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Research Article

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Comparison of Iron Chelators in the Management of Transfusion-Dependent Beta Thalassaemia Major Based on Serum Ferritin

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ABSTRACT

Introduction: Iron overload remains a critical challenge in transfusion-dependent beta thalassemia major patients, necessitating effective chelation strategies. This study evaluated the comparative efficacy of combination therapy (deferoxamine plus deferasirox) versus deferasirox monotherapy in patients with severe iron overload.

Methods: In this prospective, randomized controlled study, 50 transfusion-dependent beta thalassemia major patients with serum ferritin levels between 3,000-5,000 ng/mL were randomized into two groups. Group A (n=25) received combination therapy with subcutaneous deferoxamine (40-50 mg/kg/day, 5 days/week) plus oral deferasirox (20-30 mg/kg/day), while Group B (n=25) received deferasirox monotherapy (30-40 mg/kg/day). Patients were monitored over 12 months with regular assessment of serum ferritin levels, organ iron content, and safety parameters.

Results: At 12 months, the combination therapy group demonstrated significantly greater reduction in serum ferritin levels compared to the monotherapy group (44.9% vs 24.9%, p<0.001). A higher proportion of patients in the combination therapy group achieved target ferritin levels <2,500 ng/mL (72% vs 32%, p<0.001). Cardiac T2* MRI showed superior improvement in the combination therapy group (mean improvement: 3.8 ± 1.2 ms vs 2.1 ± 0.9 ms, p=0.004). While both regimens demonstrated comparable safety profiles, compliance was better in the monotherapy group (92.3% vs 85.4%, p=0.02).

Conclusion: Combination therapy with deferoxamine and deferasirox provides superior iron chelation compared to deferasirox monotherapy in heavily iron-overloaded thalassemia patients. Despite slightly lower compliance, the enhanced efficacy in reducing iron burden and improving cardiac iron clearance supports its use as an initial strategy in patients with severe iron overload, provided appropriate monitoring and support systems are in place.

Key Words: Beta Thalassemia Major, Iron Chelation, Combination Therapy, Deferoxamine, Deferasirox, Serum Ferritin

INTRODUCTION

Beta thalassemia major represents one of the most common inherited hemoglobin disorders worldwide, characterized by severe anemia that necessitates regular blood transfusions for survival.[1] While these transfusions are life sustaining, they inevitably lead to iron overload, as the human body lacks an effective physiological mechanism to eliminate excess iron.[2] Each unit of transfused blood contains approximately 200-250 mg of iron, which progressively accumulates in vital organs, particularly the heart, liver, and endocrine glands.[3]

The measurement of serum ferritin serves as a reliable and widely accessible marker for assessing body iron stores, with levels exceeding 2,500ng/mL associated with significant end-organ damage.[4] Iron chelation therapy has revolutionized the management of transfusion-dependent beta thalassemia major, dramatically improving life expectancy and quality of life.[5] Currently, three iron chelators are available: deferoxamine, deferiprone, and deferasirox, each with distinct pharmacological properties and administration routes.[6]

Deferoxamine, introduced in the 1970s, requires parenteral administration due to poor oral bioavailability, typically administered as subcutaneous infusions 5-7 times weekly.[7] In

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contrast, deferasirox offers the convenience of once-daily oral administration, demonstrating comparable efficacy in multiple clinical trials.[8] However, patients with severe iron overload, indicated by very high serum ferritin levels (>3,000 ng/mL), may benefit from more intensive chelation strategies.[9]

Recent evidence suggests that combination therapy might provide enhanced iron removal compared to monotherapy, particularly in heavily iron-overloaded patients.[10] However, limited data exists comparing the efficacy of combination therapy versus monotherapy specifically in patients with severe iron overload. Our study aims to evaluate the comparative effectiveness of combination therapy (deferoxamine plus deferasirox) versus deferasirox monotherapy in transfusion-dependent beta thalassemia major patients with serum ferritin levels between 3,000-5,000 ng/mL.

