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Research Article,

"Efficacy and Safety of Deferasirox in Pediatric Thalassemia Patients: Experience from a Tertiary Care Children Hospital of Bangladesh"

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Abstrect:

Background: Thalassemia is an inherited hemoglobin disorder; mostly require life-long blood transfusions, leading to chronic iron overload which causes growth failure, delayed sexual development in adolescents and vital organ dysfunctions. So, children with thalassemia need lifelong iron chelation therapy. Hence, this study conducted with the aim of to evaluate efficacy and safety of Deferasirox in pediatric thalassemia patients.

Materials and methods: This is an observational, prospective, single-centered hospital-based study conducted in a tertiary care teaching hospital from June 2018 to December 2019. Total sixty children (age 2-18 years) with beta thalassemia major and hemoglobin E beta thalassemia with iron overload were enrolled to commence deferasirox. Efficacy and safety we observed by measuring serum ferritin three monthly and SGPT, SGOT & serum creatinine monthly.

Results: The serum ferritin level of 72% patients reduced significantly after 12 months in comparison to baseline level. There was no serious adverse effect except mild abdominal pain, nausea & vomiting and transaminitis.

Conclusion: Deferasirox is efficacious in reducing iron overload of the body when administer at optimum dose over at least one year and presenting a safe as well as convenient alternative for most of the transfusion dependent pediatric thalassemia patients.

Keywords: Thalassemia, Iron overload, Deferasirox.

Introduction:

Thalassemia is a heterogenous autosomal recessive disorder of hemoglobin, leading to reduced synthesis of one of the paired globin chains. Clinical manifestations depend on the extent to which the synthesis of affected globin chains is impaired [1]. Thalassemia major and hemoglobin E thalassemia is common in south East Asia including Bangladesh. Blood transfusion remains the first line treatment in these patients. One unit blood contains 200- 250 ng of elemental iron [2], it can cause iron overload on repeated transfusions. The excess iron gets deposited in various tissues of body including brain, heart, liver, endocrine glands leading to growth retardation, endocrine abnormality and cardiac failure [3]. Iron chelation therapy is recommended for these patients to prevent such

complications. Deferoxamine has been using as the slandered treatment of iron overload for many years. But it has got decreased compliance resulting limited efficacy in iron chelation as parenteral administration over 8-12 hours 5-7 days in a week [4, 5]. Deferiprone is the first oral iron chelator, to be administered thrice daily, though it has got limited use for its serious adverse effects including arthropathy and agranulocytosis [6]. Deferasirox, a newer tridentate iron chelator having good oral bioavailability and longer half-life (8-16 hours), dose schedule is once daily without significant drug-drug interaction. It is able to enter and remove iron from cells [7, 8]. FDA has approved deferasirox in 2005, but it is manufactured in Bangladesh about 2 years ago. Effectiveness and safety study of deferasirox is rare in Bangladesh specially in pediatric thalassemia patients. It is very much essential to evaluate the effectiveness of this newer iron chelator deferasirox, particularly in pediatric patients of Bangladesh, as transfusion dependent thalassemia patients need lifelong blood transfusion and hence iron chelation is also needed throughout the life. That is why; we decided to conduct this study to evaluate the clinical effectiveness and safety of deferasirox therapy in pediatric thalassemia patients attending a tertiary care hospital, Dhaka, Bangladesh.

Materials and Methods

This observational, prospective, single-centered hospital-based study was conducted in Thalassemia Centre of the Department of Pediatric Hematology & Oncology, Dhaka Shishu (Children) Hospital & Bangladesh Institute of Child Health, Dhaka, Bangladesh. The sixty children in the age group of 2-18 years with Beta thalassemia major and Hemoglobin E beta thalassemia, to commence defrasirox, were prospectively enrolled in the study during the period of November december, 2018 and followed up for 12 months till December, 2019.

