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# Safety and Efficacy of Iron Chelators in Thalassemia Management with Ferritin Levels: A Prospective Observational Study

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**Abstract**

**Background**: Thalassemia is an inherited blood disorder that causes the body to produce less hemoglobin than normal. Alpha and beta thalassemia is caused due to the reduced or absent production of alpha and beta globin chains. Thalassemia is a treatable disorder that can be well-managed with chelation therapy. This prospective study aims to investigate the safety and effectiveness of Iron Chelators (deferoxamine, DFO and deferiprone, DFP) therapy in patients with beta-thalassemia major and increased serum ferritin. **Material & Methods:** A Prospective study was done at Tangail 250 Bed District Hospital, Dhaka, Bangladesh. Total 70 patients were selected as samples and were assessed from June 2022 to May 2023 (1 year). Iron chelators, deferoxamine (DFO) and deferiprone (DFP) were used to treat the patients. DFP was given orally at a daily dose of 60 mg/kg for 6 days a week, while DFO was given subcutaneously at a daily dose of 40-50 mg/kg for 4-6 days per week. The measurements of serum ferritin and 24-h urine iron excretion levels were used as the indicator of the efficacy and safety of this combined treatment. **Results:** Out of the 70 patients, 13 stopped taking DFO after an average of 4 months. However, 57 patients who continued to receive the combined therapy showed very satisfactory compliance. After an average of **11.6** months, their average serum ferritin levels decreased from 2637±1292 to 1580±1024 µg/ml (P = 0.002), and their average urinary iron excretion increased from 0.41±0.27 to 0.76±0.49 mg/24 h (P = 0.003). The observed side effects were gastrointestinal disorders, elevations in liver enzymes, mild neutropenia, joint symptoms, taste disorders, dizziness, and fatigue. **Conclusions:** The study showed that combined therapy with DFO and DFP is effective in reducing serum ferritin without significant toxicity.

**Keywords**:- Thalassemia, bthalassemia, iron chelators, deferoxamine, deferiprone

## INTRODUCTION

Successful iron-chelation treatment is vital for the ideal administration of thalassemia major and other bonding subordinate disorders.[1,2,3] A few patients with transfusional iron over-burden keep on creating iron-related complications and die despite the accessibility of iron chelators.[4,5,6,7] The continuous morbidity and mortality are attributable, by and large, to unfortunate consistency because of the

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need to manage iron chelators by delayed subcutaneous imbuements no less than 5 days a week. These discoveries highlight the requirement for a protected and viable orally dynamic chelator.[8,9]

The most widely used iron-chelator, deferoxamine (DFO), is administered either subcutaneously or intravenously and results in increased iron excretion in urine and feces, a reduction in serum ferritin concentrations, and a reduced rate of hepatic and heart iron accumulation.[10,11] DFO is generally well tolerated.[12,13] The introduction of hyper transfusion programs has greatly improved the quality and expectancy of life in thalassemic patients. The most serious unfriendly impacts are anaphylactic or effective skin responses and disability of visual and hear-able keenness, while, the significant impediment of DFO use is noncompliance.[14,15] The above real factors prompted a quest for oral chelators, for example, deferiprone (DFP). An extraordinary number of studies have shown that DFP is powerful in lessening serum ferritin levels and all out iron weight in patients with thalassemia major, prompts diminished cardiovascular iron levels and can be controlled with security. Agranulocytosis, arthropathy, zinc deficiency, and gastrointestinal problems are some of the major side effects.[11,16,17,18,19,20,21] Recently, the use of DFO and DFP together for iron chelation therapy has been suggested because the two chelators have shown more additive or synergistic effects on iron burden than either drug on its own. DFP enters cells more easily than DFO does, binds to intracellular iron and transfers it extracellularly to DFO, a stronger iron chelator, in plasma before being eliminated in the feces and urine. Compared to DFP or DFO alone, combined therapy appears to have a better response and includes 24-hour iron chelation therapy.[22,23] This study aims to observe prospectively the safety and efficacy of iron chelators, deferoxamine and deferiprone, in the management of thalassemia with ferritin levels.

### Objectives

- **General objective:** The objective of this research is to assess the effectiveness and safety of iron chelator therapy in the management of thalassemia.
- **Specific objective:** This study aims to investigate the management of beta thalassemia with ferritin levels with a combination of iron chelators, DFP and DFO.