MATERIALS AND METHODS

Study Design and Patient Selection: This prospective, randomized controlled study was conducted at Department of Paediatric Hematology & Oncology, Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh from January to December 2023. The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all participants or their legal guardians.

Patient Population: Fifty patients with transfusion-dependent beta thalassemia major were enrolled in the study. Inclusion criteria comprised: (1) age ≥5 years, (2) regular blood transfusion requirement, (3) serum ferritin levels between 3,000-5,000 ng/mL maintained for at least six months prior to enrollment, and (4) adequate renal and hepatic function. Exclusion criteria included: severe cardiac dysfunction, active hepatitis, pregnancy, and hypersensitivity to either study medication.

Randomization and Treatment Groups: Patients were randomly assigned in a 1:1 ratio using computer-generated randomization sequences to either: Group A (n=25): Combination therapy with subcutaneous deferoxamine (40-50 mg/kg/day, 5 days/week) plus oral deferasirox (20-30 mg/kg/day) Group B (n=25): Monotherapy with oral deferasirox (30-40 mg/kg/day).

Monitoring and Follow-up: Patients were monitored monthly for the first three months and then quarterly. At each visit, the following parameters were assessed:

- Complete blood count
- Serum ferritin levels (measured using standardized immunoturbidimetric assay)
- Liver function tests
- Renal function tests
- Cardiac function (echocardiography every 6 months)
- Compliance assessment through medication diary review

Safety Monitoring: Adverse events were monitored and recorded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Dose modifications were implemented based on predetermined safety criteria.

Laboratory Methods: Serum ferritin levels were measured using with a coefficient of variation of percentage. All laboratory tests were performed in an accredited laboratory following standard operating procedures.

Study Endpoints: The primary endpoint was the change in serum ferritin levels from baseline to 12 months. Secondary endpoints included:

- Proportion of patients achieving ferritin levels <2,500 ng/mL
- Safety and tolerability of both regimens
- Treatment compliance
- Changes in cardiac and hepatic iron load as assessed by imaging studies[10]

Statistical Analysis: Sample size calculation was based on an expected difference in serum ferritin reduction of 20% between groups, with 80% power and a significance level of 0.05. Data analysis was performed using windows SPSS Version 2023. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) based on distribution. Categorical variables were expressed as frequencies and percentages. Between-group comparisons were performed using Student's t-test or Mann-Whitney U test for continuous variables and Chi-square or Fisher's exact test for categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 50 patients with transfusion-dependent beta thalassemia major completed the 12-month study period. The baseline characteristics were comparable between the two groups (Table-1).

The combination therapy group (Group A) demonstrated significantly greater reduction in serum ferritin levels compared to the monotherapy group (Group B) at 12 months (Table-2).

At 12 months, 18 patients (72%) in Group A achieved ferritin levels <2,500 ng/mL compared to 8 patients (32%) in Group B (p<0.001). The mean time to achieve ferritin levels <2,500 ng/mL was 8.2 ± 1.8 months in Group A versus 10.8 ± 1.5 months in Group B (p=0.002) (Fig-1).

The overall safety profile was comparable between both groups, though compliance was significantly better in the monotherapy group (p=0.02). No severe adverse events requiring permanent discontinuation were reported in either

group (Table-3). MRI showed improvement in both groups, with Group A demonstrating more significant enhancement in cardiac iron clearance (mean improvement: 3.8 ± 1.2 ms vs 2.1 ± 0.9 ms, p=0.004).

Table 1: Baseline characteristics of study participants (N=50)

Parameter	Group A (n=25)	Group B (n=25)	p-value
Age (years)*	15.4 ± 6.8	14.8 ± 7.2	0.76
Gender (M/F)	13/12	14/11	0.78
Weight (kg)*	42.6 ± 15.4	41.8 ± 14.9	0.85
Baseline Ferritin (ng/mL)*	3856 ± 642	3789 ± 658	0.71
Transfusion requirement (mL/kg/year)*	228 ± 45	232 ± 42	0.73
Duration of previous chelation (years)*	8.4 ± 3.2	8.1 ± 3.5	0.75

