ORIGINAL RESEARCH

COMPARISON OF DEFERIPRONE AND DEFERRIOXAMINE FOR THE TREATMENT OF TRANSFUSIONAL IRON OVERLOAD IN CHILDREN WITH BETA THALASSEMIA MAJOR

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Background: Thalassemia major is the most common genetic disorder in Pakistan. The study was done to compare the efficacy and safety of the deferiprone with deferrioxamine for the treatment of iron overload in children with thalassemia major. **Methods:** This randomized controlled trail was conducted at thalassemia blood transfusion unit of Allied Hospital, Faisalabad (AHF)/District Headquarter Hospital (DHQ), Faisalabad. Thalassemia-Unit Hilal-e-Ahmar, Alizeb Foundation and Blood Bank Services Faisalabad from November 2010 to December 2011.Children with beta thalassemia major of age more than 2 years and less than 16 years with transfusion iron over load were randomly allocated to one of the two groups each comprising of 67 patients. One group received deferiprone given at a daily dose of 75 mg/kg in three divided doses orally while the other group received deferrioxamine at dose 50 mg/kg/24 hrs for 5 days/week as parental infusion. Changes in the serum ferritin level were assessed. Cardiac function and toxicity were also examined. **Results:** Serum ferritin was significantly reduced after 1 year in both treatment arms (p=0.01). Neutropenia observed in 13 (19.40%) non-splenectomized patients taking deferiprone. Transient elevations in ALT were observed in 3 (4.47%) children taking deferiprone. Left ventricular ejection fraction (LVEF) remained in normal range in both treatment arm but has decreased significantly in Deferrioxamine group compliance. Compliance was better in deferiprone as compared to deferrioxamine. Discontinuing percentage 2 (3%) vs 9 (13.43%). **Conclusion:** Deferiprone is a highly efficacious and safe chelation therapy for patients with thalassemia major who are non-compliant to Deferrioxamine. Deferiprone have an efficacy profile comparable to standard Deferrioxamine.

Keywords: Thalassemia deferiprone, deferrioxamine iron over load

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INTRODUCTION

Thalassemia major is the most common genetic disorder in Pakistan.[1] It is estimated that over 5000 thalassemic homozygotes are born in Pakistan each year.[2] The management of thalassemia major in most of patients in our country is with packed red cell transfusions.[3] Regular red blood cell transfusions eliminate the complication of anaemia and compensatory bone marrow expansion, permit normal development throughout childhood, and extend survival.[4]

Each 500ml of packed red cells contain about 250 mg of iron. Repeated blood transfusion rapidly saturate patients transferrin and leads to formation of non-transferrin bound iron (NTBI), which is a toxic component of plasma iron that result in free radical generation causing tissue damage.[5] Since there is no physiological way to induce excretion of iron, iron over load is an inevitable clinical consequence for transfusion dependent patient of B-thalassemia major.[6] Therefore, Iron chelation therapy is an important and integral part of their supportive care. Thalassemic patients who are not adequately chelated risk progressive liver damage retarded growth, delayed sexual maturation and reduced life expectancy.[7]

Deferrioxamine an iron chelator has established an excellent efficacy and safety profile for paediatric patients through decades of clinical use.[8] It has a drawback of poor absorption from gastrointestinal tract and short half-life. So the drug must be given as an 8–12 hours over night subcutaneous infusion or 24 hours intravenous infusion for 5–7 days per week, which makes the treatment expensive and curbs its availability in areas where medical resources are limited. Even if the resources exist the extremely burdensome regimens lead to poor compliance particularly in paediatrics patient.[9]

Recent advance has led to the development of oral iron chelator such as deferiprone. Deferiprone presents an option of convenient oral therapy to paediatric patient. Various clinical trials have demonstrated that deferiprone at appropriate doses is effective in lowering serum ferritin with good tolerability and less side effects.[10]

This study is conducted to find out if deferiprone has an efficacy profile comparable to that of standard Deferrioxamine. So that the availability of oral alternative would potentially facilitate the improved compliance and thereby will reduce morbidity and mortality.

