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Original Research Article

A concurrent parallel study to compare the efficacy and safety of oral iron chelators, defrasirox and defriprone in patients of beta thalassaemia major

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ABSTRACT

Background: This study was planned to evaluate all the cases of β thalassaemia major, already receiving one of the oral iron chelators for a comparison among the efficacy, safety and economy of deferasirox and deferiprone to establish the better option in an Indian scenario.
Methods: We identified two groups of patients: 38 treated with deferasirox and 35 treated with deferiprone. Laboratory parameters such as serum ferritin, creatinine, SGPT, Hb, CBC and urine were recorded at the time of inclusion and at 1, 3 and 6 months after the inclusion. The primary outcome variable was serum Ferritin level at the start and at the end of study. Serum ferritin level was carried out by microparticle enzyme linked immunoassay.
Results: Before the study, the mean hemoglobin level was 7.32±1.50mg/dL ranged from 4 to 10.8 in deferasirox group and 7.54±1.15mg/dL ranged from 5.5 to 8.8 in deferiprone group. At the time of inclusion, study population was characterized by a mean serum ferritin value of 4735.11±450.01 SE in deferasirox and 4315.97±340.75 SE in deferiprone group. After one month the mean serum ferritin increases to 4578.66±371.96 in deferasirox and 4388.82±316.16 in deferiprone group. After three month the mean serum ferritin reduces to 4295.60±377.37 in deferasirox and 3988.88±349.84 in Deferiprone group.
Conclusions: Thus, we conclude that deferasirox and deferiprone are well tolerated, have few adverse effects and almost have a comparable effect in lowering of the patient's serum ferritin level. Deferiprone is more cost effective but needs a strict control on compliance owing to requirement in three divided doses per day.

Keywords: Beta thalassaemia major, Defrasirox, Defriprone, Efficacy, Oral iron chelators, Safety

INTRODUCTION

Thalassemia is an inherited impairment of hemoglobin production, in which there is partial or complete failure to synthesize a specific type of globin chain. It is characterized by ineffective erythropoesis and hemolysis.[1] It requires frequent blood transfusion and so becomes the most common chronic iron overloading disorder. Excess iron deposits in various tissues of the body, particularly the

liver, heart, and endocrine organs.[2]

Once the body's storage capacity is exceeded, free iron catalyzes the formation of highly reactive hydroxyl radicals, which leads to membrane damage and denaturation of proteins. This process leads to irreversible tissue damage and ultimately to significant morbidity and mortality.[3] Evidence of iron overload is manifested as elevated liver iron concentration (LIC) values and elevated serum ferritin levels. LIC values above 15mg Fe/g dry weight, and serum ferritin values above 2500 mcg/L increases the risk of iron-induced cardiac disease.[4]

Regularly transfused patients not receiving chelation usually die within 10-20 year from iron overload toxicity; which causes irreversible damage to major organs. If chelation therapy is introduced within few years of starting transfusion they can live longer than 20 years and few have exceeded 50 years of life.[5]

Deferiprone is an oral iron chelator. It is relatively less selective; zinc is also excreted with iron. It is less expensive but joint problems and neutropenia have been reported. Deferasirox is another oral iron chelator with high selectivity and a long-term safety proven by some studies. However, there are reports of GI symptoms and rise in creatinine level. Because of oral single dose and acceptable tolerance profile this drug is frequently prescribed in patients with Thalassaemia.

This study was planned to evaluate all the cases of β Thalassaemia major in Index Medical College, Hospital and research centre, Indore and in Thalassemia Society, Indore, already receiving one of the oral iron chelators for a comparison among the efficacy, safety and economy of deferasirox and deferiprone to establish the better option in an Indian scenario.

METHODS

Study design

It is a hospital based prospective, comparative, observational study. The subjects of this study were the patients from index medical college, hospital and research centre, Indore and patients in hospitals associated with thalassemia and child welfare group, who were receiving regular blood transfusion along with any of the two oral iron chelators, deferasirox or deferiprone for more than a year.