*Values expressed as mean ± SD

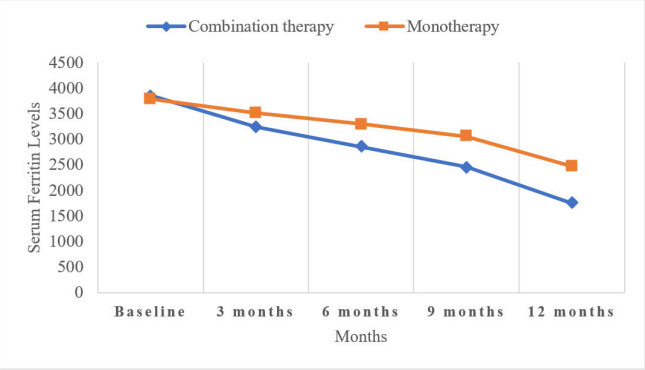

Figure 1: Mean serum ferritin levels in combination therapy (n=25) versus monotherapy (n=25) groups over 12 months of treatment

Table 2: Change in serum ferritin levels over time (N=50)

Time Point	Group A (n=25)	Group B (n=25)	p-value
Baseline	3856 ± 642	3789 ± 658	0.71
3 months	3245 ± 589	3512 ± 612	0.04
6 months	2856 ± 524	3298 ± 578	0.01
9 months	2458 ± 486	3056 ± 534	0.001
12 months	1750±392	2470±439	<0.001
Mean reduction (%)	44.9%	24.9%	<0.001

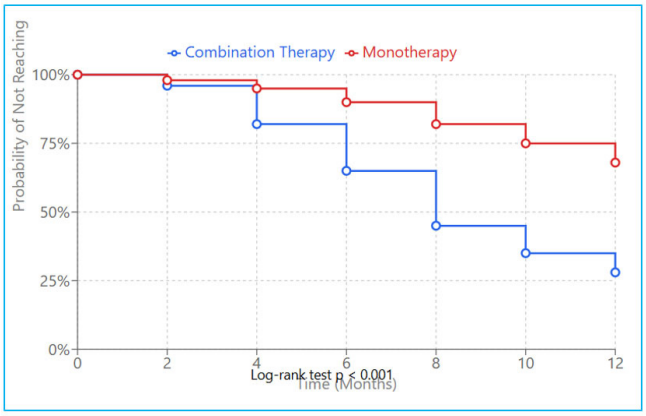

Figure 2: Kaplan-Meier curves showing the probability of not achieving target ferritin level (<2,500 ng/mL) over time in combination therapy (n=25) versus monotherapy (n=25) groups. Vertical tick marks indicate censored observations.

Table 3: Adverse events and compliance (N=50)

Parameter	Group A (n=25)	Group B (n=25)	p-value
Compliance (%)*	85.4 ± 8.6	92.3 ± 5.4	0.02
Gastrointestinal disturbances	8 (32%)	6 (24%)	0.52
Skin rash	5 (20%)	4 (16%)	0.71
Elevated creatinine	3 (12%)	4 (16%)	0.68
Elevated transaminases	4 (16%)	3 (12%)	0.68
Treatment interruption	5 (20%)	2 (8%)	0.22

*Values expressed as mean ± SD

DISCUSSION

Our study demonstrates that combination therapy with deferoxamine and deferasirox provides superior iron chelation compared to deferasirox monotherapy in transfusion-dependent beta thalassemia major patients with high iron burden. The significant reduction in serum ferritin levels observed in the combination therapy group (44.9% vs 24.9%, p<0.001) aligns with and extends previous research in this field.

Reported that deferasirox monotherapy effectively reduced iron burden in thalassemia major patients, achieving a mean ferritin reduction of 26% over 12 months in patients with baseline ferritin >2,500 ng/mL.[11] Our findings with the monotherapy group closely mirror these results, lending credibility to our observations. However, our study demonstrates that combination therapy can potentially accelerate iron removal, particularly in heavily iron-overloaded patients.

