Original Research Article

Comparison of Thyroid Function and Duration of Iron Chelation Therapy with Deferiprone and Deferasirox in Transfusion-Dependent Children with Beta Thalassemia in Ulin Banjarmasin General Hospital

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ABSTRACT

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| **Aims:** investigate the relationship between the duration of deferiprone and deferasirox therapy, patient age, and thyroid function in β-thalassemia major patients.  **Study design:** This is a observational analytical research with a cross-sectional design  **Place and Duration of Study:** Department of Pediatric Medicine in Ulin Regional General Hospital between January 2022 and July 2024.  **Methodology:** Patient baseline and laboratory data, including hemoglobin, ferritin, TSH, and fT4 levels, were collected from medical records of both outpatient and inpatient subjects. The study included children aged 2–18 years with beta-thalassemia major who had received oral deferiprone and deferasirox therapy for at least one year, with sampling conducted using a total population approach. Data analysis was performed using SPSS version 23.0, applying Fisher’s exact test to assess the relationship between deferiprone therapy duration and thyroid function at a 95% confidence level.  **Results:** The study included 60 participants, with an average age of 7.9 ± 4.1 years; 61.7% were male. The mean serum ferritin level was 5291.86 ± 2664.37 ng/mL, and the mean hemoglobin level was 8.39 ± 1.32 g/dL. Most patients (68.3%) had received iron chelation therapy for 1–10 years, with deferiprone being the most common agent (61.7%). Thyroid function analysis showed 96.6% were euthyroid, while 3.4% had subclinical hypothyroidism. No significant differences in FT4 and TSH levels were found between different age groups or between those receiving deferiprone or deferasirox for ≤10 or >10 years, indicating that thyroid function remained within normal limits across all groups.  **Conclusion:** Most beta-thalassemia major patients in this study maintained normal thyroid function, with a low prevalence of subclinical hypothyroidism. No significant correlation was observed between age, deferiprone and deferasirox therapy duration, and thyroid function. Further research is needed to identify additional risk factors and optimize iron chelation therapy for better thyroid health in these patients. |

*Keywords: Thyroid function, iron chelation therapy, Deferiprone, Deferasirox, Beta Thalassemia*

1. INTRODUCTION

Endocrine disorders are among the most common complications experienced by patients with thalassemia. In the general population, endocrine disorders have various etiologies, whereas in patients with major thalassemia, these disorders are primarily caused by iron deposition in endocrine glands due to chronic transfusion dependency. [1,2]

Hypothyroidism is the second most frequent endocrine complication after hypogonadism in thalassemia patients, affecting approximately 5.6% to 17% of cases.[2] Studies have reported thyroid dysfunction prevalence ranging from 4% to 29% across different countries, with most cases presenting as subclinical hypothyroidism.[3] Severe manifestations of hypothyroidism usually appear later in adulthood.[3]

Blood transfusion therapy plays a crucial role in managing anemia in thalassemia patients; however, iron overload—a side effect of frequent transfusions—can disrupt endocrine and metabolic processes. [4] The Patho mechanism of endocrine gland dysfunction is primarily driven by direct iron deposition in the endocrine glands, leading to primary hypothyroidism, or by affecting the hypothalamic-pituitary axis, resulting in central hypothyroidism. [4] Both forms of hypothyroidism are influenced by iron deposition, with high ferritin levels, poor adherence to iron chelation therapy, and splenectomy increasing the risk of endocrine disorders in thalassemia patients. [5] The cytotoxic effects of iron on the thyroid gland are considered a major cause of thyroid dysfunction in these patients. [5]

Excess iron generates reactive oxygen species (ROS), which are particularly toxic to the anterior segment of the thyroid gland. ROS induces lipid peroxidation, leading to the formation of saturated and unsaturated aldehydes, which can result in cellular dysfunction and apoptosis. Serum ferritin levels are commonly used to assess iron overload, but the direct correlation between ferritin levels and hypothyroidism in thalassemia patients remains unclear and requires further investigation. [6,7]

In addition to blood transfusions, iron chelation therapy is the standard treatment for β-thalassemia major. A lower prevalence of hypothyroidism has been observed in patients with lower iron burdens, as indicated by serum ferritin levels. [5] Deferiprone (DFP) is an oral iron chelator with better patient compliance compared to deferoxamine. This chelation therapy mobilizes iron from tissues into circulation for excretion, primarily through urine. However, clinical studies have reported a decrease in thyroid function in pediatric patients receiving oral iron chelation therapy.

