



Original Research Article

A study to compare the efficacy, safety & economy of oral iron chelators in patients with Thalassaemia major

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Abstract

Background: *Thalassaemia 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 erythropoiesis and hemolysis. It requires frequent blood transfusion and so becomes the most common chronic iron overloading disorder. Excess iron deposits may be in various tissues of the body, particularly the liver, heart, and endocrine organs.*

Materials and Methods: *Frequent serum ferritin values at the time of enrolment 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. 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 Thalassaemia major with more than fifteen blood transfusions in a year.*

Results: *Base line mean \pm 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 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 month 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. Arthralgia was reported by 2.85% patient in Deferasirox group and 12.12 % in Deferiprone group. Skin rashes were observed in three patients (8.57%) in Deferasirox group. For a patient of 20 Kg, per month average acquisition cost of Deferasirox is Rs.1200/ and for Deferiprone is Rs. 620.

Conclusion: 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. Deferiprone is more cost effective but needs a strict control on compliance owing to requirement in three divided doses per day. However in view of limitations to our study further well designed, randomized controlled trials with better sophisticated parameters of iron load are required to put a final remark on the most appropriate oral iron chelator suitable for the Indian population.

Keywords: *Thalassemia major, Oral iron chelators, Deferasirox, Deferiprone, Hemoglobin, Ferritin, Efficacy, Safety, Pharmacoeconomy.*

Introduction

Thalassemia is a heterogeneous group of disorders characterized by genetically determined reduction in rate of synthesis of normal globin chain of hemoglobin. It's an autosomal recessive, single gene disorder seen all over the world.¹ It is estimated that about 100 million asymptomatic heterozygous Thalassaemia carriers are present worldwide and >1,00,000 Thalassaemia babies are born annually. Of these 80% live in Middle East and south East Asia. One baby with Thalassaemia is born every hour!

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 erythropoiesis and hemolysis.² 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.³ 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.⁴ Evidence of iron overload is manifested as elevated liver iron concentration

(LIC) values and elevated serum ferritin levels. LIC values above 15 mg Fe/g dry weight, and serum ferritin values above 2500 mcg/L⁵ increases the risk of iron-induced cardiac disease.

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.⁶ An iron chelator, deferoxamine is being used since last few decades. Deferoxamine is expensive and poorly absorbed orally and needs i/v or subcutaneous infusion. Hence there's a problem of compliance on long term.

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 & rise in creatinine level. Because of oral single dose and acceptable tolerance profile this drug is frequently prescribed in patients with Thalassaemia. Untreated transfusional iron overload in Thalassaemia major is fatal in the second decade of life, usually as a result of cardiac complications.^[7, 8]

Iron overload also causes pituitary damage, leading to hypogonadism and poor growth. Endocrine complications, namely diabetes, hypothyroidism and hypoparathyroidism are also seen. Liver disease with fibrosis and eventually cirrhosis, particularly if concomitant chronic hepatitis is present, is also a serious complication. This study was planned to evaluate all the cases of β Thalassaemia major in Index Medical College, Hospital and research centre, Indore and in Thalassaemia Society, Indore, already receiving one of the oral iron chelators for a comparison among the efficacy, safety and economy of Deferasirox & Deferiprone to establish the better option in an Indian scenario.

Aims & Objectives

- To assess the degree of iron chelation produced by Deferasirox or Deferiprone by monitoring their ability to lower serum ferritin level.
- To assess the adverse effects reported by patients on Deferasirox and Deferiprone
- To monitor the potential of blood, hepatic or renal dysfunction with Deferasirox and Deferiprone by monitoring their effects on blood count, serum SGPT and serum creatinine.
- To monitor for other adverse events with constant follow up of six months for the symptoms indicating any adverse event.
- To analyze the cost effectiveness with either drug in relation to therapeutic objective.

Materials & 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 Thalassaemia 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 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

Patient Selection: It was based on the following inclusion and exclusion criteria.

Inclusion criteria

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

Exclusion criteria

1. Children below 2 years of age.
2. 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 enrolment 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

Parameters to evaluate economy of therapy

- Acquisition cost (purchase/dispensing/storage)
- Administration cost
- Monitoring cost
- Adverse effects and its treatment cost
- Cost of treatment failure

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.

It is not an experimental or interventional study so there was no involvement of any animal or any new drug molecule or newer therapy. Prior approval of the synopsis was taken from the Institutional Research Committee and Institutional Review Board of Index Medical College for this work.