All the patients were being managed according to thalassaemia international federation guidelines (2007).[2] Routine investigations and work up needed in special situations were done according to same guidelines. We retrospectively selected thalassaemia major patients who had been receiving one chelator alone for longer than one year. We identified two groups of patients: 38 treated with deferasirox and 35 treated with deferiprone. Prior approval of the synopsis was taken from the Institutional Research Committee and Institutional Review Board of Index Medical College for this work.

Patient selection

It was based on the following inclusion and exclusion criteria.

Inclusion criteria

- All children with beta Thalassaemia major more than 2 years age who are following regularly for blood transfusion.
- Children with beta Thalassaemia major taking Deferasirox on regular basis.
- Children with beta Thalassaemia major taking Deferiprone on regular basis.

Exclusion criteria

- Children below 2 years of age.
- Those not on regular follow up for blood transfusion and chelator intake.

Study Parameters

Basic epidemiological data

Age, sex, weight, age at diagnosis, duration of transfusion, previous chelation history, and complications were recorded.

Parameters to evaluate efficacy

Clinical improvement

Serum ferritin level: Frequent serum ferritin values at the time of enrollment in the study and after 1, 3, and 6 months were recorded. Serum ferritin was by using Partial Chemiluminescent Axim Abet System method after clinically ruling out any active infection. Mean change in serum ferritin from baseline was compared in both the study group with due consideration of various parameters like age, iron loading, transfusion requirement, baseline ferritin, and mean maintenance of hemoglobin.

Parameters to evaluate safety

- Monitoring of adverse effect such as abdominal pain, nausea, vomiting, constipation, rash, joint pain, headache, fever, or any other adverse event.
- Investigations such as total leucocytes count, SGPT, creatinine level at 0, 1, 3 and 6 months of registration of the patients to monitor adverse profile on blood, liver and kidney functions respectively.
- Monitoring of other parameters depending on the observed adverse events.

Statistical analysis

With due consultation with a statistician, the collected data were subjected to statistical analysis using Statistical package for Social Sciences (SPSS) version 20.

RESULTS

This is a prospective, comparative, observational study that includes the patients of thalassaemia from index medical college, hospital and research centre, Indore and patients in hospitals associated with thalassemia and child welfare group, who were receiving regular blood transfusion along with any of the two oral iron chelators, deferasirox or deferiprone for more than a year. All the patients were being managed according to thalassaemia international federation guidelines (2007).[3]

In this study a total of 73 patients were included, 39 were in deferasirox group and 34 were in deferiprone group. Out of these 4 from deferasirox group and 1 from deferiprone group were excluded in view of their non-compliance for the regular follow-up. Remaining 68 patients were studied in two groups; 35 in deferasirox and 33 in deferiprone group. All these patients were the diagnosed cases of thalassemia major with more than fifteen blood transfusions in a year. They were having serum Ferritin levels more than 1000ng/ml at the time of inclusion in the study. The baseline clinical and laboratory data were recorded on a proforma. They were followed up for a period of 6 months.

Deferiprone was given seven days a week at a dose of 75mg/kg/ day in three divided doses. Laboratory parameters such as serum ferritin, creatinine, SGPT, Hb, CBC and urine were recorded at the time of inclusion and at 1, 3 and 6 months after the inclusion. Patients were educated to report the development of any adverse events during the course of therapy.

The primary outcome variable was serum ferritin level at the start and at the end of study. Serum ferritin level was carried out by microparticle enzyme linked immunoassay on kits manufactured by Abbott Laboratories USA on Axsym automated analyzer. ECG, echocardiography and magnetic resonance imaging could not be performed due to economic constraints.

All the data was entered and analyzed using SPSS (statistical package for social sciences) version 20. Paired t test was applied to compare means of ferritin at the start and at different periods of study in the individual group. Two sample t tests were applied to compare the difference between two groups. A p-value of <0.05 was considered statistically significant.

