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Original Research Article

Safety and efficacy of combination of oral iron chelators in thalassemia major patients

Justin Thomas[1]*, Pramod Sharma[2], Manish Parakh[2], Deepshikha Mandloi[3]

[1]Department of Neurosciences, Pacific Medical College, Udaipur, Rajasthan, India
[2]Department of Pediatric Medicine, Dr SN Medical College, Jodhpur, Rajasthan, India
[3]Department of Pediatrics, Lourdes Hospital, Kochi, Kerala, India

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***Correspondence:**
Dr. Justin Thomas,
E-mail: dr.justinthomas@gmail.com

ABSTRACT

Background: To assess the safety and efficacy of combination of oral iron chelation therapy in transfusion dependent thalassemia patients and to compare it with other regimes.
Method: 150 transfusion dependent thalassemia patients with iron overload were recruited for a prospective, case control study. They were divided into 4 groups based on their chelation regime. The drugs used were deferasirox (DFX) alone, deferiprone (DFP) alone, DFP+DFX in combination, parenteral desferrioxamine (DFO) with either DFX or DFP with 50, 15, 70 and 15 in each group respectively. Doses used were DFX-30 mg/kg, DFP- 75 mg/kg/day, DFP+DFX-50 +30 mg/kg/day, DFO+DFP-25 mg/kg/d+50 mg/kg/day and DFO+DFX-25 mg/kg/d +30 mg/kg/d daily. Base line haematological, hepatic and renal profile and S. ferritin samples were collected and analyzed. Patients were monitored monthly for compliance and side effects. 30 patients were excluded during the course of study. Tests were repeated after 18 months period and the results of 120 patients were compared between the groups and statistically analyzed.
Results: There was statistically significant reduction of S. ferritin in both groups taking oral combination therapy and parenteral therapy ($p<0.0001$). There were no serious hematological, renal/hepatic side effects in any groups.
Conclusions: The oral combination therapy of iron chelators is safer and was well tolerated by all the patients and is similarly efficacious to the parenteral therapy in lowering S. ferritin.

Keywords: Thalassemia major, Chronic iron overload, Iron chelators, Ferritin

INTRODUCTION

Iron overload in thalassemia patients is inevitable. Iron induced end organ damage is a major cause of mortality and morbidity in transfusion dependent thalassemic patients.[1] Iron overload in the body is caused by repeated blood transfusions, ineffective erythropoiesis, and enhanced gastrointestinal iron absorption. When a unit of red blood cells is transfused, it adds approximately 250 mg of iron to the body, which exceeds the daily excretion limit of 1 mg of iron per day.[2] A unit of red blood cells transfused contains approximately 250 mg of iron, while the body cannot excrete more than 1 mg of iron per day. This imbalance ultimately leads to an iron overload state. Iron overload can cause tissue damage such as heart failure, liver disease and endocrinal disturbances, which could eventually cause death. Manifestations of iron overload include hypogonadism, hypothyroidism, hypoparathyroidism, diabetes, liver fibrosis, and cardiac dysfunction out of which cardiac siderosis is the leading cause of death in thalassemia major, accounting for 71% of the total deaths.[3] The iron status of multi-transfused patients can be assessed by several methods including serum ferritin, Liver iron concentration and newer

methods like T2* MRI and superconducting quantum interference device (SQUID). Serum ferritin measurement is the one which is widely used to know the iron status.[4]

Many studies have proven the efficacy and safety of combination of parenteral DFO with oral DFX or DFP.[5] This study was planned to compare the safety and efficacy of combination of oral iron chelators with regimes of either single oral chelator or a combination of oral and parenteral chelator in a view that the success of this oral combination regimen would replace the current standard therapy with parenteral DFO which is expensive and less compliant.

