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ORIGINAL ARTICLE

Evaluation of Serum Ferritin Levels in Children of South Punjab (Pakistan) having Beta-Thalassemia Major with Iron-Overload Treated with Deferasirox

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ABSTRACT

Objective: To evaluated serum ferritin levels in children having beta-thalassemia major with iron-overload treated with deferasirox.

Study Design: A prospective open-label observational study.

Place and Duration of the Study: The Outpatient Department of Hematological Disorder, Thalassemia and Bone Marrow Transplantation Centre, and Department of Biochemistry, "Bahawal Victoria Hospital, Quaid e Azam Medical College", Bahawalpur, Pakistan from February 2020 to January 2021.

Material and Methods: Children aged 2 to 17 years with diagnosis of β-thalassemia major having chronic iron overload (serum ferritin > 1000 ng/ml) and 2 or more blood transfusions per month were included. Demographic information like gender, age, and residential status, contact number along with assessment of hepatitis serology, HIV status, electrocardiogram and ophthalmic findings were noted on a pre-designed proforma specially designed for this study. Deferasirox was initiated in a dose of 20 mg/kg/day and was adjusted at 3-months interval. Serum ferritin levels were measured at baseline, 3-months, 6-months, 9-months and 12-months.

Results: In a total of 40 children, there were 23 (57.5%) male. Overall, mean age was calculated to be 9.1+4.2 years. Residential status of 28 (70.0%) children was rural. Mothers of 27 (67.5%) children were illiterate. At baseline, mean serum ferritin level was noted to be 4137+2319 ng/ml. Significant reduction in mean serum ferritin levels during the course of this study was found with the use of deferasirox as mean serum ferritin levels reduced significantly from baseline to 3-months, 6-months, 9-months and at 12-months as 3637+2119 ng/ml, 4081+2050 ng/ml, 4346+2349 ng/ml, 3252+2464 ng/ml and 2188+1195 ng/ml respectively (p<0.001).

Conclusion: Deferasirox was found to be an effective iron chelation therapy among transfusion dependent thalassemia children with iron-overload.

Keywords: serum ferritin, Thalassemia, iron-overload, deferasirox.

INTRODUCTION

Beta-thalassemia major is known to be an hereditary blood disease because of defects in beta-globin chain with free alpha-globin chains that become abnormal components in maturing red blood cells (RBCs) developing into its destruction by spleen that further leads to anemia.[1] Children with beta-thalassemia major needs regular blood transfusions for the survival hence these children become transfusion-dependent. One of the most common and major complications of the blood transfusion is iron overload and increased risk of transmitted infections.[2]

Detailed evaluation of blood donor's history and execution of FDA approved serological and "nucleic acid testing (NAT)" assay have resulted in immense reduction in infection transmission through transfusion.[3] Among children suffering with thalassemia, excessive iron is stored in major organs that result in organ damage.[4,5] Efficacious and convenient iron chelating therapies are one of the corner stones of thalassemia major treatment among children.

Deferoxamine mesylate has remained the standard treatment option for children having transfusional hemosiderosis in the past. Deferoxamine mesylate is related with disadvantages like it requires parenteral administration as slow subcutaneous or intravenous infusion in a duration usually spanning between 8 to 12 hours. Additionally, deferoxamine mesylate requires administration for 5 to 7 days a week so it frequently linked with less compliance rates that results in reduction in overall efficacy of this drug.[6,7] Deferiprone was the 1st oral iron chelation therapy but it requires administration 3 times a day. Arthropathy and agranulocytosis are some of the most commonly found adverse effects linked with deferiprone.[8]

Deferasirox is FDA approved relatively new iron chelator belonging to class of tridentate. Deferasirox is known to have good oral bio-availability and can be given once/day. No clinically serious adverse effects or drug to drug interactions are related with deferasirox while some researchers have exhibited that it enters and removes iron from cells.[9] Data from developing countries has shown that deferasirox influence decline in serum ferritin levels among patients with transfusion dependent β-thalassemia.[10] A recent trial from India revealed that deferasirox was efficacious when initiated at the right time with right dosage and resulted in significant reduction in serum ferritin levels among transfusion dependent thalassemia children.[11] Not

much data about efficacy of deferasirox exists from Pakistan so this study was aimed at evaluating serum ferritin levels in children having beta-thalassemia major with iron-overload treated with deferasirox.