The average weight in deferasirox was 22.74±6.36 kg (range 12-43 kg) and in deferiprone was 22.12±9.65 (range 8-50 Kg). Different range of weight distribution, in both the group was not statistically significant (P value=0.611) (Table 2). Reduction in serum ferritin is statistically non-significant after 1 month ($P > 0.05$) in both the drug group but it is highly significant in both the groups after 3 and 6 months ($P < 0.05$). T_{66} is t-value at degree of freedom 66. p-value of all the parameters of study are >0.05 (non-significant) except SGPT level where difference is significant between the two groups of therapy.

Table 1: Baseline patient characteristics.

Basic characteristic	Deferasirox group	Deferiprone group
No. of patients studied	35	33
Age in years mean ± SD (range)	10.82±4.47 (4-24)	9.72±5.70 (3-30)
Male: Female distribution	29:6	22:11
Body weight in Kg-mean ± SD (range)	22.74±6.36 (12-43)	22.12±9.65 (8-50)
Serum ferritin in ng/ml [mean ± SE]	4735.11±450.01	4315.97±340.75
Hemoglobin (g/dl) [mean ± SD]	7.32±1.50	7.74±1.07
Total WBC count (cu/mm)	6805±2900	6218±3187
Serum creatinine (mg/dL)	0.637±0.122	0.636±0.121
SGPT (IU/L)	63.4±11.2	81.7±14.9

Table 2: Distribution of cases according to body weight.

Distribution of Body weight	Deferasirox n = 35		Deferiprone n=33		Grand total	
	No.	%	No.	%	No.	%
Up to 20 Kg	13	37.14	15	45.45	38	55.88
20-30 Kg	19	54.28	14	42.42	33	48.53
>30 Kg	3	8.6	4	12.12	7	10.29
Total	35	51.47	33	48.53	68	100

$\chi^2 = 0.985$, df = 2, p = 0.611, Non-significant

Table 3: Distribution of the cases according to basic level of ferritin at the time of inclusion in the study.

Serum Ferritin in ng/ml	Deferasirox n = 35		Deferiprone n=33		Grand total	
	No.	%	No.	%	No.	%
1000-3000 ng/ml	9	25.71	8	24.24	17	25
3001-5000 ng/ml	12	34.39	14	42.42	26	38.23
5001-7000 ng/ml	10	28.57	6	18.18	16	23.53
>7000 ng/ml	4	11.43	5	15.15	9	13.24
Total	35	51.47	33	48.53	68	100

$\chi^2 = 1.266$, df = 3, p = 0.737, Non significant

T_{66} is t-value at degree of freedom 66. p-value of all the parameters of study are >0.05 (non-significant) except SGPT level where difference is significant between the two groups of therapy (Table 7).

DISCUSSION

This study was a hospital based prospective, comparative, observational study, conducted to compare the effectiveness, safety and economy of the two novel oral iron chelator; deferasirox and deferiprone in iron overloaded children with β-thalassaemia.

Age wise distribution of the patients

Out of total 68 patients (35 in deferasirox group and 33 in deferiprone group) mean age of the patients in deferasirox group was 10.82±4.47 (range 4-24 years) and in deferiprone group was 9.72±5.70 years (range 3-30 years). Further distribution in different age group reveals the majority of the cases in 3-10 years age group (52.94%) followed by 11-20 years (44.12%). Statistical analysis reveals a non-significant difference of age in both the group. Thus, both the drug group patients were homogenous in age wise distribution. It excludes the possibility of any variation in the response of drugs due to age differences.

Serum ferritin as an index of effectiveness of oral iron chelator

Table 1 reveals comparable baseline ferritin level in both the groups. It eliminates the possibility of a drug working with a different base line burden. The enrolled patients were characterized by a high iron burden despite the previous chelation therapy which is comparable to population studied in various studies.[6]

All the patients enrolled in study were having a high serum ferritin level despite the previous chelation therapy with one of the oral iron chelator for more than a year. With the regular compliance and 6months follow up in the study period serum ferritin level get reduced to a significant level in both the groups. At the time of inclusion, study population was characterized by a mean serum ferritin value of 4735.11±450.01 SE in deferasirox and 4315.97±340.75 SE in deferiprone group. After one month it changed to 4578.66±371.96 in deferasirox and 4388.82±316.16 in deferiprone group (Table 3 and 4).

