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Effect of Deferiprone versus Deferiprone with Deferasirox in Iron Chelation Therapy of Thalassemia Children

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Abstract
Background: *Thalassemia is an autosomal recessive hemoglobin disorder requiring life-long blood transfusion causing iron overload. Combination therapy of oral iron chelators: Deferiprone (DFP) with Deferasirox (DFX) is an efficacious and safe modality to reduce serum ferritin in multi-transfused thalassemic children. This study was carried out to evaluate the effect of Deferiprone versus Deferiprone with Deferasirox in iron chelation therapy of transfusion dependent thalassemia children.*
Methodology: *A cross sectional observational study was done in Pediatric Hematology and Oncology, Dhaka Medical College Hospital and Bangladesh Thalassemia Hospital in Dhaka from January to June 2018. Children with transfusion dependent β-thalassemia major and E-β-thalassemia having serum ferritin level >1000 ng/ml between 3 to 12 years of age were studied.*
Results: *Demographic profile of 60 cases demonstrated that there are no significant differences in age, sex and weight between DFP-monotherapy and DFP-DFX-combination groups. Initial mean serum ferritin level was 3397.48±774.48 ng/ml in DFP-monotherapy group and 3413.70±1114.05ng/ml in DFP-DFX combination group. After treatment mean serum ferritin level at 6th month was 2730.63±839.91 ng/ml in DFP-monotherapy group and 1654.20±934.90 ng/ml in DFP-DFX-combination group which shows rapid reduction of serum ferritin level in DFP-DFX-combination group. Mean dose of drugs was 72.59(±3.76) mg/kg/ day of DFP in monotherapy group and 68.68(±4.84) mg/kg/ day of DFP and 27.98(±2.13) mg/kg/ day of DFX in combination group. 12 (40.0%) patients had arthralgia in DFP-monotherapy group and 5(16.7%) patients had vomiting in DFP-DFX-combination group. No abnormalities seen in liver and renal function tests.*
Conclusion: *Deferiprone alone is capable in significant excretion of iron from the body in transfusion dependent thalassemia major patients. But combination therapy with Deferiprone and Deferasirox is more significantly effective in iron chelation and drug induced related complications.*
Keywords: *Thalassemia major, iron overload, effects of combined oral iron chelation therapy.*

Introduction

Thalassemia caused by defective globin production was previously lethal in childhood can now be treated as chronic condition. Patient may aspire to long and productive life. Consequences, mainly of iron overload, cannot be totally prevented even by present day iron chelation treatment.[1] Although medical advances in the treatment of thalassemia have led to increased survival rates, patients still suffer disease complications. It was found that the life expectancy of thalassemia patients has dramatically increased to reach into 4th and 5th decades of life with the combination of regular blood transfusions and chelation therapy. However, the frequent blood transfusion has also led to iron overload with many complications including endocrinopathies, behavioural and neurotic problems, growth failure, cardiovascular problems, liver disease, gonadal dysfunction and delayed puberty.[2,3] The detrimental effect of iron overload requires Iron Chelation Therapy (ICT) in order to reduce the excess iron load that is not eliminated properly. Oral chelators such as Deferiprone (DFP) and Deferasirox (DFX) are available also yet are much more expensive. Minimal data are available on effects of two combined oral iron chelators.[4] Thalassemia among ($n = 735$) school children in Bangladesh showed a 4.1% prevalence for the beta-Thalassemia trait and 6.1% prevalence for the HbE trait.[5]

