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Dosage and Ferritin Reduction in Paediatric Thalassemia Major: A Cross-Sectional Study

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Abstract

Thalassemia is a genetic disorder that requires regular blood transfusions, often resulting in iron overload. Iron chelation therapy with deferiprone is commonly used to manage the iron overload, yet the relationship between deferiprone dosage and ferritin level reduction remains unclear. This study aimed to find out how the dose of deferiprone affects the reduction of serum ferritin levels in children with thalassemia major. A cross-sectional analytical study was conducted involving 69 paediatric patients with thalassemia major receiving deferiprone therapy at Dr. Mohammad Hoesin Central General Hospital, Palembang. Data on patient demographics, transfusion frequency, deferiprone dose, and serial ferritin levels (3–6 months apart) were collected. The optimal dose cut-off was determined using ROC analysis, and statistical association was tested using the Chi-Square test. Most patients (56.5%) received deferiprone doses ≤77.95 mg/kgBW. Only 36.2% achieved a ferritin reduction of ≥20%, while 50.7% experienced increased ferritin levels. No statistically significant association was found between deferiprone dose and ferritin reduction ($p = 0.051$), although a trend toward lower success in the high-dose group was observed (PR 0.355, 95% CI: 0.124–1.019). The average dose of deferiprone administered in this study was below the minimum dose recommended by the FDA, which may explain the lack of significant association with serum ferritin reduction. Further research with controlled dosing and exclusion of confounding variables is recommended to evaluate deferiprone effectiveness more accurately.

Keywords: Ferritin levels, Deferiprone, Paediatric Thalassemia

1. Introduction

Thalassemia is a genetic disorder caused by impaired production of one or more globin subunits of hemoglobin. Clinically, thalassemia is classified into three types: thalassemia minor, which represents a carrier state; thalassemia intermedia, which may present with clinical symptoms and require occasional blood transfusions; and thalassemia major, the most severe form, which necessitates regular blood transfusions.[1,2] Worldwide, the number of individuals with thalassemia reached approximately 7% of the global population. Meanwhile in Indonesia, 6–10% of the population have been reported as carriers. Data from the Indonesian Thalassemia Foundation recorded 9,028 cases in 2018, and this number continues to rise annually. As of June 2021, the number of thalassemia cases in Indonesia had reached 10,973.[2–4] Despite the rising incidence of cases, the only curative intervention is bone marrow transplantation, which is limited to young patients possessing a suitably matched donor. This procedure necessitates prolonged immunosuppression

to avert or manage transplant-related immunological complications and is infrequently performed in Indonesia.[5–7] Patients with thalassemia major require regular blood transfusions to maintain hemoglobin levels above 10 mg/dL.[8,9] Blood transfusion plays a crucial role in preventing severe anemia, improving ineffective erythropoiesis, and avoiding complications.[10]

Individuals with thalassemia tend to experience iron overload due to ineffective erythropoiesis, which leads to increased intestinal iron absorption. Regular blood transfusions exacerbate this condition by introducing additional iron into the body. Continuous iron accumulation can result in iron deposition in various organs, including the heart, liver, and brain, thereby impairing and damaging their function.[10,11] To prevent these complications, regular monitoring of serum ferritin levels and iron chelation therapy are necessary to maintain iron homeostasis. Ferritin levels should be monitored every three months, as this interval is sufficient to detect significant changes without the need for more frequent testing. In addition to reflecting iron storage status, ferritin levels are also used to assess treatment effectiveness and determine whether iron chelation therapy is needed in thalassemia patients.[10]

Iron chelation therapy is essential for thalassemia patients because excess iron in the body cannot be naturally excreted effectively. Chelating agents bind and facilitate the elimination of excess iron.[9] Iron chelation therapy is typically initiated when ferritin levels reach 1,000 µg/L or when the patient has received 10–12 transfusions. Deferiprone is one of the iron chelators approved by the U.S. Food and Drug Administration (FDA). In developing countries, deferiprone is the most commonly used chelator in children due to its better compliance and lower cost compared to deferasirox.[11,12] Ramwani et al. showed that deferiprone and deferasirox were highly effective in reducing ferritin levels, whether used alone or in combination.[13] Elalfy et al. reported that 66% of patients treated with deferiprone were able to maintain ferritin levels, compared to 39% in the placebo group.[14] Similarly, a study by Binding et al. (2020) showed that 65% of patients experienced a reduction in ferritin levels during the study period, particularly those given increased deferiprone dosage.[15] Numerous studies have demonstrated the efficacy of deferiprone in reducing ferritin levels. However, studies specifically examined the relationship between deferiprone dosage and ferritin reduction on paediatric population are limited. Therefore, this study aims to investigate the relationship between deferiprone dosage and ferritin level reduction in paediatric thalassemia patients at Dr. Mohammad Hoesin Central General Hospital, Palembang.