Table 4: Paired t for Serum Ferritin at different period of study in deferasirox and deferiprone group.

Oral iron chelator	Value (Mean ±SE)	Baseline Vs 1 month		Baseline Vs 3 month		Baseline Vs 6 month	
Deferasirox (N= 35)	Serum ferritin ng/ml	4735.11±450.01	4578.66±371.96	4735.11±450.01	4295.60±377.37	4735.11±450.01	4578.66±371.96
	Reduction in ferritin	156.45±111.07		439.51±143.52		495.2±187.5	
	T-value	1.41		3.06		2.64	
	P-value	0.168		0.004		0.012	
Deferiprone (N= 33)	Serum ferritin ng/ml	4315.97±340.75	4388.82±316.16	4315.97±340.75	3988.88±349.84	4315.97±340.75	3999.76±269.23
	Reduction in ferritin	-72.85±72.14		327.09±130.4		316.21±160.59	
	T-value	-1.01		2.51		1.97	
	P-value	0.32		0.017		0.058	

After three month the mean serum ferritin reduces to 4295.60±377.37 in deferasirox and 3988.88±349.84 in deferiprone group and after six months to 4578.66±371.96 in former and 3999.76±269.23 in latter group. The reduction in serum ferritin is statistically highly significant in both the groups after 3 and 6 months (P<0.05) (Table 5).

Most of the randomized controlled studies had shown that serum ferritin levels were maintained at a dose of 20mg/kg/day of deferasirox and consistently fall at a dose of 30 mg/kg/day.[7-11] A comparable reduction in ferritin level is also obtained with deferiprone.[12-14] The results of our study are also in agreement to the referred studies reflecting a significant reduction in ferritin level. The initial first month of follow up did not show a significant reduction in both the group. However, the three months and six months period were sufficient to reduce the level to a significant extent.

Table 5: Comparison of two sample T for serum ferritin at different period of study between deferasirox and deferiprone group.

	Deferasirox (N= 35) (ng/ml)			Deferiprone (N= 33) (ng/ml)			T_{66}	P
	Mean	SD	SEM	Mean	SD	SEM		
Base Value*	4735	2662	450	4316	1957	341	0.74	0.461
Value after 1 month	4579	2201	372	4389	1816	316	0.39	0.699
Value after 3 month	4296	2233	377	3989	2010	350	0.60	0.553
Value after 6 month	4240	1908	323	4000	1547	269	0.57	0.570

* Values are rounded off to the full digit. T66 is t-value at degree of freedom 66. p-value at all the stages of study are >0.05, indicative of a non-significant difference between the two groups of therapy.

Table 6: Distribution of the cases according to the reported adverse effects.

Adverse Effect	Deferasirox (n=35)		Deferiprone (n=33)		Grand total	
	No.	%	No.	%	No.	%
Gastrointestinal	6	17.14	4	12.12	10	14.71
Arthralgia	1	2.85	4	12.12	5	7.35
Skin rashes	3	8.57	-	-	3	4.41
Other (Fever)	-		1	3.03	1	1.47
Total	10	14.71	9	13.23	19	27.94

$\chi^2 = 6.164$, df = 3 p = 0.1039, Non significant

Table 7: Comparison of two sample T for base line hemoglobin, total WBC count, creatinine and SGPT level at the time of inclusion of the patient between deferasirox and deferiprone group.