Methodology

This cross sectional observational study was conducted in department of Pediatric Hematology and Oncology, Dhaka Medical College Hospital and Bangladesh Thalassemia Hospital in Dhaka. Data were collected retrospectively from patients' record sheet who were aged between 3 to 12 years presenting with transfusion dependent β-thalassemia major and E-β-thalassemia having serum ferritin level >1000 ng/ml taking regular oral iron chelator either as DFP monotherapy (designated as group A) or combination therapy of DFP-DFX (designated as group B). A written informed consent from parents/attendants and patients were taken. A structured data collection sheet was developed using the selected variables according to the objectives. Both parents and patients were interviewed anonymously as far as possible for particulars and history. Prior to original data collection, a pre-test session was conducted among 10 cases in DMCH and necessary modification was done. Preceding the data collection, the detail of the study was explicitly explained to each eligible patient and verbal consents from the patient were obtained. Patients' data on history, physical examination, laboratory investigations and follow-ups: age, sex, body weight, size of liver and spleen, 3 monthly serum ferritin level, pre transfusion CBC with RBC indices, RBS, HBsAg, anti-HCV antibody, SGPT, serum creatinine, name, dose and duration of oral iron chelating drugs taken by them were extracted from their records and categorized in data collection sheets. From 91 study population children with thalassemia minor, comorbidities (chronic illness), after splenectomy, used previously other iron chelating agents were excluded and 60 children taking regular drugs either DFP or DFP with DFX combination were studied during the period of January to June 2018. All collected data were checked to identify error. Statistical analysis was done by SPSS-22.0 for Windows. Mean values were calculated for continuous variables, quantitative observations by frequencies and percentages. Unpaired and paired t-test was used to analyze continuous variables, shown with cross tabulation. P value <0.05 was considered as statistically significant.

Results

Among 60 patients the mean age was found 7.42±2.50 years in DFP-monotherapy group and 7.48±2.38 years in DFP-DFX-combination group. Regarding distribution of sex: male was found 22(73.3%) in DFP-monotherapy group and 13(43.3%) in DFP-DFX combination group. Female was 8(26.7%) in DFP-monotherapy group and 17(56.7%) in DFP-DFX combination group.

The mean weight was found 19.08(±4.13) kg in DFP-monotherapy group and 21.03(±7.69) kg in DFP-DFX combination group.

Table I: Distribution of mean serum ferritin levels between two groups (n=60)

Serum ferritin (ng/ml)	DFP-monotherapy (n=30)		DFP-DFX-combination (n=30)		p value
	Mean	±SD	Mean	±SD	
Serum ferritin initial	3397.48	±774.48	3413.70	±1114.05	0.948^{ns}
Serum ferritin at 3rd month	3151.62	±770.39	3158.63	±1077.33	0.977^{ns}
Serum ferritin at 6th month	2730.63	±839.91	1654.20	±934. 90	0.001^{s}

DFP- Deferiprone, DFX- Deferasirox
s=significant; ns=not significant; P value reached from unpaired t-test

Table I shows that initial mean serum ferritin level was 3397.48(±774.48) ng/ml in DFP-monotherapy group and 3413.70(±1114.05) ng/ml in DFP-DFX-combination group. At 3rd month mean serum ferritin level reduced to 3151.62(±770.39) ng/ml in DFP-monotherapy group and 315.638(±1077.33) ng/ml in DFP-DFX-combination group that was not statistically significant (p>0.05) when compared between two groups due to increment of serum ferritin level in 10 patients (33.3% cases) of DFP-DFX combination group. Mean serum ferritin level at 6th month was found 2730.63±839.91 ng/ml in DFP-monotherapy group and 1654.20±934.90 ng/ml in DFP-DFX-combination which shows rapid reduction of serum ferritin level in DFP-DFX-combination group that was statistically significant (p<0.05).

In DFP-monotherapy group, declination of mean serum ferritin level was found statistically significant (p<0.05) when compared to initial vs at 3rd month, at 3rd month vs at 6th month and initial vs at 6th month (Fig. I). In DFP-DFX-combination group, reduction of mean serum ferritin level was statistically significant (p<0.05) when compared to initial vs at 3rd month, at 3rd month vs at 6th month and initial vs at 6th month (Fig.: II).

Figure I: Bar diagram showing reduction of mean serum ferritin level in DFP-monotherapy group