2. Methods

This study employed an analytical observational design with a cross-sectional approach. The minimum required sample size was calculated to be 69 subjects using the Lemeshow formula for a single population.[16] Participants were paediatric patients aged 2 to 18 years with a diagnosis of thalassemia major who were receiving deferiprone therapy at Dr. Mohammad Hoesin Central General Hospital, Palembang. Eligible subjects had been on a stable dose of deferiprone for at least three months and demonstrated moderate-to-high medication adherence, as indicated by a Morisky Medication Adherence Scale (MMAS-8) score of ≥6.[17] Patients were excluded if they refused to participate, were receiving combination therapy involving deferiprone and other iron chelators, or lacked two serum ferritin measurements taken within a maximum interval of six months.

The independent variable in this study was the dose of deferiprone administered. The dependent variable was the reduction in serum ferritin levels, defined as the percentage change between initial and final measurements. A reduction was categorized as a ≥20% decrease, while changes <20% were classified as no reduction. Ferritin values were obtained from laboratory records within 3–6 months prior to data collection. Both primary and secondary data were collected and analyzed following the completion of data acquisition. This study has been declared ethically appropriate by Dr. Mohammad Hoesin Committee (No.DP.04.03/D.XVIII.06.08.ETIK/147/2025)

Data were processed using SPSS version 27 (Statistical Package for the Social Sciences) and presented in the form of data distribution tables, percentages, and associations. Cut-off determination for deferiprone dosage was performed using the Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC) analysis. Data analysis was conducted through univariate and bivariate approaches, with the bivariate analysis using the Chi-Square test.

3. Results

A total of 85 respondents were interviewed. Among them, 69 respondents met the inclusion and exclusion criteria, while 16 were excluded due to incomplete ferritin data. Out of the 69 paediatric patients included in this study, the majority were in the 13–18-year age group (52.2%, Table 1). Most patients were diagnosed at ≤24 months (50.7%).

Table 1. Frequency distribution of characteristics of paediatric thalassemia major patients at Dr. Mohammad Hoesin Central General Hospital, Palembang (n=69)

Characteristic	Frequency	Percentage (%)
Current Age (years)		
2–5	8	11.6
6–12	25	36.2
13–18	36	52.2
Age at Diagnosis (months)		
≤24	35	50.7
>24	34	49.3
Sex		
Male	26	37.7
Female	43	62.3
Initial Ferritin Level (µg/L)		
<1000	4	5.8
1000–2500	12	17.4
>2500	53	76.8
Final Ferritin Level (µg/L)		
<1000	1	1.4
1000–2500	16	23.2
>2500	52	75.4
Transfusion Frequency (times/year)		
≤12	40	58.0
>12	29	42.0

Table 2. Distribution of deferiprone dosage and ferritin in paediatric thalassemia major patients

	Frequency	Percentage (%)
Deferiprone Dosage (mg/kgBW)		
Dose > 77.95	30	43.5
Dose ≤ 77.95	39	56.5
Ferritin Level		
Ferritin reduction ≥20%	25	36.2
Ferritin reduction <20%	9	13.04
Ferritin increase	35	50.72

Table 3. Ferritin levels in paediatric thalassemia major patients

		Median (Min-Max)		
	n	Initial Ferritin (µg/L)	Final Ferritin (µg/L)	Median Difference (µg/L)
Ferritin reduction ≥20%	25	5800.40 (1,923.60–15,152.40)	3,934.00 (1,257.70–9,219.5)	1,648.20 (540.40–5,932.90)
Ferritin reduction <20%	9	4,561.30 (1,1168.70–15,706.50)	4,548.80 (1028– 1,5651.9)	498.60 (12,50–1,968.05)
Ferritin increase	35	3,100.00 (451.40– 10,551.49)	4,672.10 (737.3– 14,788.8)	878.70 (22.10–4237.41)

Table 4. Association between deferiprone iron chelation dose and reduction in ferritin levels in paediatric patients with thalassemia major

Deferiprone Dose (mg/kgBW)	Ferritin Reduction						PR (CI)	P *Value*
	Ferritin Reduction(≥20%)		No Reduction (<20%)		Total			
	n	%	n	%	n	%		
Dose >77.95	7	10.14	23	33.04	30	43.5	0.355 (0.124-1.019)	0.051
Dose ≤77.95	18	26.06	21	30.17	39	56.5		
Total	25	36.2	44	63.2	69	100		

Analysis of serum ferritin levels revealed that the majority of patients had initial serum ferritin concentrations exceeding 2500 µg/L, found in 53 patients (76.8%). Similarly, post-treatment measurements showed that 52 patients (75.4%) continued to exhibit serum ferritin levels above 2500 µg/L. Regarding transfusion frequency, 58% of patients received ≤12 transfusions per year.