MATERIAL AND METHODS

This prospective open-label observational study was done at "The Outpatient Department of Hematological Disorder, Thalassemia and Bone Marrow Transplantation Centre, and Department of Biochemistry, Bahawal Victoria Hospital, Quaid e Azam Medical College, Bahawalpur, Pakistan" from February 2020 to January 2021. Approval from "Institution's Ethics Committee" was taken. Informed written consent was acquired from parents/guardians of all study participants at the time of enrollment.

Children aged 2 to 17 years with diagnosis of thalassemia having chronic iron overload (serum ferritin > 1000 ng/ml) and 10 or more blood transfusions per year visiting Outpatient Department of Department of Clinical Hematology were included. Children with alanine aminotransferase above 250 U/L, positive hepatitis serology or HIV test, serum creatinine above 1.2 mg/dl, urinary protein-creatinine ratio above 0.05, uncontrolled hypertension, raised QTc interval, systemic infections in the past 1 month, intestinal malabsorption or ocular adverse effects related to past iron chelating agents were excluded. Patients missing follow-ups for any reasons were also excluded from this study. Initially, a total of 82 patients were considered for the present study but after evaluation as per inclusion and exclusion criteria, 27 were excluded. A further 15 left or missed the scheduled follow up for multiple reasons. So, 40 children were included in the final analysis.

Demographic information like gender, age, and residential status, contact number along with assessment of hepatitis serology, HIV status, electrocardiogram and ophthalmic findings were noted on a pre-designed proforma specially designed for this study. Deferasirox is available as free from the government at our institute so provided as free to all enrolled children. No funding or sponsorship was linked with the present research. Deferasirox was initiated in a dose of 20 mg/kg/day[12] and was adjusted at 3-months interval. Serum ferritin levels were measured at baseline, 3-months, 6-months, 9-months and 12-months.

Data was entered in SPSS version 26.0 for the analysis. Quantitative variables were calculated as mean and standard deviation whereas qualitative variables were expressed as frequencies and percentages. Analysis of variance (ANOVA) was applied to compare difference in serum ferritin levels considering p value<0.05 as significant.

RESULTS

In a total of 40 children, there were 23 (57.5%) male. Overall, mean age was calculated to be 9.1+4.2 years. Residential status of 28 (70.0%) children was rural. Mothers of 27 (67.5%) children were illiterate. At baseline, mean serum ferritin level was noted to be 4137+2319 ng/ml. Table 1 is showing baseline characteristics of all children enrolled in this study.

Table 1: Characteristics of Children at Baseline (n=40)

Characteristics		**Number (%) / Mean+SD**
Gender	Male	23 (57.5%)
	Female	17 (42.5%)
Age (years)	<10	29 (72.5%)
	>10	11 (27.5%)
Age (years)		9.1+4.2
Residential Status	Rural	28 (70.0%)
	Urban	12 (30.0%)
Maternal Education	Illiterate	27 (67.5%)
	Literate	13 (32.5%)
Serum Ferritin (ng/ml)		4137+2319

Significant reduction in mean serum ferritin levels during the course of this study was found with the use of deferasirox as mean serum ferritin levels reduced significantly from baseline to 3-months, 6-months, 9-months and at 12-months as 3637+2119 ng/ml, 4081+2050 ng/ml, 4346+2349 ng/ml, 3252+2464 ng/ml and 2188+1195 ng/ml respectively (p<0.001). Table 2 is showing efficacy of deferasirox among children having iron-overload transfusion dependent thalassemia. No serious drug related adverse events were reported during the course of this study.

Table 2: S.Ferritin level among children having Iron-Overload in β- thalassemia with Deferasirox

Mean Serum Ferritin Levels (ng/ml)	At Baseline	At 3-Months	At 6-Months	At 9-Months	At 12-Months	P-Value
	3637 + 2119	4081 + 2050	4346 + 2349	3252 + 2464	2188 + 1195	<0.001

DISCUSSION

Chronic iron-overload can be the cause of significant morbidity or mortality if appropriate iron chelation treatment therapy is not given timely. Experts advise iron chelating therapy if serum ferritin levels are above 1000 ng/ml or following 10 to 20 units of packed red blood cells transfusion.[13]

In this study, majority of the children (57.5%) were male. These findings are very similar to another local study from Karachi where 62% children with multi-transfused beta-thalassemia major were male.[14] in developed countries, no gender is preferred for healthcare but in developing countries like Pakistan, it is perceived that male children are usually preferred for health seeking behaviors.

