



BETA THALASSEMIA MAJOR; COMPARISON OF DEFERASIROX VERSUS DESFERIOXAMINE AS IRON CHELATOR IN MULTITRANSFUSED PATIENTS

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ABSTRACT... Introduction: β -Thalassemia major (β -TM) is a genetic haemoglobin disorder which is relatively common in some geographical areas. β -TM is characterized by severe anaemia, which needs a continuous blood transfusion regimen starting from the first months of life to prolong survival. **Objectives:** To compare mean reduction in serum ferritin level with deferasirox and desferrioxamine when used as an iron chelator in multi-transfused beta thalassemia major. **Study design:** Randomized controlled trial. **Setting:** Thalassemia clinic, The Children's Hospital and The Institute of Child Health, Lahore. **Duration of Study with Dates:** Study was carried out over a period of nine months from 28-06-2015 to 27-03-2016. **Subjects and Methods:** A total of 100 patients (50 patients in each group). The patients were randomly allocated into two groups using random numbers stable. Group-A received Deferasirox and group-B received Desferrioxamine. **Results:** Mean age of the patients was 7.42 ± 4.13 and 7.87 ± 4.13 in group-A and B, respectively. Regarding sex distribution, 26 patients (52.0%) in group-A and 28 patients (56.0%) in group-B were male while 24 patients (48.0%) in group-A and 22 patients (44.0%) in group-B were female. Reduction from baseline in group-A was 783.60 ± 413.66 ng/ml and in group-B 552.80 ± 155.45 ng/ml ($P < 0.001$) There was more reduction in group-A. In group-A baseline serum ferritin level was 2495.00 ± 1259.10 ng/ml and at 9 month 1712.00 ± 1019.36 ng/ml ($P < 0.001$). Similarly in group-B baseline serum ferritin level was 2422.80 ± 910.43 ng/ml and at 9 month 1883 ± 862.72 ng/ml ($P < 0.001$). **Conclusion:** In conclusion, deferasirox was more effective in terms of reduction in serum ferritin level when compared with desferrioxamine in multi-transfused beta thalassemia major patients.

key words: β -Thalassemia Major, Deferasirox, Desferrioxamine

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INTRODUCTION

β -thalassemia is a gathering of latently acquired issue of hemoglobin blend described by lessened amalgamation of the beta-globin chain of turmoil and transformation is in charge of its occurrence. Serious pallor brings about the homozygous state, requiring normal blood transfusions.^{1,2} It is the most widely recognized monogenic issue on the planet. Africa, India, Southeast Asia and Mediterranean territories are known for its high recurrence of occurrence.¹

As to, quality recurrence of beta-thalassemia is 5-8% and incorporate around 100,000 cases, constituting 5% of world cases and every ethnic gathering are incorporated.³ Beta-thalassemia

significant cases conceived in Pakistan are more than 5000 that need normal blood transfusions each 2-3 weeks to keep passing from iron deficiency.^{4,5} Every unit of red platelets contains 200-250 mg of iron and every year around 52 units of blood transfusions are required, aggregating overabundance press inside the body organs, similar to liver, heart and endocrine organs bringing about organ harm.⁶ Future is diminished in these patients because of iron over-burden, that is the most widely recognized reason for dismalness and mortality.⁷ So keeping in mind the end goal to deal with the abundance press over-burden, there is requirement for fruitful iron chelation.¹ Concerning, the principal line tranquilize up till now is desferrioxamine (dfo,

desferal and bland). Its course of organization is parenteral, being hexadentate chelator and its suggested measurement is 20-40mg for every kg/day. Powerful iron chelation requests its utilization for 5-6 times each week. The consistence is however poor because of parenteral course of organization. So requirement for a compelling and middle of the road press chelator having less request plan remains. Deferiprone is an oral iron chelator with three times day by day dosages, crediting agranulocytosis as the most genuine unfriendly effect.^{8,9}