Based on the data in this study, ROC curve analysis determined an optimal deferiprone dose cut-off of 77.95 mg/kgBW, identified by calculating the best sensitivity and specificity. The majority of patients in this study received a deferiprone dose of ≤77.95 mg/kgBW (Table 2). Regarding treatment outcomes, only about one-third of patients achieved a ferritin reduction of ≥20%, while more than half showed an increase in ferritin levels.

Ferritin concentrations changes revealed distinct patterns across patient groups. Patients who achieved the target reduction of ≥20% exhibited the greatest decrease in ferritin levels (1.648,20 µg/L, Table 3). In comparison, those with a reduction of less than 20% showed a more modest decline (498,60 µg/L). Conversely, patients whose ferritin levels increased during the study period tended to start with lower baseline levels but experienced a notable rise by the end of treatment.

Among the 69 children receiving the iron-chelating drug deferiprone (Table 4), only about one-third (36.2%) experienced a ferritin level reduction of 20% or more. Interestingly, those who received a higher dose (above 77.95 mg/kgBW) had a lower success rate in reducing ferritin levels (only 10.14%) compared to those on a lower dose (26.06%). This study found that no statistically significant association between deferiprone dose category and reduction in ferritin (PR 0.355, 95% CI: 0.124–1.019, *p*-value of 0.051).

4. Discussion

The majority of patients in this study were diagnosed at ≤24 months of age. This finding aligns with Wati et al., who reported that most (63.3%) patients with beta-thalassemia major were diagnosed before the age of two. This early diagnosis is consistent with the typical clinical presentation of thalassemia major, which is commonly established between 6 and 24 months of age.[18] Regarding current age distribution, the highest proportion of patients in this study was aged 13–18 years (52.2%). Rafika et al. also found that the majority of patients (41.9%) were between 12 and 17 years old, compared to the other age groups.[19] Female patients represented the majority of the study. This finding is consistent with Hawa et al, however different result was reported by Nurbahiyah et al.[20,21] These variations may be due to the autosomal recessive inheritance pattern of thalassemia, which provides equal risk for both males and females. Moreover, sex may influence ferritin levels. Sari et al. stated that there are differences in ferritin levels between menstruating and non-menstruating adolescents, attributed to significant blood loss during menstruation, which affects ferritin concentrations. This indicates that ferritin levels in females are influenced by menstruation, a process absent in males.[22]

In this study, most patients received blood transfusions ≤12 times per year. This frequency aligns with current clinical recommendations, which suggest transfusions every 3 to 4 weeks.[23] This finding is also consistent with Akbar et al, where 86.4% of patients underwent transfusions ≤12 times annually.[24] Blood transfusions are needed due to the postnatal transition from γ-globin to β-globin production, which is necessary for the formation of adult hemoglobin (HbA), composed of two α and two β chains (α2β2). In thalassemia major, defective β-globin synthesis leads to the production of abnormal erythrocytes, which are prematurely destroyed by the spleen. This results in reduced circulating red blood cells and subsequent anemia.[25]

This study evaluated serum ferritin levels at two time points: the most recent measurement and one taken 3–6 months prior. The results demonstrated that a substantial proportion of patients exhibited persistently elevated ferritin levels, with 75.4% having final ferritin levels exceeding 2500 µg/L, and 76.8% showing similar levels in the earlier measurement. Serum ferritin is a well-established marker of total body iron stores, and elevated concentrations are indicative of iron overload.[26,27] In patients with thalassemia major, increased ferritin levels are attributable to both underlying pathological mechanisms and the cumulative effects of regular blood transfusions. Ineffective erythropoiesis in these patients results in the production of abnormal erythrocytes, which are rapidly destroyed by the spleen through extravascular hemolysis. This premature breakdown releases iron from hemoglobin, which is then recycled for erythropoiesis. However, due to continuous production of defective red cells, this cycle leads to progressive iron accumulation. Additionally, regular blood transfusions further compound the iron burden. Each unit of transfused blood

contains approximately 100–200 mg of elemental iron, which cannot be excreted physiologically, thereby contributing to iron overload over time. The combination of endogenous and transfusional iron loading highlights the critical need for effective iron chelation therapy in the long-term management of thalassemia major.[10,28]

The ideal target for serum ferritin levels in patients with thalassemia is below 1000 µg/L. According to the Thalassemia Management Guidelines issued by the Indonesian Ministry of Health in 2018, ferritin levels should be monitored within the range of 1000–2500 µg/L, while levels exceeding 2500 µg/L are associated with an increased risk of cardiac complications and mortality.[29,30] Therefore, the majority of patients in this study were within a high-risk ferritin range.