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 Thalassaemia 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 Thalassaemia major with more than fifteen blood transfusions in a year. They were having serum Ferritin levels more than 1000 ng/ml at the time of inclusion in the study. The baseline clinical & 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 75 mg/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.

Table 1: Baseline Patient Characteristics

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

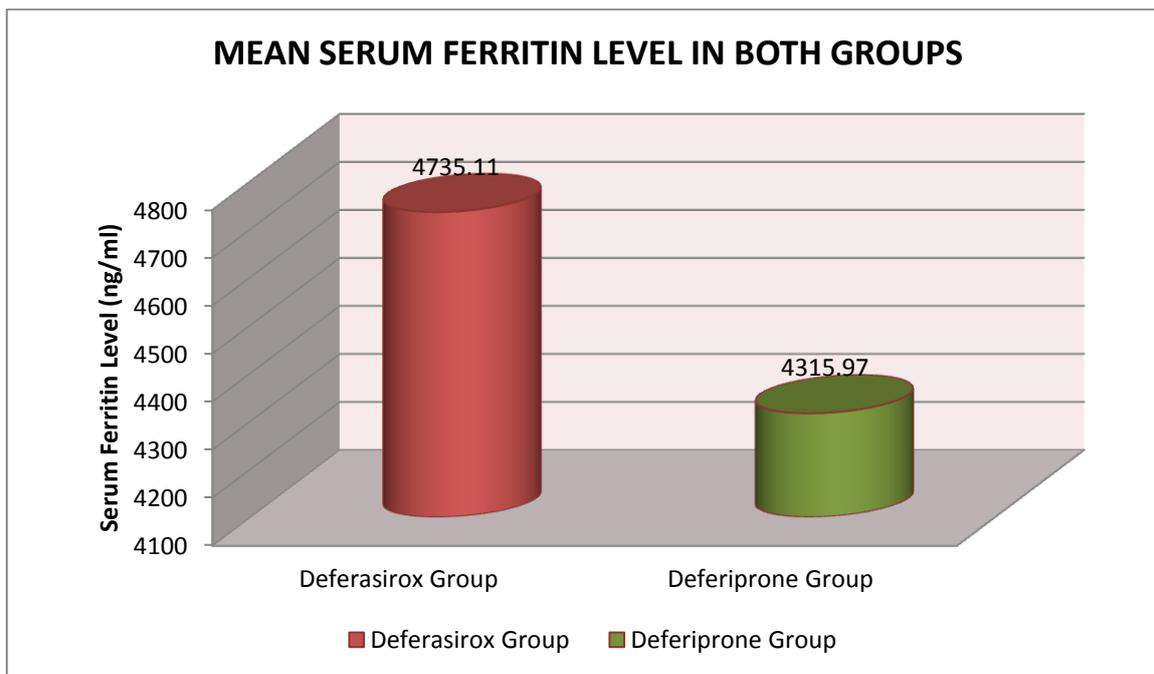


Figure 1: Mean serum ferritin level in both study groups

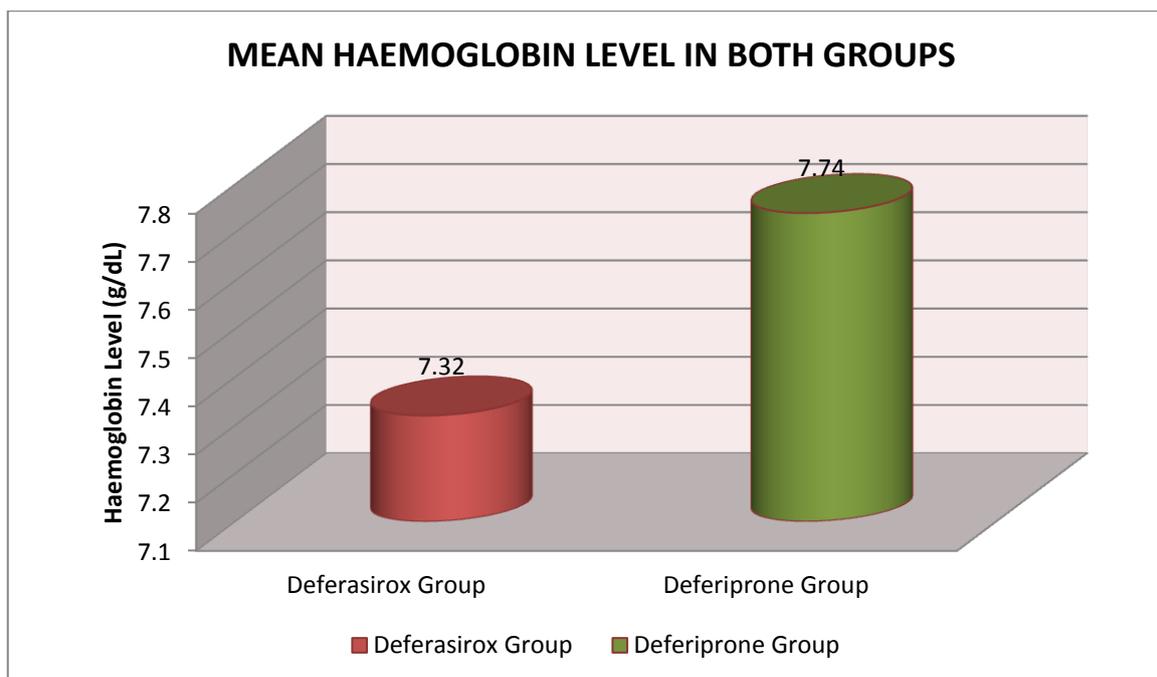


Figure 2: Mean haemoglobin level in both study groups

Table 2: Age wise distribution of the cases in different study group

Age Group	Deferasirox [n = 35]		Deferiprone [n=33]		Grand total	
	No.	%	No.	%	No.	%
3-10 years	18	51.43	18	54.54	36	52.94
11-20 years	16	45.71	14	42.42	30	44.12
21-30 years	1	2.86	1	3.03	2	2.94
Total	35	51.47	33	48.53	68	100

$\chi^2 = 0.075, df = 2, p = 0.9632, Non\ significant$

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.