METHODS

This was a non-randomized hospital based prospective, comparative study conducted in the Thalassemia day care centre of department of Pediatrics, Umaid hospital, Dr SN Medical college, Jodhpur, Western Rajasthan, India from March 2015 to August 2019. Study was approved by institutional ethics committee. A total of 150 transfusion dependent beta thalassemia patients receiving chronic transfusions with iron overload requiring treatment with chelation were initially enrolled. Patients with severe neutropenia (ANC<1.5×10×9/L) and severe thrombocytopenia (<50×10×9/L) at screening, patients with a previous reaction to DFP or DFX, cases with pre-existing renal or hepatic diseases (AST>250 IU/dl and S. creatinine>1.5 mg/dl) and those with proven infections, co-morbidities like diabetes and cardiac ailments were excluded from the study.

The 70 patients who were already on either DFX or DFP were offered the combination therapy of these two drugs on a daily basis, but in slightly reduced doses (DFX 30 mg/kg, DFP 50 mg/kg). A written informed consent was obtained from the parents of patients and the combination was administered for a total period of 18 months. Remaining 80 patients who were either on oral monotherapy or taking combined oral and parenteral therapy were taken as control groups.

A complete detailed history was obtained regarding age of diagnosis, age of first transfusion, average number of transfusion in a month and during last year, and family history. S. ferritin value was measured at the time of enrollment in respective groups. Baseline haemoglobin was calculated prior to start of chelation therapy in each case which was the average of pre-transfusion hemoglobin of last six months. Similarly average blood transfusion requirement of last 6 months were calculated prior to start of therapy. Average hemoglobin and blood transfusion requirement were calculated also during follow up. All patients undergone a thorough laboratory testing including a complete blood count, renal function tests, liver function tests and electrolytes. 17 patients with low initial platelet count (<50,000/mm^3), raised AST (>250) or neutropenia [ANC<1,500/mm^3] were excluded.

All the patients were followed up on a monthly basis to monitor for adverse drug reaction and the efficacy of the regime was assessed by noting the mean pre-transfusion hemoglobin, average monthly transfusion requirement and the serum ferritin at the end of study period. 7 patients dropped out from the study due to transfer, irregular follow up and death. 6 patients with low drug adherence also were excluded from the study on serial follow up. Finally a total of 120 patients retained in the study of which 50 patients were on combined oral chelation therapy, 15 patients only on DFP, and 40 patients only on DFX alone and 15 on DFO with either DFX or DFP. Statistical analysis was done using SPSS-20th edition by student t test, Chi-Square test and other appropriate tests were used.

RESULTS

We analyzed data from a total of 120 cases of which 83 were males. The mean age of patients was 7.9 years (range: 1-18 years). In our study majority of patients had their initial ferritin between 2000-5000, 12 cases had highly elevated S. ferritin values (>5000). Only 15.33% had s. ferritin in the desired range (<1000) before allotted to study. The mean S. ferritin of the study group was 2549±191.44 ng/ml.

Table 1: Demographic parameters of the study population.

Age (Years)	Male, n=83 (69.17%)	Female, n=37 (30.83%)	Total, n=120 (100%)
1-5	33 (27.5)	12 (10)	45 (37.5)
6-10	24 (20)	14 (11.67)	38 (31.67)
11-15	16 (13.33)	9 (7.5)	25 (20.83)
>15	10 (8.34)	2 (1.66)	12 (10)
Total	83	37	120

Oral combination therapy (DFX+DFP) received by 50 patients followed by 40 patients who received DFX alone and 15 each in DFP alone and DFO+DFX/DFP category.

For those on combination therapy, a reduced dose of oral iron chelator i.e., 30 mg/kg of DFX, 50 mg/kg of DFP was given while those on single agent 35 mg/kg of DFX or 75 mg/kg DFP was given daily. DFO was given in a dose of 25 mg/kg/day by subcutaneous infusion and along with it DFX or DFP was given in a dose of 30 mg/kg/day or 50 mg/kg/day respectively. The patients were followed up for 18 months and monitored till all 120 patients completed 18 months treatment.

