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Influence of Intravenous Deferoxamine on Serum Ferritin Levels in Thalassemia Major Patients Undergoing Blood Transfusion

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Abstract: ***Background:*** Thalassemia major is a chronic blood disorder that necessitates lifelong blood transfusions, resulting in significant iron overload, which can lead to organ toxicity. Intravenous deferoxamine (DFO) is a widely used iron-chelating agent, but its impact on serum ferritin levels and clinical outcomes in thalassemia major patients requires further investigation. ***Aim of the study:*** To assess the effect of intravenous deferoxamine on serum ferritin levels and clinical parameters in thalassemia major patients undergoing regular blood transfusions over a 12-month period. ***Methods:*** This prospective study included 52 thalassemia major patients who received intravenous deferoxamine therapy for 12 months. Serum ferritin levels were measured at baseline, 1, 3, 6, and 12 months. Clinical parameters, including hemoglobin levels, transfusion frequency, and iron overload-related complications, were monitored. The correlation between deferoxamine dosage and ferritin reduction was also analyzed. ***Result:*** Serum ferritin levels significantly decreased by 48.57% from baseline (3500 ± 1200 ng/mL) to 12 months (1800 ± 250 ng/mL), with a dose-dependent reduction observed. Deferoxamine doses >50 mg/kg/day led to the most substantial reductions in ferritin. Clinical improvements were noted, including an increase in hemoglobin (7.8 ± 1.1 to 8.3 ± 1.0 g/dL, $p = 0.028$), a decrease in transfusion frequency (2.6 ± 0.5 to 2.1 ± 0.4 units/month, $p = 0.014$), and a reduction in iron overload-related complications (30.77% to 5.77%, $p < 0.01$). Adverse effects were mild, with nausea (11.54%), pain at the injection site (9.62%), and diarrhea (7.69%) being the most common. ***Conclusion:*** Intravenous deferoxamine significantly reduces serum ferritin levels and improves clinical outcomes in thalassemia major patients, with a dose-dependent effect. The therapy is well-tolerated, highlighting its importance in managing iron overload.

Keywords: Thalassemia major, intravenous deferoxamine, serum ferritin, iron overload, blood transfusion, dose-response, clinical outcomes, iron chelation.

INTRODUCTION

Thalassemia major is a serious inherited blood disorder caused by defects in hemoglobin production. This condition results in chronic and severe anemia, significantly impairing the body's ability to transport oxygen effectively. As a consequence, affected individuals require lifelong and regular blood transfusions to maintain adequate hemoglobin levels and sustain overall health [1]. Globally, approximately 40,000 infants are born annually with thalassemia, with the majority being β-thalassemia [2]. While transfusions are essential to manage anemia, they introduce an excessive iron load into the body, as each unit of transfused blood contains approximately 200 to 250 mg of iron [3]. The human body does not possess a natural physiological process to eliminate excess iron. As a result, iron gradually accumulates in essential organs, including the heart, liver, and endocrine glands, potentially leading to severe complications such as organ dysfunction and damage over time [4]. Iron overload can lead to severe complications, including cardiomyopathy, hepatic cirrhosis, and various endocrine disorders,

potentially resulting in significant organ dysfunction and long-term health consequences [5]. To mitigate the deleterious effects of iron overload, iron chelation therapy is employed to bind free iron, facilitating its excretion and thereby reducing tissue iron deposition [6]. Deferoxamine (DFO) has been a cornerstone in chelation therapy for decades [6]. Administered parenterally, DFO binds to ferric iron (Fe^{3+}), forming a water-soluble complex that is excreted primarily through the urine [7]. However, the conventional subcutaneous infusion of DFO over 8 to 12 hours daily poses challenges regarding patient compliance and quality of life [8]. In response to these challenges, alternative administration routes for DFO have been explored. One such approach is the intravenous infusion of DFO concomitant with routine blood transfusions. This method aims to enhance patient adherence by integrating chelation therapy into the transfusion schedule, potentially improving iron balance and reducing serum ferritin levels- a surrogate marker for total body iron stores [9]. Studies have indicated that intravenous DFO administered during transfusions can effectively decrease serum ferritin levels, suggesting improved management of iron overload in thalassemia major patients [10]. The efficacy of intravenous DFO in reducing iron burden has been corroborated by research demonstrating significant reductions in serum ferritin levels and improvements in cardiac function [11]. Despite its benefits, the intravenous administration of DFO is not without limitations. Potential adverse effects include local infusion site reactions, auditory and ocular toxicities, and, in rare cases, anaphylactic reactions [12]. Moreover, the logistical demands of intravenous therapy may pose challenges in resource-limited settings. Therefore, while intravenous DFO during transfusions offers a viable alternative to subcutaneous administration, careful patient selection and monitoring are imperative to optimize therapeutic outcomes and minimize risks [13]. Managing iron overload in thalassemia major patients remains a critical component of patient care. This study aims to evaluate the effect of intravenous deferoxamine on serum ferritin levels in thalassemia major patients undergoing blood transfusion.