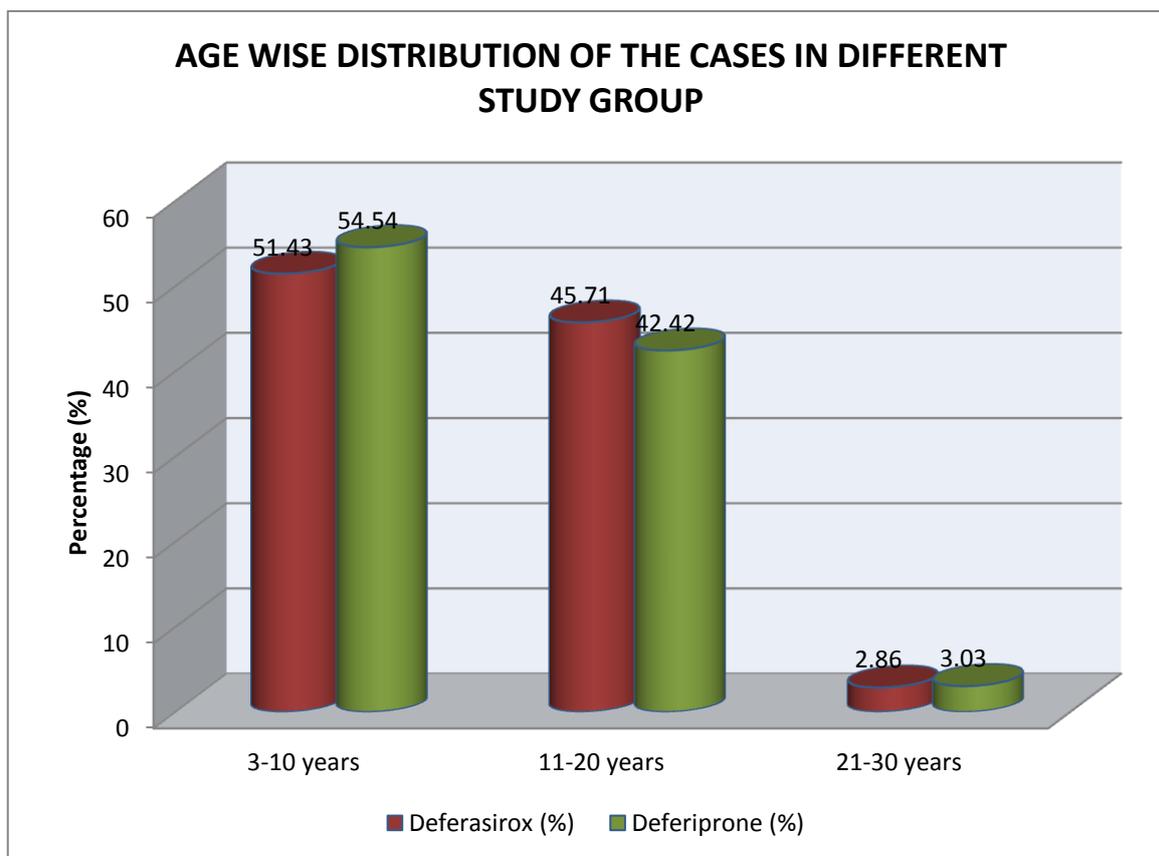


Figure 3: Age wise distribution of the cases in different study group

Table 3: 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

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

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).

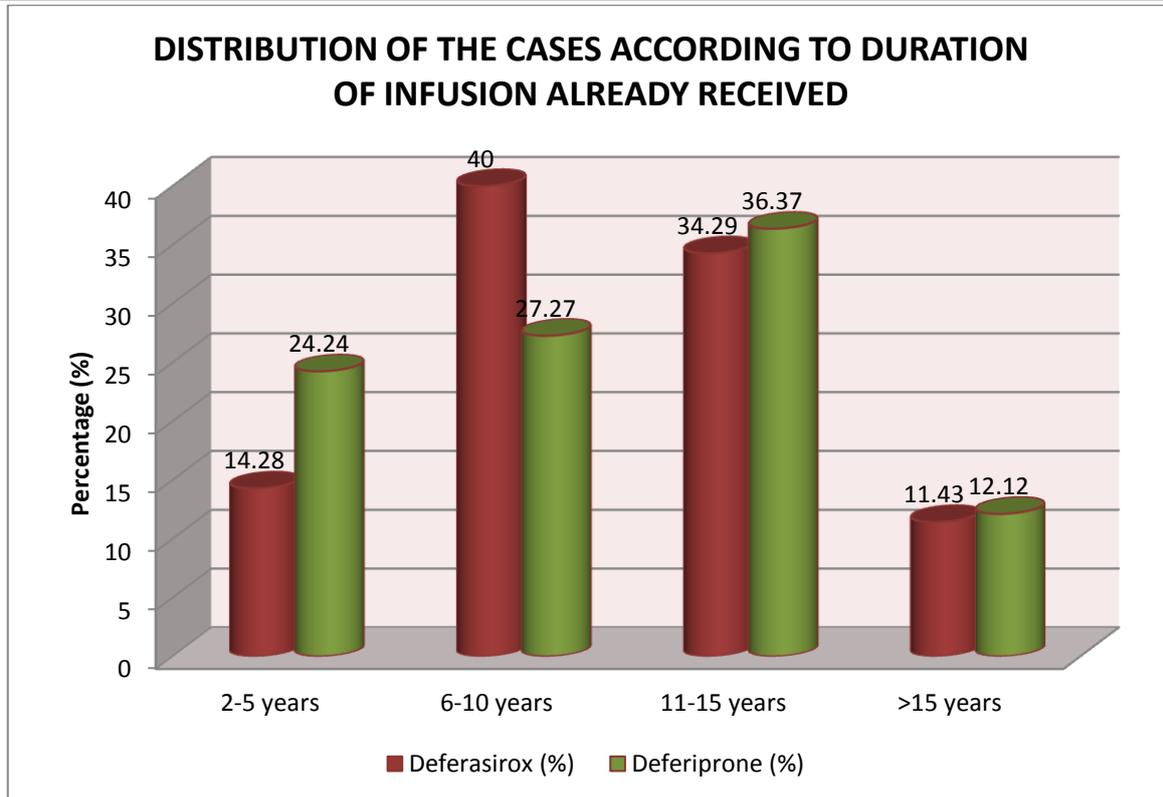


Figure 4: Distribution of the cases according to duration of infusion already received

The distribution of cases in both the group according to the mean duration of transfusion already received was not significant. Before the study, the mean hemoglobin level was 7.32 ± 1.50

mg/dL ranged from 4 to 10.8 in Deferasirox group and 7.54 ± 1.15 mg/dL ranged from 5.5 to 8.8 in Deferiprone group.