## MATERIAL AND METHODS

It is a prospective observational study that has been designed to assess the management of beta thalassemia patients with ferritin levels. This study was conducted in Tangail 250 Bed District Hospital, Dhaka, Bangladesh. The study duration was 1 year, from June 2022 to May 2023. Within this period, 70 beta thalassemia major patients of the 18 to 50 years age group came to this hospital for treatment, among which only 13 of them stopped taking DFO after 4 months of treatment. A total of 21 patients underwent splenectomy, out of which 5 patients were carriers of HCV. Among these, three were receiving antivirus therapy with interferon-a and ribavirin. All of them were receiving regular transfusions of 2 units of packed red cells, with 330 ml of 90% Ht each, once every 2 weeks, or once every 3 weeks if they had undergone splenectomy, in order to maintain an Hb level of 9-10 g/dl. All patients were

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receiving iron-chelation treatment with DFO, which was administered subcutaneously for 8-12 constant hours, in a total daily dose of 50 mg/kg, for 5-6 days a week.

**Inclusion Criteria**

The study included patients who have been diagnosed with a poor response to iron chelation therapy using DFO, despite satisfactory compliance with the treatment. These patients had serum ferritin levels above 2500 µg/ml for the past 2 years or had complications related to hemochromatosis affecting their heart, liver, or glands, even though they were compliant with DFO and had serum ferritin levels below 2500 µg/ml.

**Exclusion Criteria**

Patients with a history of anaphylactic reactions to either DFO or DFP and a previous history of neutropenia or agranulocytosis were excluded from this study.

Statistical analysis was performed using Student's t-test for paired samples. The ethical review committee of Tangail 250 Bed District Hospital approved the study. Well informed written consent paper was signed by the patients.

## RESULTS

In this study, 70 patients were selected for research purposes among which 13 patients discontinued DFO treatment after 4 months. Some experienced a rapid reduction in serum ferritin when using the combined treatment, while others found it uncomfortable to use. Two patients believed that the decrease in serum ferritin was due to the efficacy of DFP alone. The rest of the 57 patients who received combined therapy were satisfactory. Their average serum ferritin level at the start of the treatment was 2637±1292 µg/ml, and after an average of **11.5** months (range: 5–12 months), it decreased to 1580±1024 µg/ml (P = 0.002). At the beginning of the study, the mean urinary iron excretion was 0.41±0.27 mg/kg/24 h, which increased to 0.76±0.49 mg/kg/24 h after 3 months (P = 0.003). Table 1 provides details of the patient's characteristics, serum ferritin, and urine iron excretion levels.