	Deferasirox (n=35)			Deferiprone (n=33)			T_{66}	P
	Mean	SD	SEM	Mean	SD	SEM		
Hemoglobin* (g/dL)	7.32	1.5	0.25	7.54	1.15	0.20	-0.67	0.505
Total WBC count (cumm)	6805	2900	490	6218	3187	555	0.79	0.431
Creatinine (mg/dL)	0.637	0.122	0.021	0.636	0.121	0.021	0.05	0.963
SGPT	63.4	11.2	1.9	81.7	14.9	2.6	-5.69	< 0.05

The cohort of patients treated with oral deferiprone showed less myocardial iron burden and better global systolic ventricular function compared to the patients treated with oral deferasirox or subcutaneous desferrioxamine.[15] The effectiveness of deferiprone was reported by Cohen and colleagues in a 4-year observational trial.[16]

It included 187 patients with a mean age of 18 (range 10-41). Deferiprone was quite effective in lowering serum ferritin over the study period. In those patients with more severe iron overload the ferritin level dropped from 3661±1862mcg/L to 2630±1708mcg/L. Patients with lower initial ferritin levels had less dramatic results.

Hemoglobin status of the patients

Mean hemoglobin was not in palliative range compared to ideal well hyper-transfused patients in most of resource rich situations. It was not at par as studied in most of

randomized controlled studies.[7-11] Base line mean ± SD Hb at the time of enrolment was 7.32±1.5 in deferasirox group and 7.74±1.07 in deferiprone group. The most likely reason for this reduced Hb level could be a poor compliance on the part of patient, which gets a ground with the observation of significant raise in mean Hb level when patients were regularly followed for the therapy with a proper education for the regularity in the therapy. After 6 months of regular follow up mean Hb raised significantly to 8.77±0.84 and 8.69±0.9 respectively. Significant rise in hemoglobin associated with a decline in ferritin level indicates the efficacy of both the drugs to chelate the iron and to reduce the iron burden.

Incidence of adverse effects

Both the drugs were well tolerated with manageable side effects. The adverse events like G.I. upsets including abdominal pain, nausea, vomiting and diarrhoea were observed to the extent of 17.14 % with deferasirox and 12.12% with deferiprone. However, no interruption of therapy or decrease in dosage was necessitated because of these symptoms (Table 6).

Arthralgia was reported by 2.85% patient in deferasirox group and 12.12 % in deferiprone group. However, there was no significant swelling of joints and the pain subsided in all the patients with analgesics and assurance.

Skin rashes were observed in three patients (8.57%) in Deferasirox group. All the side effects gradually decreased on follow up. There was no discontinuation of therapy due to side effects of drug. This study was consistent with previous observations in children with β-Thalassaemia major.[9] In Federico's study it was seen that deferasirox is well tolerated and side effects is not significant.[17] The listed side effects for this drug was nausea, vomiting, diarrhea, abdominal pain and skin rash however, increased levels of liver enzymes and serum creatinine were not observed. Cappellini et al, observed a mild increase in creatinine level in their study but deferasirox was well tolerated by patients and significant impact on reducing the amount of liver iron and serum iron.[18] In Vichinsky et al, Study conducted in patients with sickle cell, side effects such as nausea, vomiting and abdominal pain for deferasirox was reported.[19] But the researchers noted that mild increase of creatinine and liver enzymes has occurred after taking deferasirox. Treatment in 11.4% of patients in deferasirox group and 11.1% in deferoxamine group was discontinued because of side-effects in their study. Various studies reveal deferasirox as a well tolerated drug.[20,21]

Adverse effects associated with its use are for the most part mild and self-limiting. The development of adverse effects seems to be idiosyncratic and not dose dependent. Gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain, as common and have been reported in up to 1/3 of patients. These symptoms are often mild, self-resolving, and typically do not necessitate discontinuing therapy. Skin rashes (maculopapular) are another common adverse effect that is reported in up to 10% of patients. Again, these rashes are mild and resolve with drug discontinuation. With deferiprone, gastrointestinal symptoms such as nausea, vomiting, and abdominal pain have been reported in up to 33% of patients.[22]

Arthralgias and arthritis have been associated with Deferiprone.[16] It has been reported to occur in 30-40% of patients. Some studies large trials have reported a much lower incidence of 4%. Large joint, such as the knees, are more commonly affected. 50% of cases develop with the first year of therapy. Symptoms are typically mild and resolve with discontinuation. Any special side effects were not observed with any of these two drugs.