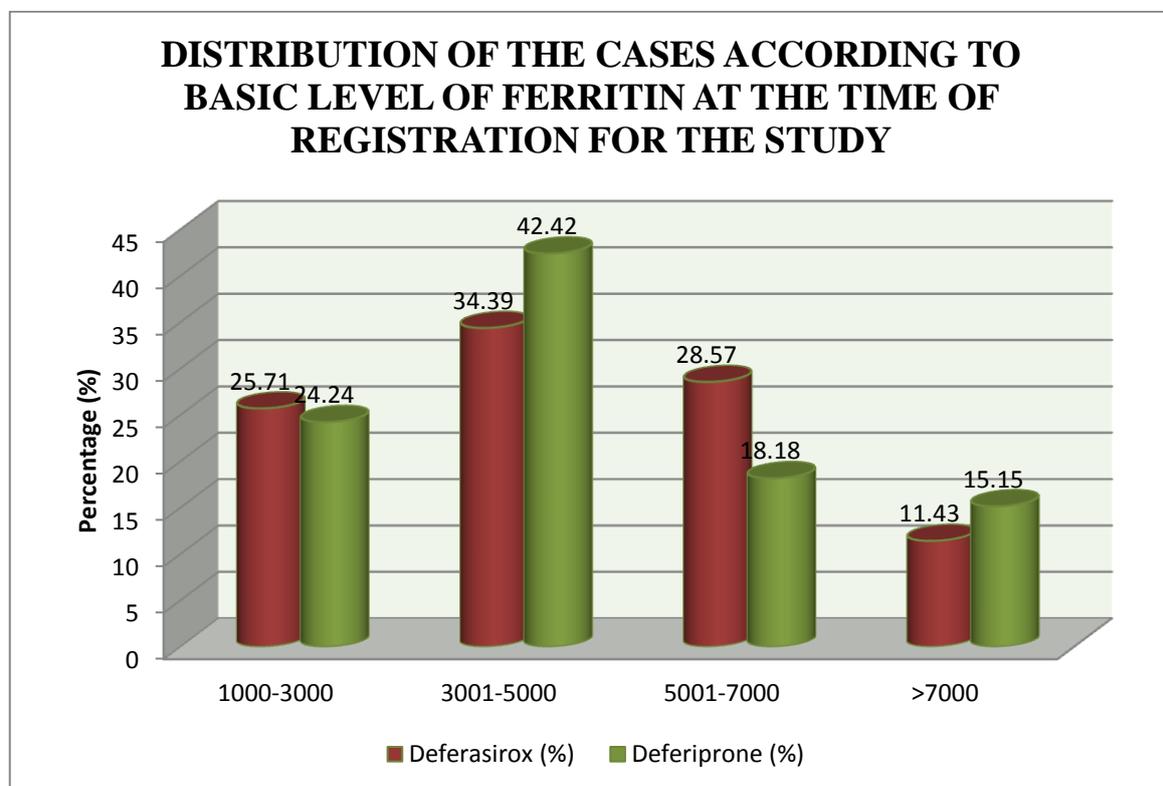


Figure 5: Distribution of the cases according to basic level of ferritin at the time of inclusion in the study

Table 4: Paired T for Serum Ferritin at different period of study in Deferasirox & Deferiprone group

Oral Iron Chelator	Value	Baseline Vs 1 month		Baseline Vs 3 month		Baseline Vs 6 month	
Deferasirox (N= 35)	Serum Ferritin ng/ml (Mean ± SE)	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 (Mean ± SE)	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 (Mean ± SE)	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 (Mean ± SE)	-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	

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 & 6 months (P < 0.05).

Table 5: Comparison of Two sample T for Serum Ferritin at different period of study between Deferasirox & 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