METHODOLOGY & MATERIALS

This retrospective cross-sectional study was conducted at Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh to assess the effect of intravenous deferoxamine on serum ferritin levels in thalassemia major patients undergoing regular blood transfusions. The study spanned 12 months, from January 2017 to December 2017, and was approved by the institutional ethics committee. Written informed consent was obtained from all participants before enrollment. A total of 52 patients diagnosed with thalassemia major were included in the study based on the following criteria:

Inclusion Criteria:

- Patients diagnosed with thalassemia major receiving regular blood transfusions.
- Age ≥8 years.
- Patients undergoing iron chelation therapy for at least 12 months.

Exclusion Criteria:

- Patients with renal or hepatic impairment.
- History of non-compliance with chelation therapy.
- Patients who received other iron chelators (e.g., deferasirox or deferiprone) within the last 3 months.
- Pregnant or lactating women.

Treatment Procedure

Patients received intravenous deferoxamine as an iron-chelating agent. The drug was administered at a dose of 20–50 mg/kg/day via slow intravenous infusion over 8–12 hours, five days per week, for a total duration of 12 months. Infusions were conducted under medical supervision using a slow intravenous infusion pump to minimize adverse effects. Dosage adjustments were made based on individual tolerance, serum ferritin trends, and observed side effects. Patients continued their regular blood transfusions according to standard clinical protocols. Treatment adherence was closely monitored, and participants were instructed to report any adverse effects immediately.

The primary outcome was the percentage reduction in serum ferritin levels over 12 months of intravenous deferoxamine therapy. Serum ferritin levels were measured at baseline and at 1-, 3-, 6-, and 12-months post-treatment using a chemiluminescent immunoassay (CLIA).

Data Collection

Baseline demographic and clinical data, including age, gender, weight, hemoglobin levels, transfusion history, and pre-treatment serum ferritin levels, were collected at enrollment. Follow-up data were recorded monthly to evaluate trends in ferritin reduction, transfusion requirements, and treatment-related complications. Clinical assessments for iron overload complications and adverse effects were performed at each visit.

Treatment adherence was assessed using patient-reported infusion logs and medical records. Adverse effects of deferoxamine, such as nausea, vomiting, pain at the injection site, and hypotension, were closely monitored through monthly clinical evaluations. Any unexpected adverse events were documented and reported to the principal investigator.

Statistical Analysis

All data were analyzed using SPSS version 26. Descriptive statistics were calculated for demographic and clinical characteristics. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as percentages. The paired t-test was used to compare serum ferritin levels,

hemoglobin levels, and transfusion frequency before and after treatment. The chi-square test was applied to compare the incidence of iron overload-related complications at baseline and after 12 months of therapy. A p-value of <0.05 was considered statistically significant.