After treatment, the mean hemoglobin of patients in all groups increased, but that was not statistically significant. WBC counts were significantly reduced in all groups (B>C>A) except group D. Platelet counts changes were statistically insignificant in all groups except in group C. S. bilirubin was raised in all the 4 groups at the end of study period, but it was not statistically significant. But

the rise in direct Bilirubin was significant in all groups except group C. Changes in B. urea, S. creatinine, AST and ALT were not significant in all the groups.

No serious side effects were noted in any groups except 3 cases of neutropenia (ANC<1500) were seen in both oral combination and DFX alone group. Severe thrombocytopenia (PLT<50,000) were seen in 3 patients of oral combination group and one case in group DFX alone group, but all counts came back to normal after stopping therapy for 1 month. Most of the side effects were gastrointestinal like nausea, vomiting and non specific abdominal pain. One to 2 cases of abnormal elevation of AST (>250 u/l) were reported in all groups. But these changes were found to be transient.

There statistically significant reduction of S. ferritin in both oral and parenteral combination group. (p<0.0001). But S. ferritin was found to be increased in single drug groups though rise was not statistically significant.

Table 2: Distribution of S. ferritin in all groups before the study.

S. ferritin (ng/ml)	Group A	Group B	Group C	Group D	Total no of cases
0-1000	0	5	0	14	19
1000-2000	5	6	3	21	35
2000-5000	37	4	8	5	54
>5000	8	0	4	0	12
Average S. ferritin	3463.04±495.2	1330.4±287.5	4057±191.4	1326.4±180.1	2549±191.44
Total	50	15	15	40	120

Table 3: Number of patients in each group, (n=120).

Group A	Group B	Group C	Group D
DFX+DFP	DFP	DFO+ DFX/DFP	DFX
50	15	15	40

Table 4: Dose of drugs in each group.

Dose of drug (mg/kg)	Group A	Group B	Group C	Group D
DFX	30	-	30	35
DFP	50	75	50	-
DFO	-	-	25	-

Table 5: Comparison of haematological parameters before and after therapy.

Parameters		Group A, (n=50)	Group B, (n=15)	Group C, (n=15)	Group D, (n=40)
Hemoglobin (g/dl)	Before study	7.9±2.92	7.73±1.34	9.22±.51	8.35±.53
Mean ± SD	After study	8.54±1.82	8.67±2.37	9.1±1.7	9.12±1.9
P value		0.1929	0.0801	0.7953	0.0622
TLC (cells/mm^3)	Before study	8426±415.4	12584±2621.9	7636±500	9175±2715.4
Mean ± SD	After study	8226.2±492.7	9780±233.3	7200±166.3	9782.9±404.8
P value		0.0307	< 0.0001	0.0034	0.1660
Platelets (Lac/mm^3)	Before study	2.8±.34	2.85±.95	2.58±.49	3.06±1.67
Mean ± SD	After study	2.77±0.1	2.47±.96	3.19±.24	2.86±1.04
P value		0.5508	0.2851	0.0002	0.5221

Table 6: Comparison of biochemical parameters.

Parameters		Group A, (n=50)	Group B, (n=15)	Group C, (n=15)	Group D, (n=40)
Bilirubin (mg/dl)	Before study	1.68±1.3	1.48±.9	1.85±.79	1.71±1.16
Mean ± SD	After study	1.88±1.5	1.55±1.48	1.91±1.8	1.99±1.9
P value		0.4779	0.8768	0.9067	0.4287
Direct bilirubin (mg/dl)	Before study	0.49±0.22	0.41±.16	0.52±.17	0.54±.18
Mean ± SD	After study	0.70±.27	0.64±.37	0.59±0.15	0.79±.32
P value		<0.0001	0.0355	0.2418	<0.0001

Continued.