Inclusion criteria:

- Patients of Beta thalassemia major & Hemoglobin E beta thalassemia.
- Age: 2-18 years,
- Transfusion dependent
- Serum ferritin level > 1000 ng/ml.
- Patients already on other chelators having unacceptable toxicities, poor compliance & inadequate response.

Exclusion criteria:

- Age less than 2 years,
- Having deranged baseline serum creatinine above upper limit of normal.
- Elevated baseline liver enzymes (SGPT, SGOT) to more than 4-fold high of upper normal limit.

Baseline serum creatinine, SGPT, SGOT level and yr. and urine albumin line for albumin were measured along with serum ferritin. Patients with serum ferritin level 1000-2500 ng/ml were started deferasirox at the dose of 30 mg/kg/day and with >2500 ng/ml at the dose of 35-40 mg/kg/day. The deferasirox tablets were taken orally by dissolving in plane water or orange juice half an hour before breakfast. The serum creatinine, SGPT, SGOT were measured at monthly interval for first 3 months and there after 3 monthly intervals. The serum ferritin level was measured at 3 monthly intervals. Effectiveness was defined s any decrease in serum ferritin from baseline value or maintenance of same value in the presence of ongoing repeated blood transfusions. Data were recorded in a predesigned case record form at 1-3 monthly intervals. The drug was discontinued temporarily, if there was altered renal and liver functions, evident by high serum creatinine (above ULN) and transaminases (5 times more of ULN), or there were adverse events like nausea, vomiting etc. The drug was restarted, once the adverse event settled. Data were collected, tabulated and subjected to statistical analysis by using SPSS 17 software. Appropriate statistical tests were applied to various tables.

Results:

Among 60 children 6 children discontinue deferasirox due to financial constrain. Data of the rest 54 children with Beta thalassemia major and Hemoglobin E Beta thalassemia on deferasirox were analyzed. The baseline and demographic parameters of the study subjects are summarized in (Table I).

Table -1: Demographic and baseline characteristics.

Parameters	Numbers (%)
Number of patients	54
Sex	
Boys	33 (61%)
Girls	21 (39%)
Male: Female ratio	1.6:1.0
Age (years)	
Meant SD	8.1 4.3
Median (range)	8.6 (2-18)
Age groups (years)	
2-<12	40 (%)
12-18	14 (%)
Serum ferritin (ng/ml)	
Mean SD	3757±2387
Median (range)	3585 (732-11574)
Deferasirox dose (mg/kg/day)	
30	15 (%)
35-40	39 (%)

Regarding serum ferritin level of study subjects on deferisirox on follow up analysis at 3 months interval and after 12 months, majority of the patients showed a fall in serum ferritin levels without any irreversible toxicity. Twenty-seven (50%) patients showed reduced serum ferritin level from baseline after 3 months and 32(59%) after 6 months. Five (9%) patients showed an increase of serum ferritin levels, after increment of dose of deferasirox to 40 mg/kg/day serum ferritin began to decrease. At the end of 12 months 39(72%) patients showed decrease serum ferritin level significantly (<1000-2000 ng/ml) than that of baseline. Among these 39, 11(20%) patients achieved serum ferritin <1000 ng/ml, and the drug was continued in low doses as maintenance therapy in 6 as well as temporary withdrawn in 5 patients with serum ferritin level <500 ng/ml. Eight (15%) patients revealed stable serum ferritin level in spite of getting regular blood transfusion. Serum ferritin level mildly increased in spite of maximum dose in 7 (13%) patients, these patients have been advised to switch over to combination chelation therapy with deferoxamine and deferiprone.

On overall assessment of 54 study subjects, 39(72%) showed statistically significant decreased of serum ferritin from baseline level after 12 months (P=0.04), 8(15%) had stable serum ferritin level same as baseline value though they were getting regular blood transfusion and in 7(13%) patients serum ferritin level was increased even on of maximum dose of deferasirox (Table 2).

Table 2: Outcome distribution of patients on deferasirox after 12 months (n=54).

