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Comparison of Compliance, Convenience, Satisfaction and Life Disturbances among Transfusion Dependent Beta-Thalassemic Children On Iron Chelation Therapy: An Observational and Cross-Sectional Study

Shambhavi Sharan[1], Sunil Gomber[2]

[1]Consultant, Department of Paediatrics, Mahavir Vatsalya Aspatal, Patna,
[2]Professor and HOD, Department of Paediatrics, UCMS, New Delhi

ABSTRACT

Objective: The gold standard of iron chelation has been Deferoxamine based on its established efficacy in multiple studies. Deferiprone and Deferasirox may have better compliance and satisfaction in view of the oral route of administration. The present study was designed to compare the compliance and satisfaction level of Deferasirox versus Deferoxamine and Deferiprone in multi-transfused thalassemic children with iron overload.

Method: In this cross-sectional, observational study 55 patients of thalassemia major on iron chelation at Thalassemia Centre of a tertiary care hospital were enrolled. The compliance, convenience, satisfaction and life disturbances were compared among the three iron chelation.

Results: 20 patients each received Deferoxamine and Deferiprone whereas 15 received Deferasirox. The decrease in ferritin was comparable. Patients on Deferiprone and Deferasirox found it more convenient with less life disturbances than Deferoxamine ($p<0.01$, $p<0.001$). Both Deferiprone and Deferasirox did not show any significant difference in convenience and life disturbances. The three groups did not differ significantly in compliance and satisfaction level.

Conclusion: Considering the comparable efficacy of the three modalities and more convenience with Deferasirox and Deferiprone along with lesser life disturbances than DFO, the oral iron chelators can be used as a preferred choice as single use or in combination. Deferasirox may be the best option among all three in view of the convenience with once daily dosing, lesser life disturbances and no significant side effects.

Keywords: *Compliance, Convenience, Satisfaction, Life disturbances, beta-thalassemic children, Iron chelation therapy*

INTRODUCTION

In India, it is estimated that nearly 8000-10000 new homozygous thalassemics are born every year presenting with anemia and failure to thrive in the latter half of first year, majority of whom are β- thalassemics. [1] Regular blood transfusion has improved the quality of life in patients with thalassemia major but the penalty of this success has been the emergence of transfusional iron overload, which leads to cardiomyopathy, liver fibrosis and endocrinopathies. [2] Beginning the iron chelation therapy early in life can help ensure good health in the long term and survival well into adult life. [3] The gold standard of chelation therapy remains the use of deferoxamine (DFO) because its long-term efficacy has been extensively documented in large multicenter

Corresponding author
Dr. Shambhavi Sharan,
Department of Paediatrics, Mahavir Vatsalya Aspatal,
Patna, Mob: 08051665511,
Email: sharan.shambhavi@gmail.com
manu072@gmail.com

trials. [4,5] Due to challenges of administering it by sub-cutaneous or intravenous infusion, compliance is often poor resulting in limited efficacy. [6,7]

Furthermore, compliance of patients was improved with the use of combination therapy because fewer painful injection of deferoxamine were required. As Deferasirox is a once-daily oral treatment, improvements in compliance compared with DFO may lead to improved patient outcomes and lower treatment costs. The availability of this effective and generally well tolerated oral therapy represents a significant advance in the management of transfusional iron overload.

The success of any therapy is determined by its ease of administration, satisfaction of the patient and compliance with the drug. In view of the aforementioned points the present study was designed to compare the Compliance, Convenience, Satisfaction and Life disturbances among the three Iron Chelators; Deferoxamine (DFO), Deferiprone (DFP) and Deferasirox (DFX).

MATERIAL AND METHOD

This was an observational and cross-sectional observational study conducted at the Thalassemia Day Care Centre in the Department of Paediatrics, University College of Medical Sciences and Guru Tegh Bahadur Hospital, Delhi from December 2008 to April 2010. The study protocol was approved from Institutional Ethics Committee of University College of Medical Sciences, Delhi. Informed consent was taken from the parents or guardians of the patients. Multi-transfused thalassaemic children >2 years of age and either sex and with serum ferritin >1500ng/ml were included in this study. Patients who had been transfused less than 10 units of blood as a part of their management were excluded.

Method of Selection: 55 children getting repeated transfusions and chelation were randomized into three chelation groups.

Group 1: This group included 20 children receiving sub-cutaneous deferoxamine in the dose of 20-40 mg/kg/day over a period of 8-10 hours, five days a week.

Group 2: This group included 20 children receiving oral deferiprone in the dose of 75-100mg/kg/day in 2-3 divided doses daily.

Group 3: This group included 15 children receiving oral deferasirox in the dose of 20-30mg/kg/day once daily.

A written informed consent was taken from all participants. Case record forms regarding personal information, examination findings and treatment details were filled. A single observer recorded all these findings to minimize observer bias. A questionnaire for assessing the convenience, compliance, satisfaction and life disturbances among the various groups was completed by the patients >12 years or the parents of children <12 years of age.