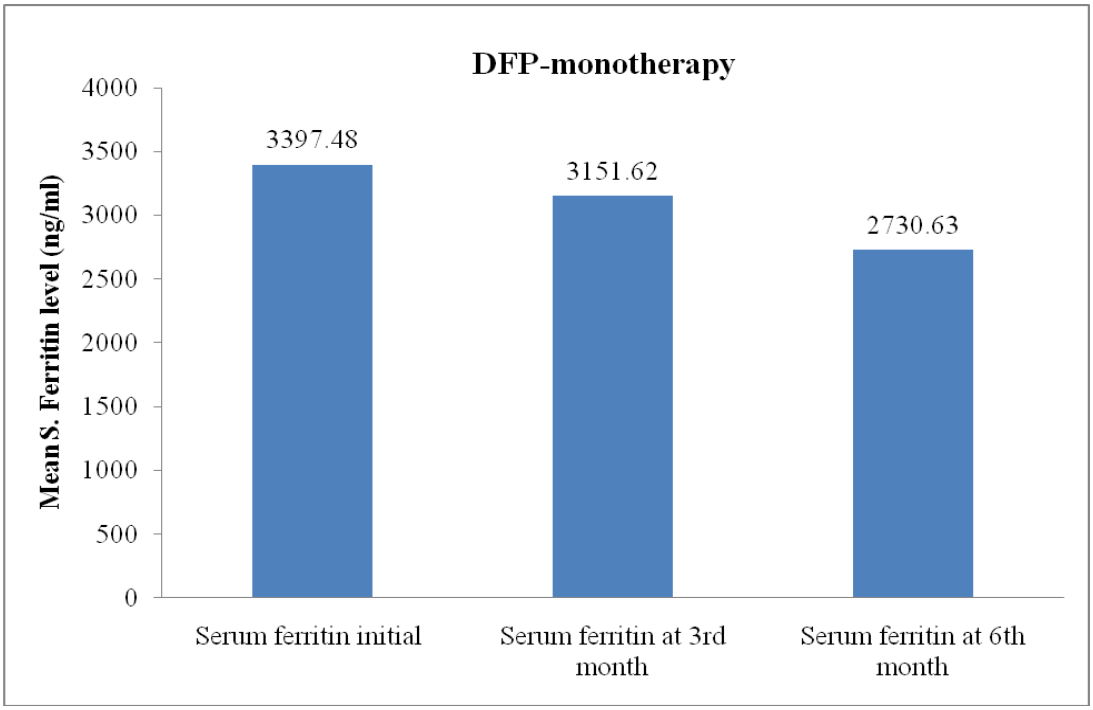


Figure II: Bar diagram showing reduction of serum ferritin level in DFP-DFX-combination group