A promising new medication utilized now a days is deferasirox (Aunra, Exjade). It is a tridentate oral iron chelator with single day by day measurement of 20-30mg for each kg. Plasma half-life is 8-16 hours. Deferasirox press complex is discharged in stool. Deferasirox causes diminishes in serum ferritin level as 2516 ± 2106 mg/ml in correlation with desferrioxamine 987 ± 915 ng/ml.¹¹ Just gastrointestinal indications are the reported dangerous impacts of this medication, with no instances of agranulocytosis.^{9,10}

Efficacy of the iron chelators is measured by more convenient biochemical test, serum ferritin levels, that have been shown to parallel the liver iron concentration. This simple blood test is an effective way to monitor serum levels of iron without the need of an invasive procedure such as liver biopsy.

In children hospital currently both deferasirox and desferrioxamine are being used.

I want to observe the efficacy of deferasirox as an iron chelator in our own patients of beta thalassemia major receiving regular blood transfusions. The importance of this study lies in the fact that an effective oral iron chelator is of utmost need to improve the compliance of iron chelation therapy. My study will definitely help to see reduction in serum ferritin level by this newer oral iron chelator and will help in choosing the better drug for chelation in children with beta thalassemia major as no local data is available regarding this subject.

OBJECTIVES

Objective of the study was

To compare mean reduction in serum ferritin level with deferasirox and desferrioxamine when used as an iron chelator in multi-transfused beta thalassemia major.

OPERATIONAL DEFINITIONS

Multi Transfusions

Patients of beta thalassemia major requiring regular blood transfusions (once in every 3 weeks) to maintain adequate hemoglobin and oxygen carrying capacity for survival and have taken more than nine blood transfusions.

Reduction in Serum Ferritin Level

Was assessed at baseline and then after 9 months to see reduction.

Beta Thalassemia Major

Homozygous state characterized by reduced synthesis of beta globin chain diagnosed by Hb electrophoresis and have Hbf 95%.

Hypothesis

There will be more reduction in Mean serum ferritin level with deferasirox than desferrioxamine in patients of beta thalassemia major.

MATERIAL AND METHODS

Study Design

Randomized controlled trial.

Setting

Thalassemia clinic, The Children's Hospital and The Institute of Child Health, Lahore.

Duration of Study

Study was carried out over a period of nine months from 28-06-2015 to 27-03-2016.

Sample Size

Sample size of 100 cases (50 in each group) was calculated with 95% confidence level, 80% power of test and taking mean \pm SD of serum ferritin level in both groups i.e. 2516 ± 2106 ng/ml in deferasirox group versus 987 ± 915 ng/ml in desferrioxamine group when used as iron chelator

in multitransfused beta thalassemia major.

Sampling Technique

Non-probability purposive sampling.

SAMPLE SELECTION

Inclusion Criteria

Diagnosed male and female cases of beta thalassemia major, age 3-18 years, who got multiple blood transfusions (as per operational operation) with at least 9 transfusions, and have developed iron overload i.e. serum ferritin level >1000ng/ml were included in this study.

Exclusion Criteria

- Cases of beta thalassemia major with compound heterozygosity, as diagnosed on Hb Analysis.
- Receiving combined iron chelation therapy.
- Patients of thalassemia major having chronic renal failure i.e. having GFR <60ml/min/1.73m² for >3 months and/or chronic liver disease diagnosed on liver biopsy.

Data Collection Procedure

After getting approval from hospital ethical committee, 100 patients meeting the inclusion criteria were included. Informed consent was taken from parents after explaining detail administration of the drug. Patients attending the thalassemia clinic of the Children's Hospital, Lahore with the diagnosis of beta thalassemia major and fulfilling inclusion and exclusion criteria was selected for this study. The patients were randomly allocated in two groups using random numbers table. Group-A received deferasirox and group-B received desferrioxamine. Drug was then started in recommended dosage, deferasirox oral once daily and desferrioxamine subcutaneous once daily. Patients were prospectively followed at 0, 3, 6 and 9 months of starting treatment with desferrioxamine and deferasirox, and their reduction in serum ferritin was measured at the end of 9 months. These patients were transfused once after 3 weeks. Samples for serum ferritin levels were collected by researcher by standard venepuncture technique under strict aseptic conditions. Serum was separated and stored at -30°C for automated immunodiagnostic system.