Parameters	Total number	Percentage	P value
Reduced S. Ferritin	39	72%	0.003 Significant
Stable S. Ferritin	08	15%	
Increased S. Ferritin	07	13%	

Mean serum ferritin level decreased from baseline level (3757±42387 ng/ml) to 1852±1397 ng/ml which was statistically significant (P value 0.003) (Table 3)

Table -3: Mean serum ferritin level at baseline and on deferasirox (n=54).

Parameter	At baseline	At 6^{th} month	At 12^{th} month	P Value
Mean S Ferritin (ng/ml)	3757±2387	2738±1658	1852±1397	0.003 Significant

Adverse effects: Out of 54 study subjects, about 5% patients experience nausea, vomiting abdominal discomfort as well mild diarrhea, and another 4.5% developed mild skin rash. Diarrhea was self-limiting after temporary withheld of the drug. In addition, 10% showed raised SGPT and/or SGOT (up to 120 U/L), 5% patient showed progressive increase serum creatinine (up to 1.7 mg/dl). Dose correlation were not observed in patients with transaminitis but the patients with high serum creatinine needed temporary withdrawal of deferasirox.

Discussion:

In transfusion dependent thalassemia patients iron overload is the one of the most important determinants of morbidity and mortality. The life span and quality of life of these patients improved dramatically after advent of iron chelator deferoxamine and deferiprone. But non-compliance to these drugs on the background of prolong parental administration of deferoxamine and serious side effects of deferiprone with multiple daily doses motivated extensive search for a better chelator which would be safe and easy to administer apart from being equally or more efficacious. Deferasirox was made to combat above problems and approved by FDA in 2005. This study was conducted in our thalassemia center to evaluate the efficacy and safety of this drug in Bangladeshi thalassemia children. We did this study in pediatric patients as most of data available on deferasirox in adults [9, 10]. The age of our patients was 2-18 years as Bangladesh Government declared the pediatric age group include up to 18 years. This age group also supported by Indian Academy of Pediatrics [11]. Deferasirox is not recommended in children <2 years of age, that is why we exclude the children with <2 years. So, our data signify an outcome primarily in children. Boys were predominance in our study as male: female ratio was 1.6to:1.0) which is not similar to study abroad [10], where female patients are more (male: female=1.0:1.3). This difference might be due to female patients are neglected in our society. The dose of deferasirox was 30 mg/kg/day in patients with serum ferritin >1000 to 2500 ng/ml and 35-40 mg/kg/day as to achieve a negative iron balance, a minimum of 30 mg/kg/day is required according to different investigators [12,13]. Regarding efficacy of deferasirox, among the 54 study subjects, 39(72%) showed statistically significant decreased of serum ferritin from baseline level after 12 months (P=0.003), and mean serum ferritin level decreased from baseline level (3757±2387 ng/ml) to 1852±1387 ng/ml which was statistically significant (P value 0.003). Almost similar efficacy was found by different studies [12,14,15,16,18] but higher than other study [13]. The reason behind nonresponse to deferasirox in case of 7 patients might be the status of bio-availability of drug [20], inadequate adherence to dose schedule, intake of highly iron-rich food and entry of more transfusional iron because of frequent transfusion [21]. Regarding adverse effect, about 5% patients experience nausea, vomiting abdominal discomfort as well mild diarrhea, and another 4.5% developed mild skin rash which were similar to few studies [22], but lower than other study [18]. Diarrhea was self-limiting after temporary withheld of the drug. In addition, 10% showed raised SGPT and/or SGOT (up to 120 U/L), 5% patient showed progressive increase serum creatinine (up to 1.7 mg/dl) which were similar to few studies [19], but lower than other study [18, 23]. Dose correlation were not observed in patients with transaminitis but the patients with high serum creatinine needed temporary withdrawal of deferasirox.

Conclusion:

Deferasirox is efficacious in reducing iron overload of the body when administer at optimum dose over at least one year and presenting a safe as well as convenient alternative for most pediatric transfusion dependent pediatric thalassemia patients.

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