and analyzed using SPSS software version 24. **Results**: About 7.5% (7) of the patients reported to be highly adherent, 48.4% (45) moderately, and 41.9% (39) were poorly adherent. The mean (SD) serum ferritin value was lowest (1281.71±326.85 ng/ml) in highly adherent children. Association between the age and serum ferritin with adherence to deferasirox done using one-way ANOVA was found to be statistically significant among the three different groups (p=0.000). Illiteracy negatively affected the degree of adherence, while belonging to a nuclear family positively affected the degree of adherence to deferasirox. **Conclusion**: A very low-adherence level was observed in this study which needs to be improved through adequate measures.

Key words: *Adherence, Children, Deferasirox, Thalassemia*

Repeated blood transfusion is the mainstay of care for children with beta-thalassemia major [1]. There are two major benefits of transfusion as follows: First, it corrects anemia, and second, it suppresses the ineffective erythropoiesis. Chronic blood transfusions (CBT) prevent many of the serious growth, skeletal, and neurological complications of beta-thalassemia major. However, once began, the transfusion-related complications become a major source of morbidity out of which body iron overloading is an important issue which necessitates the use of iron chelators [2]. Iron chelation therapy significantly improves myocardial T2 and left ventricular function [3-5]. Since long, the standard iron chelation therapy in thalassemia used to be deferoxamine [6], a subcutaneous or intravenous infusion, generally 8–12 h per day, 5–7 days per week, and was associated with poor adherence in some patients [7]. We all know that good adherence is essential to reduce the risk of complications and mortality due to iron overload. In 2005, deferasirox, an oral chelator, was approved for use by the United States Food and Drug Administration. Deferasirox has been proved to be very safe and effective in beta-thalassemia major children; however, the issue arises about the adherence to this novel oral iron chelator [8].

Adherence to long-term therapy for chronic diseases in developed countries averages around 50% [9]. In developing countries, the adherence rates are even poor. Poor adherence to medication is widely observed in chronic diseases and is a major challenge in clinical practice. Poor adherence to medication poses a negative impact on treatment outcomes and acts as a burden to heath-care cost [10]. In India, very few studies have studied the factors that impact adherence to deferasirox chelation therapy. Therefore, this study was conducted to observe the adherence to oral deferasirox among transfusion dependent beta-thalassaemic children.

MATERIALS AND METHODS

After getting due approval from the institutional ethics committee, this observational, analytical, and cross-sectional study was conducted at the thalassemia day care center of a 750-bedded tertiary care teaching institution of western Odisha, India. This study spanned over a period of 1 year from November of 2015 to October of 2016. The study population and target population being the same, i.e., all beta-thalassemia major children receiving

CBT and receiving oral deferasirox. The major confounders of this study are age (in years), gender, literacy of informants, and type of family. The major outcome analyzed was the percentage of thalassaemic children with good adherence to deferasirox. The inclusion criteria being the diagnosed cases of beta-thalassemia major children (based on high-performance liquid chromatography report) aged between 2 and 14 years of age in whom iron chelation was started after getting transfused with at least 20 units of packed red blood cell and with a serum ferritin level of >1000 µg/dL. Thalassemia heterozygotes, sickle-thal children, thalassemia with HbD or HbE and critically ill children were excluded from the study.

After satisfying the predefined inclusion and exclusion criteria, 91 children were enrolled for the study using simple consecutive sampling. The children were excluded who were coming for the second time to the hospital. After explaining in detail about the study procedures in the local language, written informed consent was obtained from the legal heir of the study participants. The basic demographic profiles were collected by interview schedule of informants. All primary caregivers were handed over a pretested and prevalidated questionnaire called Morisky Medication Adherence Scale (MMAS-8) [11] which is a self-reporting questionnaire available in English. The MMAS-8 was translated into local vernacular language and was tested among primary caregivers of 10 thalassaemic children, and necessary corrections were done to the translated version of the questionnaire with expert consultation which was again applied to another 10 thalassemics. This translated questionnaire was assessed for reliability with a Cronbach's alpha 0.72.

MMAS-8 (Fig. 1) is composed of 8 items, out of which the items from 1 to 7 are yes/no questions (except item 5) where no answers receive a score of 1.0, and yes answers receive a score of 0. The score is reversed for item 5. Item 8 is measured based on a 1 to 5 Likert scale. The total scores range between 0 and 8, where 8 is considered as high adherence, 6–8 as moderate adherence, and <6 as poor adherences. The confidentiality of data is well maintained. Double data entry was done by two separate persons (principal investigator and co-principal investigator). Data checking was done manually by them. Data validation was done using EpiData version 3.0. Basic demographic characters such as age, gender, level of literacy of primary caregiver, and type of family were collected.

The outcome variables were percentage of patients with high, moderate, and poor adherence, respectively and inter-group correlation with age, gender, serum ferritin levels, and level of literacy (aged 7 years or above who can read and write with understanding) of the primary caregiver and type of family (nuclear family defined as family group consisting of two parents and their children (one or more) and/or joint family defined as a family in which many generations living in the same household, all bound by the common relationship), respectively, was studied. The causes of nonadherence were also collected in the three different groups.

Data normalcy was tested using Shapiro-Wilk test where p>0.05 indicated normal data distribution. Descriptive statistics included means and standard deviations for continuous variables and percentages for categorical variables. Adherence levels across groups were compared using Chi-square and/or Fischer's exact test. Multivariate analysis was performed between the three groups. The results were considered to be significant where p<0.05.