The data was collected by using proforma (attached).

Data Analysis

Data collected through the specified proforma was entered SPSS (statistical package for social sciences) version 12.0. The quantitative data (age and serum ferritin level) were analyzed as means and standard deviation. The qualitative data (gender) was reported as frequency and percentages.

RESULTS

One hundred patients (50 patients in each group) were recruited in present study during the study period of nine months from 28-06-2015 to 27-03-2016.

Group-A received deferasirox and group-B received desferrioxamine.

In both groups, majority of the patients were between 5-10 years old. Mean age of the patients was 7.42 ± 4.13 and 7.87 ± 4.13 in group-A and B, respectively (Table-I).

Regarding sex distribution, 26 patients (52.0%) in group-A and 28 patients (56.0%) in group-B were male while 24 patients (48.0%) in group-A and 22 patients (44.0%) in group-B were female (Table-II).

In group-A baseline serum ferritin level was 2495.00 ± 1259.10 ng/ml and at 9 month 1712.00 ± 1019.36 ng/ml ($P < 0.001$). Similarly in group-B baseline serum ferritin level was 2422.80 ± 910.43 ng/ml and at 9 month 1883 ± 862.72 ng/ml ($P < 0.001$). (Table-III).

Reduction from baseline in group-A was 783.60 ± 413.66 ng/ml and in group-B 552.80 ± 155.45 ng/ml ($P < 0.001$) There was more reduction in group-A. (Table-IV).

DISCUSSION

There have been significant changes in the administration of thalassemia real patients amid the most recent 3 decades.

Age (year)	Group-A (Deferasirox)		Group-B (Desferrioxamine)	
	No.	%	No.	%
< 5	14	28.0	11	22.0
5-10	24	48.0	26	52.0
11-18	12	24.0	13	26.0
Total	50	100	50	100
Mean±SD	7.42±4.13		7.87±4.13	

Table-I. Distribution of cases by age

Gender	Group-A (Deferasirox)		Group-B (Desferrioxamine)	
	No.	%	No.	%
Male	26	52.0	28	56.0
Female	24	48.0	22	44.0
Total	50	100	50	100

Table-II. Distribution of cases by gender

Ferritin Level	Group-A (Deferasirox) Mean±SD	Group-B (Desferrioxamine) Mean±SD
Baseline serum Ferritin level	2495.00±1259.10	2422.80±910.43
After 9 months serum ferritin level	1712.00±1019.36	1883±862.72
P value	P < 0.001	P < 0.001

Table-III. Serum ferritin levels at baseline and at 9 month

Ferritin Level	Group-A (Deferasirox) Mean±SD	Group-B (Desferrioxamine) Mean±SD
Reduction from base line	783.60±413.66	552.80±155.45
P value	P < 0.001	

Table-IV. Reduction in serum ferritin levels

Iron deficiency related complexities can be wiped out with consistent red platelet (RBC) transfusions and compensatory bone marrow (BM) extension, allow typical advancement all through youth, so augmenting survival.¹² Then again, a “second infection” is seen as a consequence of these transfusions while treating the primary.¹³ This second ailment is of steady amassing of tissue iron that, if untreated, is lethal in the second decade of life. With new headways in iron-chelating treatment for iron over-burden, the anticipation of thalassemia major in the course of the most recent 20 years has been advanced.

In the mid 1960s, deferoxamine mesylate, was initially presented in transient studies in iron-stacked patients and got acknowledgment as standard treatment over 10 years after the fact in those nations managing high expenses of this treatment. Expanded survival was watched a

quarter century, in all around chelated patients, including free of iron-actuated confusions, and significantly enhanced personal satisfaction. Without a doubt, over this period, there have been most critical change in horribleness and mortality connected with a hereditary malady as a consequence of iron-chelating treatment for thalassemia major.