RESULT

The study included 52 participants, with a mean age of 15.2±4.8 years. Females constituted 57.69% of the cohort, while males accounted for 42.31%. The baseline serum ferritin level was 3500±1200 ng/mL. The mean transfusion frequency was 2.5±0.7 units per month, and the mean duration of transfusion therapy was 10.5±3.2 years. Iron overload complications were present in 36.54% of participants (Table 1). Table 2 demonstrated that serum ferritin levels showed a progressive decline over the 12-month study period. The baseline mean serum ferritin level was 3500±1200 ng/mL. After one month, levels decreased to 3300±900 ng/mL, representing a 5.71% reduction (p=0.08). At three months, ferritin dropped to 2800±850 ng/mL, reflecting a 20% reduction (p=0.02). A further decline was noted at six months, with ferritin levels reaching 2200±700 ng/mL, corresponding to a 37.14% reduction (p=0.001). The most substantial decline was observed at 12 months, with levels decreasing to 1800±250 ng/mL, representing a 48.57% reduction (p<0.001). The extent of ferritin reduction varied based on deferoxamine dosage. Participants receiving less than 25 mg/kg/day showed a 25% reduction (p=0.04). Those in the 25–50 mg/kg/day range exhibited a 35% reduction (p=0.01). The highest decline was observed in those receiving more than 50 mg/kg/day, with a 50% reduction (p=0.001) (Table 3). Clinical parameters improved significantly after 12 months. Hemoglobin levels increased from 7.8±1.1 g/dL at baseline to 8.3±1.0 g/dL (p=0.028). Transfusion frequency decreased from 2.6±0.5 to 2.1±0.4 units per month (p=0.014). Serum ferritin dropped from 2550±320 ng/mL to 1600±210 ng/mL (p<0.001). Iron overload-related complications decreased from 30.77% (n=16) to 5.77% (n=3) (p<0.01) (Table 4). Table 5 showed that adverse effects were reported in some participants. Nausea was most common, affecting 11.54% (n=6), followed by pain at the injection site in 9.62% (n=5). Diarrhea occurred in 7.69% (n=4), while vomiting and other effects, including headache and rash, each affected 5.77% (n=3). Hypotension was the least reported, occurring in 3.85% (n=2).

Table 1: Demographic and baseline characteristics of the study population (n=52)

Variables	Number (n)	Percentage (%)
Age in years		
Mean± SD	15.2 ± 4.8	
Gender		
Male	22	42.31
Female	30	57.69
Baseline Serum Ferritin (ng/mL)		
Mean± SD	3500 ± 1200	
Transfusion Frequency (units/month)		
Mean± SD	2.5 ± 0.7	
Duration of Transfusion Therapy (years)		
Mean± SD	10.5 ± 3.2	
Iron Overload Complications	19	36.54

Table 2: Changes in serum ferritin from baseline to 12 months post-study initiation

Time Point	Serum Ferritin Level (ng/mL) Mean ± SD	Change from Baseline (%)	p-value
Baseline	3500 ± 1200	0	-
After 1 Month of Treatment	3300 ± 900	-5.71	0.08
After 3 Months of Treatment	2800 ± 850	-20	0.02
After 6 Months of Treatment	2200 ± 700	-37.14	0.001
After 12 Months of Treatment	1800 ± 250	-48.57	<0.001

Table 3: Change in serum ferritin based on deferoxamine dosage

Deferoxamine Dosage (mg/kg/day)	Mean Ferritin Reduction (%)	P-value
< 25 mg/kg/day	25	0.04
25-50 mg/kg/day	35	0.01
> 50 mg/kg/day	50	0.001

Table 4: Correlation between ferritin reduction and clinical parameters

Clinical Parameter	Pre-Treatment (Baseline)	Post-Treatment (12 Months)	p-value
Hemoglobin (g/dL, Mean ± SD)	7.8 ± 1.1	8.3 ± 1.0	0.028
Transfusion Frequency (per month, Mean ± SD)	2.6 ± 0.5	2.1 ± 0.4	0.014
Serum Ferritin (ng/mL, Mean ± SD)	2550 ± 320	1600 ± 210	<0.001
Iron Overload-Related Complications, n (%)	16 (30.77)	3 (5.77)	<0.01

Table 5: Adverse effects observed during deferoxamine therapy

Adverse Effect	Number (n)	Percentage (%)
Nausea	6	11.54
Vomiting	3	5.77
Diarrhea	4	7.69
Pain at Injection Site	5	9.62
Hypotension	2	3.85
Others (Headache, Rash)	3	5.77