Parameters		Group A, (n=50)	Group B, (n=15)	Group C, (n=15)	Group D, (n=40)
SGPT (U/L)	Before study	66.68±14.57	49.86±25.16	85.26±68.94	43.32±33.8
Mean ± SD	After study	59.02±17.02	42.06±17.86	63.0±14.25	52.75±6.19
P value		0.1220	0.3359	0.2309	0.0868
SGOT (U/L)	Before study	71.68±111.7	52.86±34.28	81.73±64.56	50.62±49.1
Mean ± SD	After study	67.88±8.18	49.26±21.41	74.2±19.51	61.71±11.2
P value		0.8109	0.7327	0.6691	0.1677
Urea (mg/dl)	Before study	30.14±15.13	28.66±9.69	27±6.1	34.83±12.4
Mean ± SD	After study	23.94±7.64	28.93±5.44	24.6±3.13	24.48±17.1
P value		0.0612	0.9257	0.1860	0.1256
Creatinine (mg/dl)	Before study	0.85±0.3	0.84±0.15	1±0.581	0.88±0.25
Mean ± SD	After study	0.82±0.15	0.93±0.13	0.8±0.21	0.84±0.09
P value		0.5286	0.0900	0.2203	0.3440

Table 7: All adverse side effects.

Organ site	Side effect	Group A	Group B	Group C	Group D
Neurological	Peripheral neuropathy	0	0	0	0
	Headache	0	0	0	2
	Convulsions	0	0	0	0
	Hearing loss	0	0	0	0
	Diminution of vision	0	0	1	0
Dermatological	Erythema	0	0	0	0
	Alopecia	0	0	0	1
	Injection site irritation, induration	0	0	6	0
	Nail changes	0	0	0	0
	Ulceration	0	0	0	0
Gastrointestinal	Mild nausea, vomiting, gastric irritation,	5	7	0	2
	Anorexia and diarrhea	2	1	0	2
Hematologic	Neutropenia	3	0	0	3
	Thrombocytopenia	3	0	0	1
Hepatic	Abnormal elevation of transaminases	1	2	1	1
Renal/metabolic	Elevated BUN and creatinine	0	0	0	0
	Reddish discoloration of urine	8	10	0	0
Pulmonary	Acute pneumonitis	0	0	0	0
Musculoskeletal	Joint pain	1	2	0	1
Other	Fever, chills Fatigue	0	0	0	0

Table 8: Comparison of S. ferritin before and after study in all groups.

No. of cases	Group A, (n=50)		Group B, (n=15)		Group C, (n=15)		Group D (n=40)	
S. ferritin	**Before study**	**After study**	**Before study**	**After study**	**Before study**	**After study**	**Before study**	**After study**
0-1000	0	8	5	5	0	2	12	17
1000-2000	5	21	6	5	3	5	23	16
2000-5000	37	21	4	4	9	7	5	6
>5000	8	0	0	1	3	1	0	1
Mean ferritin	3463.04± 495.2	2138.54± 556.4	1330.2± 7.5	1819.4± 968.9	4057± 191.4	2320.06± 225.2	1326.4± 180.1	1641.19± 1795.2
P	<0.0001		0.0714		<0.0001		0.0569	

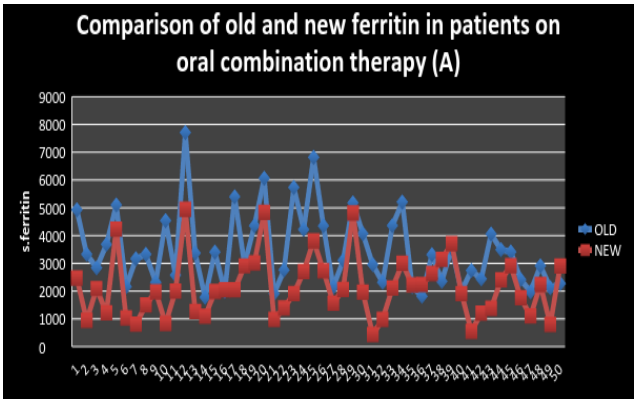

Figure 1: New and old serum ferritin levels in patients with oral combined chelation therapy.