In the present study, we noted that mean serum ferritin levels reduced significantly from baseline to study end point (1-year follow up) during the course of treatment with deferasirox. These findings are very similar to another study done in India where the researchers found that statistically significant reduction in serum ferritin levels was observed with the use of deferasirox among children having transfusion dependent thalassemia during the course of the study (p=0.04).[11] A study from Agha Khan University Hospital Karachi Pakistan analyzing 63 children with thalassemia having iron-overload found that

deferasirox resulted in significant reduction in serum ferritin levels (from 5254+3540 ng/ml at baseline to 4701+2989 at final analysis, p=0.01).[15] A local study done by Ejaz MS et al from Karachi found deferasirox in multi-transfused children with beta-thalassemia major to reduce serum ferritin levels but no statistical significance was noted in outcomes (p=0.929).[14] The difference in findings between our results and Ejaz MS et al in terms of reduction in serum ferritin levels could be due to the fact that Ejaz MS et al had total duration of follow up period as 6 months while we followed up patients for duration of 1 year.

Being a prospective study with 1 year follow up data of children suffering with transfusion dependent thalassemia with iron-overload is one of the major strength of this study. Our study had some limitations as well. Being a single center with a relatively small sample size, our findings cannot be generalized. We also did not have any comparator groups or randomization in the present study so the design itself had its limitations.

CONCLUSION

Deferasirox was found to be an effective iron chelation therapy among children of β-thalassemia major with iron-overload. Further studies comparing deferasirox with other available iron chelators with long follow ups should be planned to further evaluate the effectiveness of deferasirox.

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REFERENCES

1. Fibach E, Rachmilewitz EA. Pathophysiology and treatment of patients with beta-thalassemia - an update. F1000Res. 2017;6:2156.
2. Yasmeen H, Hasnain S. Quality of life of Pakistani children with β-Thalassemia Major. Hemoglobin. 2018;42(5-6):320-325.
3. Lindholm PF, Annen K, Ramsey G. Approaches to minimize infection risk in blood banking and transfusion practice. Infect Disord Drug Targets. 2011;11(1):45-56.
4. Hakeem GL, Mousa SO, Moustafa AN, Mahgoob MH, Hassan EE. Health-related quality of life in pediatric and adolescent patients with transfusion-dependent ß-thalassemia in upper Egypt (single center study). Health Qual Life Outcomes. 2018;16(1):59.
5. Voskaridou E, Terpos E. New insights into the pathophysiology and management of osteoporosis in patients with beta thalassemia. Br J Haematol. 2004;127:127–39.
6. Roberts DJ, Rees D, Howard J, Hyde C, Alderson P, Brunskill S. Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD004450.
7. Fisher SA, Brunskill SJ, Doree C, Gooding S, Chowdhury O, Roberts DJ. Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia. Cochrane Database Syst Rev. 2013;(8):CD004450.
8. Yang LP, Keam SJ, Keating GM. Deferasirox: a review of its use in the management of transfusional chronic iron overload. Drugs. 2007;67(15):312211-30.
9. Taher A, Cappellini MD. Update on the use of deferasirox in the management of iron overload. Ther Clin Risk Manag. 2009;5:857-68.
10. Chaudhary P, Pullashat V. Deferasirox; Appraisel of saftey and efficacy in long term therapy. J Blood Med. 2013;4:101–10.
11. Panigrahi M, Swain TR, Jena RK, Panigrahi A, Debta N. Effectiveness of deferasirox in pediatric thalassemia patients: Experience from a tertiary care hospital of Odisha. Indian J Pharmacol 2020;52(3):172-8.
12. Taher A, Cappellini MD, Vichinsky E, Galanello R, Piga A, Lawniczek T, et al. Efficacy and safety of deferasirox doses of >30 mg/kg per d in patients with transfusion-dependent anaemia and iron overload. Br J Haematol. 2009;147(5):752-9.
13. Porter J, Viprakasit V. Iron overload and chelation. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, editors. Guidelines for the Management of Transfusion Depenedent Thalassaemia (TDT). 3rd ed. Nicosia: Thalassaemia International Federation; 2014. p. 42-97.
14. Ejaz MS, Baloch S, Arif F. Efficacy and adverse effects of oral chelating therapy (deferasirox) in multi-transfused Pakistani children with β-thalassemia major. Pak J Med Sci. 2015;31(3):621-5.
15. Shaikh MS, Adil SN. Iron chelation in patients with transfusion dependent thalassemia: an insight on response to deferasirox. J Coll Phy Surg Pak. 2015;25(7):553-4.