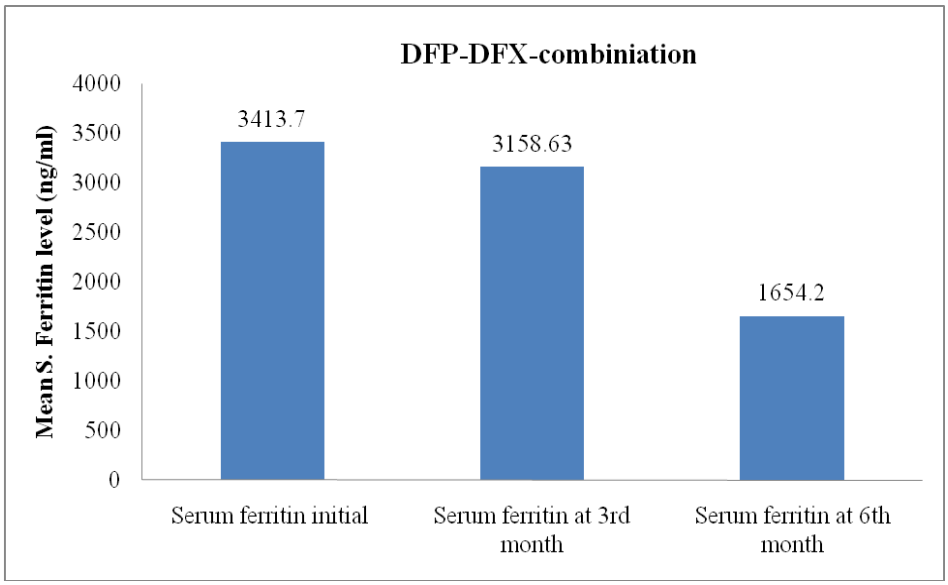


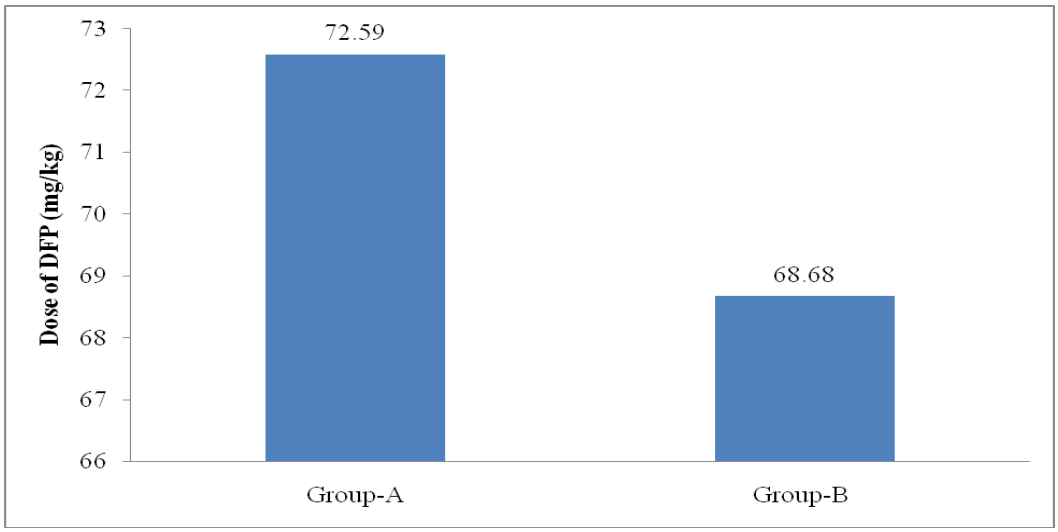
Table II: Distribution of mean dose of drugs

	Dose of drugs		
	Group-A	Group-B (Combination)	
	DFP-monotherapy	DFP	DFX
Mean±(SD)	72.59(±3.76)	68.68(±4.84)	27.98(±2.13)
Range (min-max)	63.80-78.20	60.00-75.0	23-31.25
P value	0.001[s]		

P value reached from unpaired t-test

Table II shows mean dose of drugs was 72.59(±3.76) mg/kg body weight/day in DFP-monotherapy group (Group A) and 68.68(±4.84) mg/kg body weight/day in DFP and 27.98(±2.13) mg/kg body weight/day in DFX combination group (Group B) which shows dose of DFP was significantly higher in group A (DFP-monotherapy).

Figure III: Bar diagram showing mean prescribed dose of DFP in two groups



12(40.0%) patients had arthralgia in DFP-monotherapy group and not found in DFP-DFX-combination group. Five (16.7%) patients had vomiting in DFP-DFX-combination group and not found in DFP-monotherapy group. No abnormalities seen in liver and renal function tests.

Discussion

In the present study the mean age was found 7.42±2.50 years in DFP-monotherapy group and 7.48±2.38 years in DFP-DFX-combination group. The difference was not statistically significant (p>0.05). In a study of Hassan and Tolba the mean age was found 9.7±1.9 years in DFO group and 8.9±2.2 years in DFX group.[6] Gomber et al. study revealed 49 multi-transfused children with Thalassemia with a mean (SD) age 11.6 (6.21) years.[7] Riaz et al. reported mean age 10.8 (± 4.5) years.[8] In this study sex distribution of the population was observed that male was 22 (73.3%) in DFP-monotherapy group and 13(43.3%) in DFP-DFX combination group. Female was 8(26.7%) in DFP-monotherapy group and 17(56.7%) in DFP-DFX combination group. Similar observation was found in a study of Hassan and Tolba: male was 10(33.3%) in DFO group and 9(30.0%) in DFX group; Gomber et al.: male was found 30(61.2%) and female was 19(38.8%); Riaz et al.: among 79 patients 46 (58.2%) were male while 33 (41.8%) were female.[6-8] In a study of Mourad et al. it was observed that there were no significant differences in the initial serum ferritin levels, age or sex distribution between the two groups.[9] All observations were approximately similar to our study. In the present study the mean weight was observed 19.08(±4.13) kg in DFP-monotherapy group and 21.03(±7.69) kg in DFP-DFX combination group. The difference was not statistically significant (p>0.05). In a study of Hassan and Tolba the mean weight was found 25.0 ± 6.4 kg in DFO group and 23.4 ± 6.1 kg in DFX group.[6] The difference was also not statistically significant (p=0.307).