DISCUSSION

Our study was a hospital based non randomized prospective comparative study. The main objective of our study was whether combining oral chelating drugs is effective in reducing serum ferritin in Iron overloaded multi transfused Thalassemia Major patients. 50 patients were finally enrolled for oral combination therapy and 40 patients DFX alone, 15 patients DFP alone, 15 patients combination of parenteral plus oral i.e., DFO and either DFP or DFX. None were given triple combination therapy. The baseline parameters were similar in all 4 groups. Follow up of our patients for 18 months found that the oral combination therapy of iron chelators is safer and is well tolerated by all the patients. The major side effects are gastrointestinal like nausea and vomiting and non specific abdominal pain. Neutropenia was observed in 3 patients in both oral combination therapy and DFX alone group. Severe thrombocytopenia was seen in 3 patients in oral combination group. But all these parameters were reversed after stopping the therapy for 1 month and never recurred on re-administration.

Voskaridou et al reported treating a thalassemic patient with two drugs simultaneously, daily DFX, at 30 mg/kg/d and DFP, at 75 mg/kg/d and this combination was very effective and very safe for the patient.[14] He reported this in British journal of hematology in 2011. There after many authors started analyzing the efficacy of oral combination therapy. But total number of patients enrolled in these studies were small. A previous study by Chowdhury et al in which of 15 patients with 5 patients DFX alone, 5 patients DFP alone and 5 patients with combination of both on an alternate day basis.[14] That study found that the sequential therapy of both drugs in alternate days in usual doses was well tolerated by multi-transfused iron overloaded thalassemic patients. The side effects of each drugs given individually were not observed on patients of alternate day therapy.

Alavi et al studied the efficacy of combination therapy in a 25 year old thalassemic patent non-complaint to DFO injection and found that continuous chelation achieved by using combined oral iron chelators might be promising in alleviating iron overload in patients who do not comply with DFO and also who have developed high cardiac siderosis .Side effects are minimal and were comparable to that of single drug therapy.[8] In another study Hossein et al from Iran studied the effect of oral combination therapy in reducing cardiac and liver Iron status by using MRI T2* values.[12] There was also another study by Gomber et al also analyzed urinary Iron excretion in addition to cardiac and liver iron status.[15] These authors concluded that combination of oral iron chelators is efficacious in reducing cardiac and hepatic iron load and it increased the urinary excretion of Iron more effectively than single drug alone. Our study also found efficacy and safety of oral combination and we compared it with parenteral therapy also. Parenteral therapy using DFO all though efficacious in reducing S. ferritin it is expensive and compliance is poor among patients.

Table 9: Year wise summary of various studies published before which analyzed efficacy of oral combination therapy.

Author	Region	Year	N	Results	Side effects
Berdoukas et al[6]	USA	2009-10	4	Significant improvement in s. ferritin, LIC, LVEF and T2*MRI	No serious side effects
Farmakis et al[10]	Greece	2010-11	16	Significant improvement in LVEF, endocrinal functions	No adverse effects
Chowdhury et al[7]	India	2012-13	5	Reduction of S. ferritin values	No serious side effects
Elalfy et al[9]	Egypt	2013-14	48	Significant reduction in S. ferritin, LIC and improvement in quality of life, compliance and T2* values	No serious side effects
Song et al[10]	China	2013-14	8	positive pharmacokinetic drug interaction in combination therapy	No adverse events
Todadri et al[13]	India	2014-15	36	Safe and efficacious	Minor adverse events
Gomber et al[15]	India	2015-16	6	Safe and efficacious in reducing ferritin, cardiac and hepatic iron and improving urinary iron excretion	Arthropathy of large joints
Karami et al [12]	Iran	2017	6	Significant reduction in cardiac and liver iron	No adverse events

The limitations of our study were non-randomized design, improper supply of medicines by government, not using MRI T2* as a method of assessing hepatic and cardiac Iron status. We concluded compliance among patients just based on personal interviews only. However, we included all 4 groups including those taking parenteral therapy which was not done before. However large, randomized control trials are recommended before defining optimal dosing, duration and defining proper guidelines.