Two trained individuals who were blinded to the Iron Chelation Therapy (ICT) groups, interviewed the patients or their parents. Serum ferritin was also tested. All these assessments were done at the end of the study.

Assessment of compliance was based on the responses given on a 4-point Likert scale of always, most of the times, sometimes, never (Annexure I).

The patients' rated their convenience on a 4 -point Likert scale of very convenient, convenient, inconvenient and very inconvenient (Annexure I).

Assessment of satisfaction level among the groups was recorded on 4-point Likert scale of Very satisfied, Satisfied, Dissatisfied and Very Dissatisfied.

For determining life disturbances among the groups a set of 3 questions were constituted and patients answered on a 4-point Likert scale of Very satisfied, Satisfied, Dissatisfied and Very Dissatisfied

The psychometric properties (internal consistency and reliability) were checked. Cronbach's alpha was applied for checking the internal consistency which gave a value of 0.752. Values > 0.70 can be considered satisfactory. Patients were also asked regarding pain and irritation at the injection site of Deferoxamine, painful knees in Deferiprone group and any gastrointestinal disturbances or skin rash in Deferasirox group.

STATISTICAL ANALYSIS

The study data was analyzed using the GraphPad software. The change in serum ferritin values in the three groups was assessed using One-way ANOVA. One-way ANOVA was also applied to the satisfaction questionnaire followed by Tukey test to compare the mean total score among the three groups.

RESULTS

Of the 55 patients 20 were in the Deferoxamine group, 20 in Deferiprone group and 15 in Deferasirox group. The mean age was 10.039 years (2.5- 26 years). 52.73% patients were females.

Table 1: Distribution of number of cases, mean age, sex and serum ferritin in different groups (n=55)

Group	Mean Age±SD (yrs)	Range(yrs)	Male	Female
1 (n=20)	9.7±4.42	3-19	8	12
2 (n=20)	10.85±6.14	2.5-26	11	9
3 (n=15)	9.57±6.77	2.5-23	7	8
Total (n= 55)	10.082±5.69	2.5-26	26	29

All patients enrolled into the study were from 2.5- 26 years of age. There was no significant difference in the mean age.

Table 2: Mean serum ferritin values and Fall in mean serum ferritin in each group at the start and end of the study

Group	Serum Ferritin (ng/ml) Mean±SD		
	At the start of the study	At the end of the study	Change (Mean)
1 (n=20)	4230.99±1872	4151.28±1686.5	79.71
2 (n=20)	3461.84±1600.4	3445.03±1570	16.81
3 (n=15)	4835.48±3153.3	4729.45±2570.54	106.03
Total (n=55)	4116.16±2240.4	4052.14±1961.8	64.02

Serum ferritin levels had high variability in each group also in between the groups. Only 20% patients had a serum ferritin between 1500-2500ng/ml. 80% cases had a ferritin >2500ng/ml. Mean serum ferritin in males and females were 3859.012 ng/ml and 4346.707 ng/ml respectively. The overall change of ferritin and the change of serum ferritin within the groups was statistically insignificant (p >0.05). Deferasirox group had the maximum decrease in ferritin levels though it was not significant.

Table 3: Comparison of compliance among groups

	Group 1	Group 2	Group 3	p value
Always/ Most of the times	16/20 (80%)	16/20 (80%)	13/15 (86.67%)	Group 1 & 2, p value >0.05, Not Significant Group 1 & 3, p value >0.05, Not Significant Group 2 & 3, p value >0.05, Not Significant
Sometimes/ Never	4/20 (20%)	4/20 (20%)	2/15 (13.33%)	
Total Score (Mean±SD)	2.05±0.6	2.05±0.8	1.67±0.9	
SEM	0.14	0.17	0.23	

Table 3 depicted the comparison of compliance. 53.3% of patients in group 3 were taking their drug always in comparison to 15% in group 1 and 20% in group 2. Hence it can be said that compliance with deferasirox was more than that with deferoxamine or deferiprone. Although, statistically there was no difference.

Table 4: Comparison of convenience among groups

	Group 1	Group 2	Group 3	p value
Very Convenient/ Convenient	7/20 (35%)	17/20 (85%)	14/15 (93.33%)	Group 1 & 2, p value <0.01, Significant Group 1 & 3, p value <0.001, Extremely Significant Group 2 & 3, p value >0.05, Not Significant
Inconvenient/ Very Inconvenient	13/20 (65%)	3/20 (15%)	1/15 (6.67%)	
Total Score (Mean±SD)	2.75±0.98	2±0.66	1.8±0.91	
SEM	0.14	0.16	0.14	

Subjects on Deferasirox and Deferiprone found it more convenient than those on Deferoxamine as depicted in table 4. Whereas the treatment was equally satisfactory in all the groups (Table 5). Deferoxamine group had higher percentage of patients who experienced life disturbances as opposed to Deferiprone and Deferasirox.