MATERIAL AND METHODS

This randomized controlled trail was conducted at thalassemia blood transfusion-unit of Allied Hospital, Faisalabad (AHF)/District Headquarter Hospital (DHQ), Faisalabad, Thalassemia Unit Hilal-e-Ahmar, Alizeb Foundation and Blood Bank Services Faisalabad during November 2010 to December 2011. Children with beta thalassemia major of age more than 2 years and less than 16 years with iron overload secondary to transfusion, were randomly allocated to one of the two groups each comprising of 67 patients. Prior chelation therapy was permitted but not mandatory. The serum ferritin level for entry into this study was >1000 ug/l. Patients were excluded if they had known toxicity to deferrioxamine or deferiprone, deranged liver function test, renal function test, neutropenia and thrombocytopenia.

Informed written consent was obtained. Patients were randomized to receive deferiprone or Deferrioxamine 1:1 manner. The study duration was 52 weeks. One group was given deferiprone 75 mg/kg in daily 3 divided doses in the form of Tab. Ferrinil 500 mg manufactured by global pharmaceuticals. The other group was given deferrioxamine 50 mg/kg 5 days a week as subcutaneous or intravenous infusion available in form of Inj. desferal 500 mg manufactured by Novartis.

Complete blood count with differential counts, biochemistry testing included electrolytes, glucose, liver function test and renal function tests performed at base line and then 3 monthly. Physical examination, ECG, Echocardiography, audiometry, growth assessment and ophthalmological examination were performed at base line and 6 monthly afterwards. Serum ferritin was assessed monthly during the study and changes were determined using baseline and final ferritin level. Compliance was assessed by counting the number of tablets returned in bottles at each visit for Deferrioxamine the number of vials returned at each visit were counted. The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fell outside the predetermined ranges. The main efficacy end point was change in serum ferritin. Data was analysed with SPSS version 10. Mean and standard deviation was calculated for all quantitative variables like age, serum ferritin level frequency and percentages were calculated for all qualitative variables. Independent sample *t*-test was used to compare the serum ferritin levels in both groups. $p<0.05$ was taken as significant. Testing for statistical significance for difference between base line and end of study for each treatment group was performed using student's *t*-test. Using a two sided test, $p<0.05$ was considered to be statically significant.

RESULTS

The percentage of patients discontinuing deferiprone (DFP) and Deferrioxamine (DFO) was 2 (3%) vs. 9 (13.43%) respectively. Adverse events resulted in discontinuation in one (1.5%) of patients on deferiprone and 3 (4.47%) of patients on Deferrioxamine. The remainder discontinuation was due to lose to follow up. A baseline serum ferritin value in two groups is shown in table-1.

The mean dose of DFP 78.2±1.4 mg/kg/day and mean dose of DFO was 51.8±6.9mg/kg×5days/week.

The patients in both treatments arms showed a decrease in serum ferritin level after 1 year which was statistically significant ($p=0.0001$).

Neutropenia was observed in 13 (19.40%) non-splenectomized patients, taking deferiprone and none in patients treated with DFO. The patients fully recovered after 11 days following withdrawal of deferiprone. The gastrointestinal adverse events that patients experienced with deferiprone were generally transient in nature and lasted about one week maximum. Two consecutive amino transferase (ALT) >5xULN were observed in 3 (4.47%) treated with deferiprone and none treated with deferrioxamine. The elevations were transient in majority of patients even with continued drug administration. In one patient a persistently elevated ALT led to interruption of deferiprone therapy. Treatment was permanently discontinued and ALT returned to normal.

None of the patient experienced clinical heart failure or arrhythmia during the study. Left ventricular injection fraction (LVEF) remained with in normal ranges in all patients receiving either deferiprone or Deferrioxamine. Audiometric and visual assessment remained normal in both treatment arms. Growth measurements were also remained normal.