CONCLUSION

The combined oral chelation therapy in thalassemia offers promise of easier administration, better compliance and may lead to an improvement of patient quality of life by preventing or even reversing iron overload complications. It is safe and efficacious. However larger randomized trials studies are required before recommending oral combination therapy in all Iron overloaded multi transfused thalassemia major patients.

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REFERENCES

1. Whipple CH, Bradford WL. Mediterranean disease-thalassemia (erythroblastic anemia of Cooley); associated pigment abnormalities simulating hemochromatosis. J Pediat. 1936;9:279-311.
2. Mishra AK, Tiwari A. Iron overload in Beta thalassaemia major and intermedia patients. Maedica (Bucur). 2013;8(4):328-32.
3. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR: Thalassemia Clinical Research Network. Complications of beta-thalassemia major in North America. Blood. 2004;104:34 39.
4. Brittenham GM, Cohen AR. Hepatic iron stores and plasma ferritin concentration in patients with sickle cell anemia and thalassemia major. Am J Hematol. 1993;42:81-5.
5. Voskaridou E, Christoulas D, Terpos E. Successful chelation therapy with the combination of Deferasirox and Deferiprone in a patient with thalassaemia major and persisting severe iron overload after single agent chelation therapies. Blackwell Publishing Ltd, Br J Hematol. 2011;154:654-65.
6. Berdoukas V, Carson S, Nord A, Hofstra T, Claster S, Wood J, Coates TD. Combination of Two Orally Active Iron Chelating Agents: Efficacy and Safety In a Clinical Setting. Am Society Hematol Annual Meeting Exposition. 2011;10-13.
7. Chowdhury P, Chowdhury D, Chaudhury N. Safety and efficacy of sequential oral iron chelation therapy in transfusion induced siderosis in thalassemia syndrome. EGM Iron summit at Newdelhi, India. 2013.
8. Alavi S, Sadeghi E, Ashenagar A. Efficacy and safety of combined oral iron chelation therapy with Deferasirox and Deferiprone in a patient with beta-thalassemia major and persistent iron overload. Blood Res. 2014;49:65-73.
9. Elalfy MS, Wali Y, Tony S. Comparison of two combination iron chelation regimens, Deferiprone and Deferasirox versus Deferiprone and deferoxamine, in pediatric patients with thalassemia major. Blood. 2013;122:559.
10. Song TS, Hsieh YW, Peng CT, Chen TL, Lee HZ, Chung JZ, Hour MJ. Combined Versus Monotherapy OR Concurrent Therapy FOR Treatment of Thalassaemia. *In Vivo*. 2014;28(4):645-64.
11. Farmaki K, Tzoumari I, Pappa C, Oral chelators in transfusion-dependent thalassemia major patients may prevent or reverse iron overload complications. Blood Cells Mol Dis. 2011;47(1):33-40.
12. Karami H, Kosaryan M, Amree AH, Darvishi-Khezri H, Mousavi M. Combination Iron Chelation Therapy with Deferiprone and Deferasirox in Iron-Overloaded Patients with Transfusion-Dependent β-Thalassemia Major. Clin Pract. 2017;7(1):912.
13. Totadri S, Bansal D, Bhatia P, Attri SV, Trehan A, Marwaha RK. The deferiprone and deferasirox combination is efficacious in iron overloaded patients with β-thalassemia major: A prospective, single center, open-label study. Pediatr Blood Cancer. 2015;62(9):1592-6.
14. Voskaridou E, Christoulas D, Terpos E. Successful chelation therapy with the combination of deferasirox and deferiprone in a patient with thalassaemia major and persisting severe iron overload after single-agent chelation therapies. Br J Haematol. 2011;154:654-6.
15. Gomber S, Jain P, Sharma S. Comparative efficacy and safety of oral iron chelators and their novel combination in children with thalassemia. Indian Pediatr. 2016;53:207-10.

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