Table 5: Comparison of Satisfaction among groups

	Group 1	Group 2	Group 3	p value
Very Satisfied/ Satisfied	16/20 (80%)	17/20 (85%)	11/15 (73.33%)	Group 1 & 2, p value >0.05, Not Significant Group 1 & 3, p value >0.05, Not Significant Group 2 & 3, p value >0.05, Not Significant
Dissatisfied/ Very Dissatisfied	4/20 (20%)	3/20 (15%)	4/15 (26.67%)	
Total Score (Mean±SD)	2±0.65	1.95±0.61	2.13±0.64	
SEM	0.15	0.14	0.17	

Table 6: Comparison of Life Disturbances among groups

Group	Score (Mean±SD)	SEM
1	9.95±0.14	0.32
2	11.2±1.2	0.28
3	11.87±0.36	0.1

Between Group 1 & 2, p value <0.01, Significant
Between Group 1 & 3, p value <0.001, Extremely Significant

Between Group 2 & 3, p value >0.05, Not Significant

Pain at the injection site was reported by 30% of patients on Deferoxamine infusion similar to 44% by Haghpanah et al. Arthropathy was present in 2/20 (10%) of patients on Deferiprone. None of the patients in any group reported any hematological abnormality like neutropenia or agranulocytosis. Deferasirox was free of any side effects during the study period.

53.3% of patients in group 3 were taking their drug always in comparison to 15% in group 1 and 20% in group 2. Hence it can be said that compliance with deferasirox was more than that with deferoxamine or deferiprone.

Deferoxamine group was statistically significantly different from group 2(p=0.005) and group 3(p=0.00). The difference in the mean total scores between group 2

and group 3 was not significant.

DISCUSSION

There are very few studies on Indian Thalassemic children regarding the iron chelation therapy. Hence this study was planned to compare the safety and compliance of Deferasirox versus Deferoxamine and Deferiprone. There were no major differences in the patient population randomized to receive deferoxamine, deferiprone or deferasirox with regard to baseline demographics or disease characteristics. Most patients (90.9%) had received prior chelation therapy.

The fall in serum ferritin at the end was comparable in the three groups though the fall in absolute mean values was slightly more in deferasirox group, which could be explained by the fact that the patients found it more convenient and it interfered least with daily activities. Deferasirox was given at a dose of 20 mg/kg/day to start with which has been shown to have a similar efficacy as deferoxamine at doses of 20- 40 mg/kg/day; as in our study. [7,8] In an Indian study by Dhamija et al Deferasirox required dose escalation to 40mg/kg/day in (35/50) 70% cases. [9] Despite high doses (15/50) 30% could not achieve negative iron balance. Increasing the dose of deferasirox would have improved the efficacy in majority of the cases.

Improved satisfaction with, and convenience of deferasirox compared to DFO has been shown in studies [10-13] which may translate into improved compliance. Similarly in the present study, patients on Deferasirox and Deferiprone found it more convenient compared to DFO but satisfaction with Deferasirox was comparable to Deferiprone and Deferoxamine. Although the difference in compliance was not significantly different in the three groups in the present study; 53.3% patients on deferasirox were taking their drug always compared to 20% on Deferiprone and 15% on DFO.

In an Iranian study, Haghpanah et al reported better compliance ($p< 0.001$) and convenience ($p<0.001$) with Deferasirox vs DFO but comparable satisfaction, similar to the present study. [14] Their subjects experienced similar life disturbances. Our patients on Deferiprone and Deferasirox had fewer life disturbances than those on DFO. The difference was extremely significant in case of Deferasirox ($p<0.001$), which can mean better drug acceptability in the long term. Goulas et al also reported that higher percentage of patients receiving DFO felt that their treatment negatively influenced their body and skin appearance and limited ability to work, attend school and perform daily tasks ($p=0.0066$). The adherence to treatment rate and self-esteem was the lowest in DFO ($p<0.05$) vs Deferasirox or combination of DFO and Deferiprone. [15]

Some studies have proven combination therapies to be very efficacious. A randomized prospective study reported that while both forms of combination therapy, Deferiprone(DFP) with Deferasirox(DFX) and DFP with DFO, were effective in reducing iron overload in multi-transfused beta thalassemia major, patients who received DFP and DFX showed a higher decline in serum ferritin, greater improvement in cardiac T2, higher treatment satisfaction ($p<0.001$), better compliance($p<0.001$) and more improvement in quality of life ($p<0.001$), with no toxicity. [16]

30% of patients on DFO reported pain at the injection site. Arthropathy was reported in 10% cases of Deferiprone. Though reported in literature; none of our patients had any adverse effects with Deferasirox.

Thus, keeping in mind the convenience and better tolerability in view of lesser life disturbances, with no reported adverse effects in the present study; Deferasirox the once daily oral iron chelator can be the preferred modality of iron chelation in iron overloaded thalassemia patients.

CONCLUSION

Patients using Deferasirox and Deferiprone found it more convenient as compared to Deferoxamine. All three chelators were effective, and equally satisfactory; however Deferasirox was found to be the best in view of its ease of administration, convenience, minimal interference with daily activities and absence of any significant side effects. Patient's convenience and compliance has a bearing on the adherence to therapy, with possible consequences on the effectiveness of therapy and survival.

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