Parameters to assess the safety on leucocytes, kidney and liver

White blood cell count and creatinine were within normal range in all patients before the study and there was no significance difference between two groups. Leukopenia was not seen in any of the patient in any group. Deferiprone is associated with several adverse effects. The most concerning is agranulocytosis. In clinical trials neutropenia has been reported in up to 5% with agranulocytosis typically reported in <1%.[23] Patients that develop agranulocytosis typically do so during the first year of therapy, but it has been reported up to 19 months after deferiprone initiation. It has yet to be elucidated if the neutropenia and agranulocytosis is an idiosyncratic reaction or a dose-related direct myelotoxicty. Frequent monitoring of white blood cell counts is recommended. consideration should be given to avoiding deferiprone in patients with myeloproliferative disorders.

Higher baseline SGPT observed in this study is due to disease spectrum of thalassaemia itself i.e. hepatic hemochromatosis. Elevations of liver transaminases have been reported during deferiprone treatment. An early trial suggested that deferiprone was associated with progressive liver fibrosis.[24] Liver enzyme elevations tend to be mild and reversible. In a recent pediatric trial 12% of patients experienced a mild elevation in ALT.[25] Only 1 patient had an elevation greater than twice the upper limit of normal at 3 and 6 months. Deferiprone was continued in all patients without incident. The contribution of deferiprone to worsening liver disease is often difficult to determine because of the natural progression associated with chronic iron overload. Other co-existing diseases, such as hepatitis, or other medications associated with hepatotoxicity contribute to the difficulty of assigning culpability to deferiprone. No significant rise in serum creatinine was noted to the extent of interruption of therapy (Table 7).

The most concerning adverse effect with deferasirox is acute renal insufficiency.[21, 22] This has been reported in up to 1/3 of patients in trials. Generally, the elevations are mild and transient, however up to 10% of patients can have an increase greater than 33% above baseline. These abnormalities almost always resolve following drug

discontinuation. Our study does not report significant rise in creatinine level, perhaps it needs a long duration follow-up.

CONCLUSION

Total 68 patients, 35 in deferasirox and 33 in deferiprone group were studied. At the time of inclusion, study population was characterized by a mean serum ferritin value of 4735.11±450.01 SE in deferasirox and 4315.97±340.75 SE in deferiprone group. After one month the mean serum ferritin increases to 4578.66±371.96 in deferasirox and 4388.82±316.16 in deferiprone group. After three month the mean serum ferritin reduces to 4295.60±377.37 in deferasirox and 3988.88±349.84 in deferiprone group. After six month the mean serum ferritin reduces to 4578.66±371.96 in deferasirox and 3999.76±269.23 in deferiprone group. Reduction in serum ferritin is statistically highly significant in both the groups after 3 and 6 months ($P < 0.05$). Base line mean ±SD hemoglobin at the time of enrollment was 7.32±1.5 in deferasirox group and 7.74±1.07 in Deferiprone group. After 6 months of regular follow up mean hemoglobin was raised significantly up to 8.77±0.84 and 8.69±0.9 respectively in both the groups. There were no significant changes in total White blood cells count, creatinine and SGPT level with the six months of study. About 19 (28%) patients reported side effects, 14.71 % with deferasirox and 13.23% with deferiprone but none of them required interruption of therapy due to them. The adverse events like G.I. upsets including abdominal pain, nausea, vomiting and diarrhea were observed to the extent of 17.14 % with deferasirox and 12.12% with deferiprone. Thus, we conclude that deferasirox and deferiprone are well tolerated, have few adverse effects and almost has a comparable effect in lowering of the patient's serum ferritin level.

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