In the present study the initial mean serum ferritin level was 3397.48(±774.48) ng/ml in DFP-monotherapy group and 3413.70(±1114.05) ng/ml in DFP-DFX-combination group. At 3rd month mean serum ferritin level reduced to 3151.62 (±770.39) ng/ml in DFP-monotherapy group and 315.638(±1077.33) ng/ml in DFP-DFX-combination group. It was observed that there was increment of serum ferritin level in 10 patients (33.3% cases) of DFP-DFX combination group after 3 months treatment with DFP-DFX combination. Mean serum ferritin level at 6th month was found 2730.63±839.91 ng/ml in DFP-monotherapy group and 1654.20±934.90 ng/ml in DFP-DFX-combination group which shows rapid reduction of serum ferritin level in DFP-DFX-combination group that was statistically significant (p<0.05). Gomber et al. observed after 12 months of respective chelation therapy, serum ferritin values decreased from a mean of 3140.5 ng/mL to 2910.0 ng/mL in DFP alone group, 3859.2 ng/mL to 3417.4 ng/mL in DFX alone group and from 3696.5 ng/mL to 2572.1 ng/ mL in the combination group. The combination therapy was more efficacious in causing fall in serum ferritin levels compared to DFP and DFX monotherapy (*P*=0.035 and 0.040, respectively).[7] The combination of DFP and DFX was found to be the most efficacious in the present study which produced a significant fall in mean serum ferritin values. These results are in agreement with those of Farmaki et al. and a few other case reports of Balocco et al.; Voskaridou et al.[10-12] The study of Mourad et al. revealed that 14 patients receiving DFX, serum ferritin levels showed a decrease from 5506 ± 635 ng/ml (mean ± SEM) to 4856 ± 699 ng/ml at 6 months (P=0.07) and to 3998 ± 604 ng/ml at 12 months (P <0=001). Eleven (11) patients receiving DFP each day and DFX on 2 day each week, serum ferritin levels dropped from 4153 ± 517 ng/ml to 3005 ± 393 ng/ml at 6 months (P < 0.02) and to 2805 ± 327 ng/ml at 12 months (P < 0.01).[9]

In this study it was observed that in DFP-monotherapy group, mean serum ferritin level was significantly decreased (p<0.05) when compared to initial vs at 3rd month, at 3rd month vs at 6th month and initial vs at 6th month from 3397.48 ng/ml to 3151.62 ng/ml and to 2730.63 ng/ml respectively. Waheed et al. also found significant difference between basal serum ferritin and final serum ferritin in DFP-monotherapy group (p=0.001).[13] In our study it was observed that in

DFP-DFX-combination group, mean serum ferritin level was significantly decreased ($p<0.05$) when compared to initial vs at 3rd month, at 3rd month vs at 6th month and initial vs at 6th month from 3413.7 ng/ml to 3158.63 ng/ml and to 1654.2 ng/ml respectively. Waheed et al. also found significant difference between basal serum ferritin and final serum ferritin in DFO group ($p=0.001$).[13]

In the present study mean dose of drugs was found 72.59(±3.76) mg/ kg body weight/ day of DFP in monotherapy group (Group A) and 68.68(±4.84) mg/ kg body weight/ day of DFP and 27.98 (±2.13) mg/ kg body weight/ day of DFX in combination group (Group B) which shows dose of DFP was significantly higher in group A (DFP-monotherapy) ($p=0.001$). The mean doses of DFP and DFX were 84.4±5.2 (61-100 mg/kg/day) and 33.4±5.2 (20-40 mg/kg/day) respectively in study of Totadri et al.[14] The mean dose of DFX was 23.5±4.9 mg/kg/day and the maximum dose was 40 mg/kg/day in study of Eshghi et al.[15]

In this study it was observed that 12(40.0%) patients had arthralgia in DFP-monotherapy group and not found in DFP-DFX-combination group. Five (16.7%) patients had vomiting in DFP-DFX-combination group and not found in DFP-monotherapy group. In the study done by Ellis erosive arthritis was found 5% to 20% in DFP-monotherapy group in which the dose was 75 - 100 mg/kg/day.[16]

No abnormalities seen in liver and renal function tests. No statistically significant difference in serum creatinine and SGPT levels between two groups before and after chelation therapy in study of Hagag et al.[17]

Conclusion

Deferiprone alone is capable in significant excretion of iron from the body in transfusion dependent thalassemia major patients. But combination therapy with Deferiprone and Deferasirox is more significantly effective in iron chelation and drug induced related complications.

Limitation

The results of the study may not reflect the exact picture of the country as the study population was selected from one selected hospital in Dhaka city.

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