In this study, the average dose administered was 73.41 ± 14.62 mg/kgBW with most patients received a dose of ≤77.95 mg/kgBW. These findings indicate that the administered doses were, on average, below the recommended range established by the U.S. Food and Drug Administration (FDA), which suggests a deferiprone dose of 75–100 mg/kgBW to achieve optimal therapeutic efficacy.[1] This discrepancy may be due to weight gain over the course of therapy and the lack of ongoing evaluation of the drug's effectiveness in individual patients.

The majority of patients in this study showed a rise in serum ferritin concentrations. These results are similar to Wati et al. findings, who reported 69.44% of patients showed increased ferritin levels, while only 30.56% exhibited a reduction.[18] Several factors may contribute to these outcomes, including suboptimal dosing, drug side effects, and interindividual variability in response to therapy.[30,31] Suboptimal dosing of deferiprone can significantly limit its chelation efficacy. Deferiprone's effectiveness in binding and facilitating the excretion of excess iron is known to be dose-dependent. When administered below the recommended therapeutic range, its capacity to remove stored iron is insufficient, particularly in patients with a high iron burden.[32,33] Adverse drug reactions, such as gastrointestinal disturbances (e.g., nausea, vomiting, abdominal discomfort), may impair patient adherence or limit drug absorption. In such cases, even if the drug is prescribed at an appropriate dose, reduced absorption or inconsistent intake can compromise treatment efficacy.[34,35] Interindividual variability in response to iron chelation therapy can arise from differences in pharmacokinetics, metabolism, and iron load distribution. Some patients may metabolize or respond to deferiprone differently due to genetic polymorphisms or comorbid conditions such as liver dysfunction, which affects iron storage and ferritin expression.[36,37]

In this study, patients who achieved a ≥20% reduction in ferritin had higher baseline ferritin levels compared to those who did not. Conversely, patients with lower initial ferritin tended to show smaller reductions or even increases. These findings are consistent with Goel et al, which reported greater ferritin reductions in patients with higher baseline levels, particularly among those with transfusion-dependent thalassemia. This suggests that initial iron burden may influence the degree of response to chelation therapy.[38]

Although a higher proportion of patients receiving doses ≤77.95 mg/kgBW achieved a ferritin reduction of ≥20%, the result was not statistically significant. This result may suggest that within the observed dose range, increasing the deferiprone dose above 77.95 mg/kgBW does not necessarily translate into a higher likelihood of achieving a ≥20% ferritin reduction. This may be attributed to the limited sample size, which reduced the power to detect a significant association, as reflected by the wide confidence interval (0.124–1.019).

Binding et al. have reported that 65% of patients showed decreased ferritin levels during the study period, particularly among those receiving higher doses and those with higher initial iron burdens.[15] Similarly, Kontoghiorghes et al concluded that the amount of iron excreted increases with both higher deferiprone doses and greater iron load.[31] These findings show the need for further analysis of additional factors that may influence treatment effectiveness, including the actual dose of deferiprone administered. In this study, the average dose was below the minimum recommended by the FDA (75–100 mg/kgBW), which may have limited its therapeutic efficacy as deferiprone's ability to reduce serum ferritin is dose-dependent.[31,39]

Several limitations may have affected the findings of this study, such as difficulty accessing the patients because many thalassemia patients were from areas outside of Palembang, making follow-up challenging. This study's cross-sectional design limits the ability to assess causality or temporal changes in ferritin levels in response to deferiprone dosing. In addition, important confounders such as duration of therapy, treatment adherence, and baseline iron burden were not consistently documented and therefore could not be controlled for. These factors may have influenced the variability in ferritin response and should be addressed in future prospective studies. Furthermore, not all patients had complete serial ferritin data, which limited the sample size available for analysis.

5. Conclusion

This study explored the association between deferiprone dosage and serum ferritin reduction in paediatric patients with thalassemia major. The findings revealed that although most patients received deferiprone at lower-than-recommended doses, only a limited number experienced a meaningful decrease in ferritin levels. Interestingly, no significant correlation was found between the dosage administered and the reduction in ferritin, suggesting that dosing alone may not be sufficient to achieve optimal therapeutic outcomes. This indicates the need to consider other contributing factors, such as treatment duration, patient adherence, timing and method of administration, and potential organ dysfunction. Further longitudinal studies or controlled clinical trials with larger sample sizes are recommended to confirm these findings and to more accurately assess the dose-response relationship between deferiprone and ferritin reduction.

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