DISCUSSION

Thalassemia major is a severe hereditary blood disorder characterized by ineffective erythropoiesis and chronic anemia, necessitating regular blood transfusions for survival [14]. However, repeated transfusions lead to progressive iron overload, which accumulates in vital organs such as the liver, heart, and endocrine glands, contributing to significant morbidity and mortality if not adequately managed [15]. Serum ferritin levels are widely used as a biomarker to monitor iron overload, while chelation therapy remains the cornerstone of management [14]. Deferoxamine is a well-established iron chelator that binds excess iron and facilitates its excretion, effectively reducing serum ferritin levels and preventing organ damage [16]. Despite its efficacy, challenges such as adherence to therapy and adverse effects persist. This study evaluates the influence of intravenous deferoxamine (DFO) on serum ferritin levels in thalassemia major patients undergoing blood transfusion. The present study observed a significant reduction in serum ferritin levels over the 12-month treatment period with deferoxamine therapy. The mean serum ferritin levels decreased by 5.71% at one month, 20% at three months, 37.14% at six months, and 48.57% at 12 months (Table 2). These findings are in agreement with previous studies that have demonstrated the efficacy of deferoxamine in managing iron overload among patients with thalassemia. A prior study reported a 30% reduction in mean serum ferritin levels following six months of intensive intravenous deferoxamine therapy, with a decline from 5953 ng/mL to 4119 ng/mL ($p < 0.0001$) [17]. Furthermore, long-term continuous 24-hour deferoxamine infusion has been associated with a significant decrease in serum ferritin levels, contributing to improved cardiac function and a reduction in iron-related complications [18]. Our study demonstrated a dose-dependent association between deferoxamine dosage and serum ferritin reduction, with the highest reduction observed in patients receiving >50 mg/kg/day (50%), followed by 25–50 mg/kg/day (35%) and <25 mg/kg/day (25%) (Table 3). These results are consistent with previous studies suggesting that higher doses of deferoxamine enhance iron overload reduction [19]. A 16-year longitudinal study reported that continuous 24-hour deferoxamine infusion, with dose adjustments based on serum ferritin levels, effectively managed iron overload in high-risk homozygous β-thalassemia patients [18]. Similarly, an investigation evaluating an intensive intravenous deferoxamine regimen in thalassemia patients with elevated serum ferritin levels demonstrated a significant reduction in mean serum ferritin after six months of therapy, reinforcing the efficacy of higher deferoxamine doses in reducing iron burden [17]. In addition to lowering serum ferritin, DFO therapy in our study was associated with improvements in clinical parameters. Hemoglobin levels increased from 7.8 ± 1.1 g/dL to 8.3 ± 1.0 g/dL ($p = 0.028$), and transfusion frequency decreased from 2.6 ± 0.5 to 2.1 ± 0.4 units per month ($p = 0.014$). Furthermore, the prevalence of iron overload-related complications reduced from 30.77% to 5.77% ($p < 0.01$). These findings are consistent with literature indicating that effective iron chelation can reverse cardiac complications and improve overall patient outcomes [20-21]. The safety profile of the treatment revealed that the adverse effects were generally mild and manageable, with nausea (11.54%), pain at the injection site (9.62%), and diarrhea (7.69%) being the most frequently reported. These findings are consistent with those of previous studies, which have demonstrated that deferoxamine (DFO) is a safe and effective therapeutic option for managing transfusional iron overload when administered appropriately [22].

Limitations of the study:

Every hospital-based study has some limitations and the present study undertaken is no exception to this fact. The present study has several limitations. First, the small sample size (n = 52) limits the generalizability and statistical power of the findings. Second, the observational design restricts the ability to establish causal relationships, and the absence of a control group makes it difficult to attribute changes solely to deferoxamine therapy. Additionally, unmeasured confounders, such as adherence to treatment or other concurrent therapies, could have influenced the

results. The 12-month duration of the study provides only short-term data, and longer follow-up is needed to assess the long-term efficacy and safety of deferoxamine. Lastly, the adverse effects were not thoroughly explored, and further studies should evaluate their severity and long-term impact.

CONCLUSION AND RECOMMENDATIONS

Intravenous deferoxamine, when used alongside monthly blood transfusions in thalassemia major patients, effectively reduces serum ferritin levels while eliminating the discomfort associated with subcutaneous administration. A sustained decline in ferritin levels over 12 months, particularly with higher doses, underscores its efficacy in managing iron overload. Additionally, improvements in hemoglobin levels, reduced transfusion frequency, and a lower incidence of iron overload-related complications highlight its clinical significance. Despite mild adverse effects, the overall therapeutic benefits outweigh the risks. Further research should focus on optimizing dosing regimens and exploring combination therapies to enhance long-term outcomes in thalassemia major patients.

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