	Yes	No
1. Do you sometimes forget to take your medication?		
2. People sometimes miss taking their medications for reasons other than forgetting, over the past 2 weeks, were there any days when you did not take your medication?		
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?		
4. When you travel or leave home, do you sometimes forget to bring your medication?		
5. Did von take all your medication yesterday?		
6. When you feel like your symptoms are under control, do you sometimes stop taking your medication?		
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		
8. How often do you have difficulty remembering to take all your medication?		
Never/rarely		
Once in a while		
Sometimes		
All the time		

Figure 1: Morisky medication adherence scale

RESULTS

Among 91 total patients, 67% (61) were male and 33% (30) were female. The mean age (in years) was 9.8±2.6 (range 6–14 years). Poor adherence to deferasirox was found in 42.9% (39) of the study participants, 48.4% (45) were moderately adherent and 7.5% (7) of the patients reported to be highly adherent. To study the association between age and adherence, we did one-way ANOVA test (Table 1) and found that there is the high statistically significant difference in the mean age of the patients belonging to the three different groups (highly adherent, moderately adherent, and poorly adherent) as evidenced by F=22.2 (2,88), p=0.000. After doing Tukey's *post-hoc* analysis, it was observed that the mean age of highly adherent group (7.6±1.7 years) was significantly lower than that of poorly adherent group (11.5±1.9 years), p=0.000 and the mean age in moderately adherent group (8.7±2.3 years) too was significantly lower as compared to poorly adherent group (p=0.000).

Table 1: Group characteristics of the study participants

Study variable	Highly adherent group	Moderately adherent group	Poorly adherent group	p
Mean age (in years)	7.6±1.7	8.7±2.3	11.5±1.9	0.000**
Mean serum ferritin (in ng/ml)	1281.71±326.85	2065.87±923.77	3677.00±1046.90	0.000**
Male % (n)	8.2 (5)	54.1 (33)	37.7 (23)	0.365
Female % (n)	6.7 (2)	40 (12)	53.3 (16)	
Primary caregiver literate % (n)	11.1 (5)	66.7 (30)	22.2 (10)	0.000**
Nuclear family	18.2 (6)	51.5 (17)	30.3 (10)	0.009*

*p<0.05=significant and **p<0.001=highly significant

We also found the statistically significant difference in the mean serum ferritin levels of the three respective groups {F=38.25 (2,88), p=0.000}. The mean serum ferritin level (in ng/ml) of the highly adherent group (1281.71±326.85) was significantly lower than that of moderately adherent group (2065.87±923.77), (p=0.001) and that of the poorly adherent group (3677.00±1046.90), p=0.000. Among males and females, there was no significant difference in the level of adherence (Pearson Chi-square=2.016 (2), p=0.365). Within all males, the mean age of the three different groups, respectively, are significantly different from each other as evidenced by F=13.85 (2,58), p=0.000. The mean age (in years) in poorly adherent males (11.3±1.9) was significantly higher than that of moderately adherent males (8.7±2.4), p=0.000 and that of highly adherent males (6.8±1.3), p=0.000 too. However, among females, only the poorly adherent ones differed from the moderately adherent ones in their respective mean age (11.8±1.9 vs. 8.8±2.1), p=0.002.

Similarly, the mean serum ferritin levels (in ng/ml) among highly adherent males (1318.40±388.04) was significantly lower than that of moderately adherent males (2172.39±952.61), p=0.000 and that of poorly adherent males (3541.48±1033.69), p=0.000. Among females, the mean serum ferritin levels (in ng ml) among highly adherent females (1190.00±123.03) was not significantly lower than that of moderately adherent females (1772.92±803.66), p=0.087. The overall literacy of the primary caregivers was 49.5%. The association between literacy and level of adherence was highly statistically significant (Pearson Chi-square=15.533 (2), p=0.000). Thirty-six percent of the children belonged to nuclear families and belonging to a nuclear family was strongly associated with high adherence (Pearson Chi-square=9.355 (2), p=0.009).

DISCUSSION

In the 91 patients enrolled, a male preponderance (67%) was observed. A similar preponderance of males (69.5%) was observed in studies conducted previously at Odisha, India [12]. The overall high adherence to deferasirox was very low in this study (7.5%) with younger children being more adherent than older ones. This may be attributed to the fact that more care is being taken by their parents when the children are younger or maybe older children are asked to take their medication on their own which might have led to poor reported adherence in them. A similar finding was observed in a study done in Jordan in 2014, in which poor adherence to deferasirox among older children was attributed to lack of parenteral monitoring [13].

As expected the serum ferritin values are lower in more adherent children which suggests that adherence to deferasirox effectively reduced iron overload. A previous study also showed a significant decrease in serum ferritin levels with deferasirox treatment in 296 transfusion-dependent β thalassemia patients [14]. Not much effect of gender predisposition on the level of adherence could be observed here. It implies primary caregivers may not be discriminating their children on the basis of gender.

The literate primary caregiver was associated with good adherence. This may be because parents with better literacy levels can understand the need of oral iron chelator for their children which encourages them to ensure better compliance. A child belonging to a nuclear family was associated with better adherence in this study which may be attributed to more attention to children in a small nuclear family.

This study provides an opportunity to target interventions directed to improve adherence levels among beta-thalassemia major children receiving CBT. As our state is a resource poor setting and the part of the state where we are residing is the poorest among the poor in terms of literacy and family structure, and the adherence to the drug was pitiable. Hence, in our opinion, a multidisciplinary approach in all aspects is needed in future to increase the adherence of the oral iron chelator - deferasirox in beta-thalassaemic children.

Being a facility-based study, the results of this study cannot be generalized to the whole population, and there are chances of recall bias due to self-reporting by patient caregivers. A qualitative analysis would be a better option in this scenario, but could not be done due to lack of resources. Hence, a follow-up qualitative study at a definite regular time interval by the investigator should be done in the future.

CONCLUSION

Poor adherence was seen in less than one-half of the study participants. Illiteracy, higher age, and joint family are the surrogate parameters of poor adherence to the medication.

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