**Table 1:** The patient's characteristics, serum ferritin, and 24 hours urine iron excretion levels.

| Age (years) | Duration of therapy (months) | HCV carrier | Transfusion units per year | Fe intake (mg/kg/24 h) | Serum ferritin (µg/ml)at the initiation of combined treatment | Serum ferritin (µg /ml)after 11.5 months of combined treatment | Urine Fe excretion (mg/kg/24 h) at the initiation of combined treatment | Urine Fe excretion (mg/kg/24 h) after 3 months of combined treatment |
|---|---|---|---|---|---|---|---|---|
| 20 | 18 | - | 49 | 0.68 | 4501 | 1370 | 0.234 | 0.64 |
| 37 | 18 | - | 47 | 0.47 | 940 | 1530 | 1.00 | 1.563 |
| 20 | 14 | - | 48 | 0.62 | 1025 | 865 | 0.273 | 0.397 |
| 23 | 21 | - | 49 | 0.55 | 2790 | 1641 | 0.294 | 0.475 |
| 35 | 26 | - | 52 | 0.854 | 4689 | 1312 | 0.276 | 0.609 |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 30 | 9 | - | 49 | 0.67 | 4618 | 3675 | 0.151 | 0.424 |
| 25 | 14 | - | 51 | 0.678 | 1267 | 891 | 0.301 | 0.709 |
| 22 | 12 | - | 47 | 0.65 | 4324 | 1076 | 0.694 | 1.51 |
| 25 | 12 | - | 52 | 0.65 | 2212 | 540 | 0.904 | 1.83 |
| 33 | 24 | - | 50 | 0.90 | 4292 | 3512 | 0.196 | 0.29 |
| 25 | 12 | + | 34 | 0.510 | 1074 | 829 | 0.07 | 0.042 |
| 23 | 11 | - | 42 | 0.63 | 4085 | 3008 | 0.807 | 1.628 |
| 25 | 11 | - | 37 | 0.46 | 2369 | 1503 | 0.953 | 1.8 |
| 32 | 5 | - | 49 | 0.63 | 1673 | 1050 | 0.546 | 0.617 |
| 30 | 6 | - | 48 | 0.867 | 1625 | 447 | 0.204 | 0.576 |
| 50 | 6 | - | 51 | 0.920 | 1721 | 1693 | 0.320 | 0.5 |
| 24 | 24 | - | 34 | 0.614 | 1475 | 808 | 0.038 | 0.202 |
| 33 | 16 | - | 36 | 0.55 | 2554 | 1941 | 0.333 | 0.54 |
| 25 | 6 | - | 52 | 0.723 | 1593 | 83 | 0.555 | 0.634 |
| 18 | 11 | - | 49 | 0.723 | 2880 | 1400 | 0.493 | 0.868 |
| 27 | 12 | - | 52 | 0.768 | 4058 | 3400 | 0.418 | 0.707 |
| 20 | 16 | - | 49 | 0.886 | 1705 | 1065 | 0.162 | 0.566 |
| 37 | 7 | - | 52 | 0.783 | 2450 | 1510 | 0.32 | 0.608 |
| 20 | 14 | - | 48 | 0.62 | 1025 | 865 | 0.273 | 0.397 |
| 49 | 8 | - | 48 | 0.79 | 4047 | 3426 | 0.295 | 0.555 |
| 23 | 11 | - | 42 | 0.63 | 4085 | 3008 | 0.807 | 1.628 |
| 37 | 7 | - | 52 | 0.783 | 2450 | 1510 | 0.32 | 0.608 |
| 29 | 18 | - | 50 | 0.65 | 1961 | 932 | 0.419 | 0.826 |
| 20 | 18 | + | 49 | 0.68 | 4501 | 1370 | 0.234 | 0.64 |
| 37 | 18 | - | 47 | 0.47 | 940 | 1530 | 1.00 | 1.563 |
| 23 | 21 | - | 49 | 0.55 | 2790 | 1641 | 0.294 | 0.475 |
| 35 | 26 | - | 52 | 0.854 | 4689 | 1312 | 0.276 | 0.609 |
| 30 | 9 | - | 49 | 0.67 | 4618 | 3675 | 0.151 | 0.424 |
| 25 | 14 | - | 51 | 0.678 | 1267 | 891 | 0.301 | 0.709 |
| 22 | 12 | - | 47 | 0.65 | 4324 | 1076 | 0.694 | 1.51 |
| 25 | 12 | - | 52 | 0.65 | 2212 | 540 | 0.904 | 1.83 |
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| 24 | 24 | - | 34 | 0.614 | 1475 | 808 | 0.038 | 0.202 |
| 33 | 16 | + | 36 | 0.55 | 2554 | 1941 | 0.333 | 0.54 |
| 25 | 6 | - | 52 | 0.723 | 1593 | 83 | 0.555 | 0.634 |
| 18 | 11 | - | 49 | 0.723 | 2880 | 1400 | 0.493 | 0.868 |
| 27 | 12 | - | 52 | 0.768 | 4058 | 3400 | 0.418 | 0.707 |
| 20 | 16 | - | 49 | 0.886 | 1705 | 1065 | 0.162 | 0.566 |
| 20 | 18 | - | 49 | 0.68 | 4501 | 1370 | 0.234 | 0.64 |
| 37 | 18 | - | 47 | 0.47 | 940 | 1530 | 1.00 | 1.563 |

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|---|---|---|---|---|---|---|---|---|
| 20 | 14 | - | 48 | 0.62 | 1025 | 865 | 0.273 | 0.397 |
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| 35 | 26 | - | 52 | 0.854 | 4689 | 1312 | 0.276 | 0.609 |
| 30 | 9 | + | 49 | 0.67 | 4618 | 3675 | 0.151 | 0.424 |
| 25 | 14 | - | 51 | 0.678 | 1267 | 891 | 0.301 | 0.709 |
| 22 | 12 | - | 47 | 0.65 | 4324 | 1076 | 0.694 | 1.51 |
| 25 | 12 | - | 52 | 0.65 | 2212 | 540 | 0.904 | 1.83 |
| Mean± s.d | | | | 0.69 ± 0.13 | 2637±1291 | 1580±1023 | 0.41±0.27 | 0.76±0.49 |
| P-values | | | | | P =0.002 | | P =0.003 | |

## DISCUSSION

In this study, two patients of 25 (8%) experienced arthralgia with no symptoms and signs of arthritis. They were not forced to discontinue chelation therapy. Both patients had high serum ferritin.