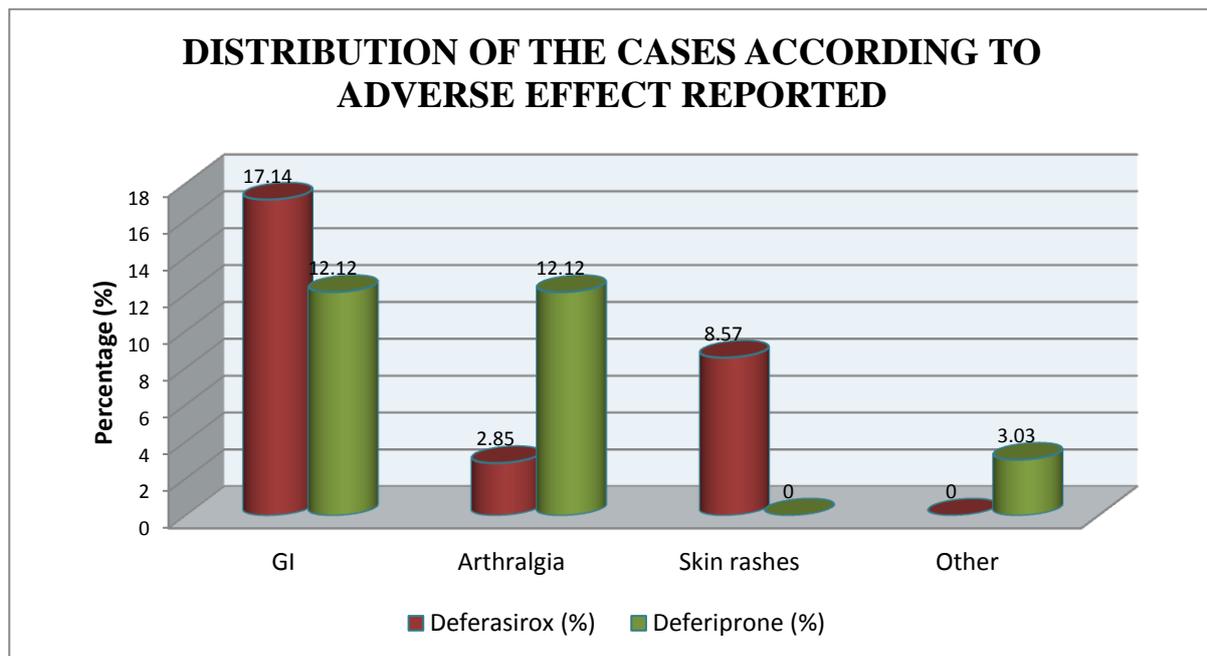


Figure 6: Distribution of the cases according to the reported adverse effects

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.

Experiences with these newer drugs are of few years throughout the world (approx. 10-12 years for Deferiprone and 7-8 years for Deferasirox).

The subjects of this study were the patients from Index Medical College, Hospital and research centre, Indore and patients in Hospitals associated with Thalassaemia 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]

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.

Distribution of cases according to body weight

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) to show any variation in the progress of the disease and the drug effect.

Distribution of the cases according to duration of infusion already received

The distribution of cases in both the group according to the mean duration of transfusion already received was not statistically significant. It eliminates the chances of differences in both the study group due to a difference in total period of exposure to transfusion.

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.^[9]

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 6 months 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.

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 & 6 months (P < 0.05).

Most of the randomized controlled studies had shown that serum ferritin levels were maintained at a dose of 20 mg/kg/day of Deferasirox and consistently fall at a dose of 30 mg/kg/day.^[10-14] A comparable reduction in ferritin level is also obtained with Deferiprone.^[15-17] 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 was sufficient to reduce the level to a significant extent.

Deferiprone has been reported to remove cardiac iron efficiently but not so efficient in controlling hepatic iron content.^[18] However, John C Wood et al^[19] shows both the drugs equally effective in removal of cardiac iron load in a gerbil animal model, but Deferasirox removed more hepatic iron for a given cardiac iron burden.

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.^[20]

The effectiveness of Deferiprone was reported by Cohen and colleagues in a 4 year observational trial.^[21] 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 ± 1862 mcg/L to 2630 ± 1708 mcg/L. Patients with lower initial ferritin levels had less dramatic results.

Question of great concern is whether serum ferritin is so reliable for determining outcome of iron chelation and formulating policies? It is not a completely reliable marker for this purpose. However it is easy to perform, noninvasive and readily available and cheaper option. Its utility has been studied along with other parameters in various studies.^[9] We also relied on serum ferritin for estimation of iron loading status. We have not done novel methods like T2* MRI or LIC for same; which can tell us more accurately whether iron from the tissues is decreasing or not.

Hemoglobin status of the Patients

Mean hemoglobin was not in palliative range compared to ideal well hypertransfused patients in most of resource rich situations. It was not at par as studied in most of randomized controlled studies.^[10-14] Base line mean \pm SD Hb at the time of enrollment 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 diarrhea 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.