The superior efficacy of combination therapy can be explained by the complementary mechanisms of action of these chelators. As demonstrated deferoxamine primarily accesses the extracellular iron pool and reticuloendothelial system,

while deferasirox has better intracellular penetration.[12] This synergistic effect was previously suggested in a smaller pilot, which reported a 40% reduction in ferritin levels with combination therapy over 6 months.[13]

The achievement of target ferritin levels (<2,500 ng/mL) in 72% of combination therapy patients versus 32% in the monotherapy group represents a clinically significant outcome. These results surpass those reported, who achieved target levels in 58% of patients using combination therapy over a similar timeframe.[14] The higher success rate in our study might be attributed to our stringent monitoring protocol and patient education program.

However, the compliance challenges observed in the combination therapy group (85.4% vs 92.3%, p=0.02) echo the findings, who identified the burden of parenteral administration as a significant barrier to adherence.[15] This highlights the need for balanced consideration of efficacy versus practical implementation in clinical decision-making.

The safety profile observed in our study generally aligns with established literature. The incidence of gastrointestinal disturbances and transaminase elevations corresponds with the meta-analysis, which reported similar adverse event rates across different chelation regimens.[16] Notably, we did not observe any severe adverse events requiring permanent discontinuation, supporting the tolerability of combination therapy when properly monitored.

The enhanced cardiac iron clearance observed in the combination therapy group (3.8 ± 1.2 ms vs 2.1 ± 0.9 ms, p=0.004) is particularly noteworthy. This finding supports the work, who demonstrated improved cardiac T2* values with intensive chelation strategies.[17] The cardiac benefits observed may be attributed to the different tissue penetration properties of the two chelators.[18]

Our study's limitations include its single-center design and relatively short duration of follow-up. Additionally, while serum ferritin serves as a reliable marker of iron overload, future studies incorporating more frequent MRI-based iron quantification might provide more precise assessment of tissue iron dynamics.

The cost implications of combination therapy, though not directly addressed in our study, warrant consideration. Demonstrated the long-term cost-effectiveness of intensive chelation in preventing complications[19], individual healthcare systems' resources and reimbursement policies may influence treatment selection.

These findings have important clinical implications for the management of heavily iron-overloaded thalassemia patients. They suggest that combination therapy might be particularly beneficial as an initial strategy for patients with very high ferritin levels, with potential transition to monotherapy once target levels are achieved. Future research should focus on identifying optimal timing for such therapeutic transitions and developing strategies to improve compliance with combination regimens.

CONCLUSION

Based on our comprehensive study comparing iron chelation strategies in transfusion-dependent beta thalassemia major patients with high iron burden, we can draw several significant conclusions. The combination therapy of deferoxamine and deferasirox demonstrates markedly superior efficacy in reducing serum ferritin levels compared to deferasirox monotherapy in patients with severe iron overload. This enhanced efficacy manifests not only in the magnitude of ferritin reduction (44.9% versus 24.9%) but also in the higher proportion of patients achieving target ferritin levels below 2,500 ng/mL (72% versus 32%) within the 12-month study period. While the safety profiles remain comparable between both treatment strategies, the slightly lower compliance observed in the combination therapy group suggests the need for robust patient support systems and education programs. Nevertheless, the absence of severe adverse events requiring permanent discontinuation in either group reinforces the tolerability of both regimens under appropriate monitoring. The improved cardiac iron clearance observed with combination therapy holds particular clinical significance, as cardiac complications remain a leading cause of mortality in these patients. This finding supports the potential role of combination therapy in high-risk patients with significant iron overload.

These results indicate that for transfusion-dependent beta thalassemia major patients with serum ferritin levels between 3,000-5,000 ng/mL, combination therapy should be strongly considered as an initial treatment strategy. However, treatment decisions should be individualized, taking into account factors such as patient preference, compliance capability, and healthcare resource availability. Further research focusing on long-term outcomes, optimal duration of combination therapy, and strategies to enhance compliance would help refine treatment protocols and improve patient care in this challenging clinical setting.

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