Unyielding gathering of iron inside tissues is the most essential outcome of life-sparing transfusions in thalassemia, bringing about dynamic organ brokenness that if untreated with chelating treatment is fatal.¹³ There have been already reported exhaustive audits with respect to the poisonous quality of iron.¹⁴ Here, we will quickly consider the locales and poisonous quality of chelatable iron vital in patients with thalassemia.

There are two primary stores in the body for overabundance of iron, in reticuloendothelial cells and parenchymal tissue. In the reticuloendothelial cells, it has all the earmarks of being generally safe, in any case it might bring about noteworthy harm when put away in the parenchymal tissues.¹³

A chelating specialist may treat iron overburden by complexing with iron and advancing its discharge. Presently a drug for clinical use, deferoxamine B is the main iron-chelating agent. It is a trihydroxamic chelator delivered by *Streptomyces pilosus*, demonstrating relative specificity for ferric iron.¹⁶

Because of poor oral retention and fast digestion system in plasma, deferoxamine¹⁷, presents its central downside: the prerequisite for delayed parenteral implantations amid which plasma iron levels achieve a level at 12 hours already.¹⁴ There are intensive past surveys of deferoxamine as well-springs of iron chelation.¹⁴

Numerous reasonable issues are however connected with chelation treatment including exact appraisal of body iron load, important for the viability of deferoxamine, and also to that of new chelators entering clinical trials. There are several issues, that emerge as often as possible in the administration of patients with thalassemia, for instance, identified with fitting age for the start of deferoxamine treatment, the support of harmony between its viability and poisonous quality, and the issues of consistency with deferoxamine.

As there was yearning to have a specialist that could be managed advantageously to patients of any age, and over a scope of iron weights, so to satisfy this need, an oral iron chelating agent deferasirox was created. Past clinical studies demonstrated the capability of deferasirox to address this issue, and the present study was performed to contrast this agent with deferoxamine.²¹ Since entanglements of endless iron overburden have been best concentrated on in β -thalassemia, this population of patients was utilized for the show of adequacy for deferasirox.

As the pathogenesis of interminable iron overburden is comparable in various fundamental sorts of pallor requiring transfusion, the adequacy results are all the more extensively material.

Deferasirox is an once-a-day oral iron chelator created for the treatment of ceaseless iron overburden from blood transfusions. A phase 3 trial was directed to exhibit the adequacy of deferasirox in consistently transfused patients with β -thalassemia matured 2 years or more established. Patients were randomized and got treatment with deferasirox ($n = 296$) or deferoxamine ($n=290$), with dosing of each as indicated by pattern liver iron focus (LIC). The essential endpoint was upkeep or decrease of LIC; auxiliary endpoints included security and fairness, change in serum ferritin level, and net body iron adjust. In both arms, patients with LIC estimations of 7 mg Fe/g dry weight (dw) or higher had critical and comparative measurements subordinate diminutions in LIC and serum ferritin, and consequences for net body iron adjust. Be that as it may, the essential endpoint was not met in the general populace, conceivably because of the way that relatively bring down measurements of deferasirox in respect to deferoxamine were directed to patients with LIC values under 7 mg Fe/g dw. The most well-known antagonistic occasions included rash, gastrointestinal unsettling influences, and gentle nonprogressive increments in serum creatinine. No agranulocytosis, arthropathy, or development disappointment was connected with deferasirox treatment. Deferasirox is an unequivocal once-a-day oral treatment for the treatment of iron overburden identified with blood transfusions.²²

Deferasirox (ICL670, Exjade; Novartis) is an individual from another class of tridentate iron chelators, the N-substituted bis-hydroxyphenyl-triazoles.²² It is orally bioavailable and its terminal end half-life ($t_{1/2}$) is somewhere around 8 and 16 hours, taking into consideration once-a-day administration. Digestion system and end of deferasirox and the iron chelate ($\text{Fe}[\text{deferasirox}]_2$) is basically by glucuronidation followed by hepatobiliary discharge into the defecation. No

critical medication sedate associations have been recognized to date. Preclinical studies exhibited the capacity of deferasirox to enter and expel press from cells.²³

Past studies in grown-up patients with β -thalassemia major uncovered that adequate iron from the body could conceivably be expelled to surpass that managed as a feature of a constant transfusion regimen if treated with deferasirox.²⁴ Amid 1 year time span, this multinational stage 3 randomized trial contrasting deferasirox with deferoxamine was started in pediatric and grown-up patients with β -thalassemia getting standard blood transfusions keeping in mind the end goal to encourage assess its adequacy in body press decrease. β -thalassemia was chosen as the model illness for exhibit of viability over the scope of patients at danger of iron over-burden.