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 were consistent with previous observations in children with β -Thalassaemia major.^[12] In Federico's study^[22] it was seen that Deferasirox is well tolerated and side effects is not significant. 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^[23] 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. In Vichinsky et al. study^[24] conducted in patients with sickle cell, side effects such as

nausea, vomiting and abdominal pain for Deferasirox was reported. 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^[25, 26] reveal Deferasirox as a well tolerated drug. 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.^[27]

Arthralgias and arthritis have been associated with Deferiprone.^[22] 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 within 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 & 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^[28] neutropenia has been reported in up to 5% with agranulocytosis typically

reported in <1%. 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 myelotoxicity. 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. We chose to continue the drug with high serum SGPT also. A few patients showed a rise in SGPT but it was not consistent and significant. Few of them showed decreasing trend of SGPT towards baseline at follow up. No one required discontinuation of therapy due to it.

Serum SGPT values were high in highly iron overloaded children. There was decrease in serum SGPT at regular course after a period of 6 months. In condition of high iron overload there is severe hepatic hemochromatosis with more and more number of hepatocytes are laden with iron. This causes increase in serum SGPT in these children due to inflammation. However after good iron chelation, as iron is removed from the hepatocytes; inflammation of these cells also decreases resulting in decrease in SGPT levels. This correlation of serum SGPT and serum ferritin is an important outcome. Exact iron loading of organs by doing liver iron concentration after a liver biopsy or by doing T2* MRI for cardiac iron overload is not always possible in resource limited situations; monitoring SGPT values can be a crude guide. However more research work needs to be done in this field.^[29]

Elevations of liver transaminases have been reported during Deferiprone treatment. An early trial suggested that Deferiprone was associated with progressive liver fibrosis.^[29] It was a small trial involving 19 patients of which 5 were considered to have progression of liver fibrosis.

Subsequent trials involving larger numbers of patients have not demonstrated liver toxicity. Liver enzyme elevations tend to be mild and reversible. In a recent pediatric trial 12% of patients experienced a mild elevation in ALT.^[30] 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.

The most concerning adverse effect with Deferasirox is acute renal insufficiency.^[25, 26] 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.

Comparison of the Economy

Total cost of therapy is more with Deferasirox as compared to Deferiprone treatment. Monthly acquisition cost (for a patient of 20 Kg) for Deferasirox is Rs. 1200/, while for Deferiprone it is 620/. This cost includes the cost of purchase of the medicine with consideration that cost of follow up with therapy is almost same with both the drug. Incremental cost per month with Deferasirox is 580 with no significant incremental effectiveness. Some concession on drug purchase and monetary incentives for investigations is done by manufacturers in developing countries.

Cost-effective analysis of the present study showed treatment with Deferiprone is economical than with Deferasirox. However it needs thrice a day therapy so patient needs a proper education

for the compliance. Good compliance could be ensured by repeated counselling. Also the fear for occasional agranulocytosis needs further care and regular follow up with WBC count.

Limitations to the Study

This was an observational non-interventional study. Numbers of subjects followed in this study were less (35 in Deferasirox and 33 in Deferiprone). Duration and compliance with previous iron chelation therapy was not considered owing to poor record maintained by the patient. First, the duration of the study was significantly shorter to put a final remark on the long term efficacy or safety. More authentic methods like LIC, T2 *MRI for tissue iron estimation have not been used in this study due to financial strain.

Conclusion

The present study was a prospective, comparative, observational study with inclusion 68 patients of Thalassaemia from Index Medical College, Hospital and research centre, Indore and patients in Hospitals associated with Thalassaemia 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 these patients were being managed according to Thalassaemia international federation guidelines (2007). Total 68 patients, 35 in Deferasirox and 33 in Deferiprone group were studied. 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). Mean 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). Before the study, the mean hemoglobin level was 7.32 ± 1.50 mg/dL ranged from 4 to 10.8 in Deferasirox group and 7.54 ± 1.15 mg/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. 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 & 6 months ($P < 0.05$). Base line mean \pm 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 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 month 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. Arthralgia was reported by 2.85% patient in Deferasirox group and 12.12 % in Deferiprone group. Skin rashes were observed in three patients (8.57%) in Deferasirox group. For a patient of 20 Kg, per month average acquisition cost of Deferasirox is Rs.1200/ and for Deferiprone is Rs. 620. 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. Deferiprone is more cost effective but needs a strict control on compliance owing to requirement in three divided doses per day. However in view of limitations to our study further well designed, randomized controlled trials with better sophisticated parameters of iron load are required to put a final remark on the most appropriate oral iron chelator suitable for the Indian population.

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