Table-1: Characteristic of patients at start of study

Chelation Regimen	Age (Years)	Pre-transfusion Hb (g/dl)	Baseline Ferritin (ug/l)
DFP n=67	5.9±9.2 (3–16 Yrs)	8.9±0.5 (8.2–9.7)	4453±2855 (1014–6859)
DFO n=67	6.0±6.4 (4.5–16 Yrs)	8.2±0.5 (7.2–9.3)	4070±1358 (1972–6028)

DFP=Deferiprone; DFO=Deferrioxamine

Table-2: Changes in serum ferritin (SF) levels after 1 year of treatment with different iron chelation regimens

Chelation Regimen	Basal SF (ug/L)	Final SF (ug/L)	*p*-value (Paired *t*-test)
DFP n=65	4453±2855 (1014–6859)	3057±2479 (880–4100)	0.0001
DFO n=58	4070±1358 (1972–6028)	2682±1340 (670–3825)	0.0001
p-value (Independent Sample *t*-test)	0.354	0.188	

SF=Serum Ferritin

DISCUSSION

This comparative study demonstrated that deferiprone was reasonably well tolerated in patients with beta thalassemia major. There was no life threatening adverse effects when compared to deferrioxamine. Although absolute magnitude of the reduction of iron overload may be over or under estimated because in this study changes in serum ferritin level was observed only and changes in liver iron concentration was not observed due to unavailability of SQUID and unwillingness of parents for liver biopsy. But studies conducted by Angelucci E *et al*[10], Zannineri *et al*,[11] Fischer R[12] suggested that changes in serum ferritin generally parallels the changes in liver iron concentration, also we observed caution to exclude all condition that can effect serum ferritin levels.

Iron chelation is an important and integral part of treatment of patients with beta thalassemia major who are transfusion dependent. Adherence to parenteral deferrioxamine treatment is poor. Thus resulting in inadequate chelation and eventually complications of iron toxicity in non-compliant patients.[13,14] Considerable efforts have been devoted to find an orally active chelator as an alternative to deferrioxamine and clinical trials with deferiprone started in the 1980. Clinical studies revealed that deferiprone was capable of decreasing serum ferritin levels and the decline was significant.[15]

In the present study, a statistically significant decrease in serum ferritin level was achieved by deferiprone. Similar results were previously obtained in several nonrandomized trials investigating the role of deferiprone in chelation therapy. Another study also reported a significant decrease in serum ferritin level after 12 months of deferiprone therapy in thalassemic patients.[16] These results are in contrast with Cohen AR *et al*[17], who observed in a study on 187 patients that a significant proportion of patients did not respond to deferiprone and left therapy. While in a prospective controlled trial by Galanello R *et al* serum ferritin increased in the deferiprone group.[18]

The mean LVEF values did not change significantly after 1 year of observation in both of groups either receiving deferiprone or deferrioxamine. However LVEF decreased among the patients receiving deferrioxamine, though not below the lower normal range, this is in concordance with studies that showed that deferiprone decreases myocardial iron overload and improves left ventricular ejection fraction(LVEF).[19]

Clinical experience has shown that the most serious side effect of deferiprone is neutropenia and agranulocytosis, which occurs in approximately 0.5% of patients and is more frequently observed in the first months of therapy as well as in patients with an intact spleen.[20] This study also confirmed that neutropenia is a common finding in chelated patients with deferiprone with an intact spleen. None of the patients treated with deferrioxamine in this trial developed agranulocytosis. Transient fluctuating increases in serum ALT levels were observed throughout the study in patients receiving either deferiprone monotherapy. Previously, changes in ALT were attributed to concomitant hepatitis C virus (HCV) infection although more recent studies have revealed that fluctuation in ALT occur regardless of hepatitis C status. In the present study none of the patients suffered from HCV infection, but mean ALT levels were higher than the upper normal. The ALT levels normalized by the end of 1 year of treatment. As reported in other studies[21] nausea was the most prominent side effect observed during the first few weeks of therapy with deferiprone. However, neither antiemetic therapy nor cessation of deferiprone therapy was necessary and the nausea was transient, i.e., it did not reappear during the course of the study. In one patient suffering from arthralgia of her left knee, the symptoms were relieved by short term anti-inflammatory therapy and temporary discontinuation of deferiprone for a few days, confirming previous studies.[22,23] Compliance to oral deferiprone was generally better than compliance to parenteral deferrioxamine therapy, as observed in other studies.[24]

CONCLUSION

We concluded that deferiprone at standard doses is a highly efficacious and safe chelation therapy for patients with thalassemia major who are non-compliant to deferrioxamine chelation therapy as the compliance of deferiprone therapy is better than the compliance of deferrioxamine and the deferiprone is likely to have an efficacy profile comparable to that the standard deferrioxamine.

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