In present study, reduction from baseline ferritin level in group-A (Deferasirox) was 783.60 ± 413.66 ng/ml and in group-B (Desferrioxamine) was 552.80 ± 155.45 ng/ml. Reduction was significant in both groups but in Deferasirox group, serum ferritin level more reduction was occurred than Desferrioxamine group.

In as study by Porter et al reduction in serum ferritin level with deferasirox was 2516 ± 2106 mg/ml in comparison with desferrioxamine 987 ± 915 ng/ml.¹¹

CONCLUSION

In conclusion, deferasirox was more effective in terms of reduction in serum ferritin level when compared with desferrioxamine in multi-transfused beta thalassemia major patients.

Deferasirox is a novel once-daily oral agent for the treatment of chronic iron overload related to blood transfusions. Its use has been investigated in pediatric patients 3-18 years of age. The availability of a well-tolerated, effective, and conveniently administered oral iron chelator should permit application of chelation therapy to a larger patient population in need. It should also facilitate patient compliance, a critical factor in

effective patient management, and thereby help maintain low iron burdens in patients requiring frequent blood transfusions.

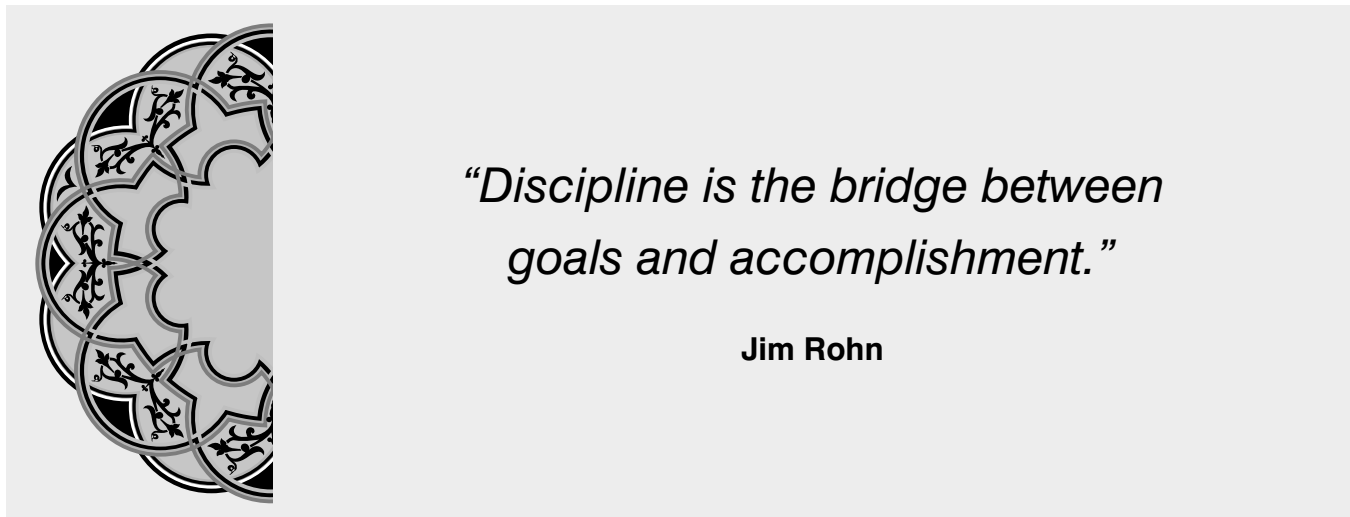
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