Combined therapy using both DFP and DFO has been found to have synergistic effects in reducing iron burden. DFP can easily enter cells and chelate iron intracellular. This intracellular iron can then be transferred to the stronger iron chelator DFO in the plasma. This combined therapy approach can achieve higher levels of iron excretion that cannot be achieved by either drug alone, without compromising compliance or risking potential toxicity. The therapy has been found to reduce serum ferritin levels in patients who had failed to respond satisfactorily to either DFP or DFO alone.[22,23,24,25,26,27,28,29,30]

Several studies have proved the efficacy and safety of combined iron-chelation therapy. Wonke et al. 23 administered a combination therapy of 75-110 mg/kg/day of DFP and 2 g of DFO for 2-6 days to five patients with severe iron burden. After 6-12 months of treatment, there was a substantial decrease in serum ferritin levels, though statistically insignificant. Neither of the drugs caused any adverse effects. Additionally, the study showed that the two drugs had additive effects when given on the same day, as seen in urine iron excretion studies. In a study conducted by Balveer et al,[24] seven patients with mean serum ferritin levels over 6000 µg/ml for 12 months were given 75-85 mg/kg/day of DFP and 1 g of DFO for two days. The results showed a significant decrease in serum ferritin ($p<0.01$) with minor side effects that were attributed to DFP, such as gastrointestinal symptoms.

Mourad et al,[25] treated 11 noncompliant or low-income patients who received subcutaneous DFO less than 4 days a week and had serum ferritin levels of 43000 µg/ml. They used a combination of DFP at 75 mg/kg/day and DFO at 2 g/day twice weekly, which led to a statistically significant decrease in serum ferritin levels ($P<0.01$) and a reduction in 24-hour urine iron excretion after 12 months of treatment. However, during the first month, all patients excreted more iron in response to the combined treatment than their calculated iron intake from blood transfusion. The most common side effects were nausea, joint pain, fatigue, loss of appetite, headache, transient skin rash, and abdominal discomfort. Metaxa et al. 26 treated 25 patients who had poor compliance with DFO and serum ferritin levels above 2000 µg/ml. They administered a combination of DFP at 75 mg/kg/day and DFO

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at 40 mg/kg/day for 3 days per week, which resulted in a statistically significant decrease in serum ferritin levels (P<0.0001) and a significant increase in 24-hour urine iron excretion (P<0.0001).

Two serious adverse events were observed during a study. Agranulocytosis was observed in two patients, while neutropenia was observed in four patients. Another study conducted by Kattamis et al,[27] showed that a combination therapy of 50 mg/kg/day of DFP and 3 g/day for 3 days of DFO for a duration of 12 months resulted in a significant decrease in serum ferritin (P<0.007) and a significant increase in 24-hour urine iron excretion (P<0.007) in 18 patients with severe iron burden. However, agranulocytosis was observed in two patients. Several subsequent studies 28-30 also showed a decrease in serum ferritin achieved by combined treatment.

The study conducted on 57 patients with beta-thalassemia showed a significant reduction in serum ferritin (P = 0.002) and an increase in mean 24-hour urine excretion (P = 0.003). This was achieved by administering DFO subcutaneously at a dose of 40-50 mg/kg/day over 8-12 hours for 4-6 days and DFP orally at a dose of 60 mg/kg/day for 6 days a week. This treatment schedule is effective for patients who have had a poor response to iron chelation therapy with DFO despite satisfactory compliance, resulting in serum ferritin levels above 2500 µg/ml, indicating a high iron burden. It is also beneficial for patients who have complications of the heart, liver, or glands due to hemochromatosis, despite satisfactory compliance with DFO and relatively low serum ferritin levels. The reduced daily dose of DFP was chosen to improve compliance and reduce side effects while maintaining efficacy.

The proposed schedule for combined chelation therapy can be administered safely as none of our patients experienced any major toxic events. Most of the patients in the study reported gastrointestinal symptoms such as nausea, but these were temporary and resolved within the first two months of therapy. 5 patients who had chronic HCV infection showed elevations in aspartate aminotransferase and alanine aminotransferase serum levels, about two-fold normal. However, these elevations were temporary and values were restored to pre-treatment levels after short-term discontinuation of DFP. Most studies of DFP have found that ALT levels fluctuate, especially in the first months of treatment.[10,11] Agranulocytosis has been considered to be the most serious side effect of DFP.[19,20,31,32] All 57 patients who participated in this study did not develop agranulocytosis, but four patients developed mild neutropenia. Among these patients, three were women, and two had chronic hepatitis C. A recent study by the Italian Group showed that patients with hepatitis C who were treated with DFP were more prone to agranulocytosis or mild neutropenia. Joint symptoms were observed in 13-20% of patients who received deferiprone, according to various studies.[17,18,32,33]

**Limitations**

The limitation of this study was its single-centre nature, which may cause a loss of data. As it's a capital-centered study, it does not project the overall situation of the country.

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## CONCLUSIONS

To summarize, the patients have shown excellent adherence to the combined therapy with DFO and DFP, which resulted in a significant reduction of their serum ferritin levels and an increase in 24-hour urine excretion. The combined iron-chelation therapy was not only successful but also safe, as no major toxicities were reported. The patients experienced only transient elevations of liver enzymes, mild neutropenia and gastrointestinal disorders.

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