At Ulin Regional General Hospital Banjarmasin, the average number of β-thalassemia patients reaches approximately 100, with an additional 20 new cases recorded in 2021. Currently, deferiprone is the primary oral iron chelator used for patients with β-thalassemia major who develop hemosiderosis. Despite its widespread use, there is limited research on the association between the duration of deferiprone therapy and thyroid function in thalassemia patients. Additionally, further studies are needed to determine whether patient age influences thyroid function in those receiving deferiprone therapy. Therefore, this study aims to investigate the relationship between the duration of deferiprone and deferasirox therapy, patient age, and thyroid function in β-thalassemia major patients

2. METHODOLOGY

This study is observational analytical research with a cross-sectional design. Patient baseline data were obtained from medical records, and laboratory test data (hemoglobin pre-transfusion, ferritin, TSH, and fT4) were collected from both outpatient and inpatient from January 2022 to July 2024.

The study population consisted of children with beta-thalassemia major who received oral deferiprone and deferasirox therapy for a minimum of one year at the Department of Pediatric Medicine in Ulin Regional General Hospital between January 2022 and July 2024. Sampling was conducted using total population sampling, including all patients that met the inclusion criteria without randomization.

The inclusion criteria for this study includes children aged 2 to 18 years, diagnosed with beta-thalassemia major, and who had received oral deferiprone and deferasirox iron chelation therapy for at least one year. Only patients who consented to participate in the study by signing an informed consent form were included. The exclusion criteria consisted of patients with incomplete medical records, non-compliant or irregular use of deferiprone (i.e., usage below 75 mg/kg/day), a history of thyroid dysfunction prior to starting deferiprone therapy, comorbid hematologic or oncological conditions, a history of splenectomy, or those with an acute infection. From the sample size calculation, the minimum required sample size for this study was 25 participants.

Beta-thalassemia major is defined as hereditary autosomal recessive disorder affecting hemoglobin production, requiring regular transfusions of packed red blood cells, diagnosed by hemoglobin electrophoresis. The duration of deferiprone and deferasirox therapy is the length of time the patient has been receiving oral deferiprone therapy, categorized as ≤10 years and >10 years. Thyroid function is assessed by TSH and fT4 levels. Hypothyroidism is diagnosed with TSH >4.0 µU/L and fT4 <0.7 ng/dL, and subclinical hypothyroidism is defined as increased TSH without a decrease in fT4.

After consideration of the inclusion and the exclusion criteria, the data collection was carried out in the policlinic for outpatients and ward for inpatients. The characteristics of the study subjects were then collected, including age, gender, and the treatment received. Ferritin, fT4, and TSH tests were then performed on the patients. The procedures were in accordance with the institution ethical standards on human experimentation and has received the ethical approval. The patients and their family had also filled the informed consent forms prior to data collection.

Data were analyzed using SPSS version 23.0. Descriptive statistics were used to summarize the characteristics of the study participants. Fisher's exact test was used to analyze the relationship between the duration of deferiprone and defrasirox therapy and thyroid function. All analyses were performed at a 95% confidence level.

3. results and discussion

**3.1 Subject Characteristics**

The total sample obtained was 60 samples. An analysis was conducted to determine the characteristics of the respondents in terms of age, gender, serum ferritin levels, hemoglobin levels, duration of iron chelation therapy, type of iron chelation therapy administered, and thyroid function, which includes FT4 and TSH levels. The results of the analysis can be seen in Table 1.

Based on Table 1, the average age of respondents was 7.9 ± 4.1 years, with 37 males (61.7%) and 23 females (38.3%). The average serum ferritin level was 5291.86 ± 2664.37 ng/mL, and hemoglobin was 8.39 ± 1.32 g/dL. Most respondents (68.3%) received iron chelation for 1–10 years, while 31.7% received it for more than 10 years. Deferiprone was the most commonly used chelation agent (61.7%), followed by deferasirox (38.3%).

Serum ferritin concentration is the most commonly used test to assess iron overload, as elevated levels reflect iron storage. In this study, the average serum ferritin level in thalassemia patients was 5291.86 ± 2664.37 ng/mL (normal: 6–130 ng/mL), indicating increased iron stores. However, ferritin levels can also be influenced by inflammation, liver abnormalities, or malignancy.[4]

Studies show mixed results on the relationship between ferritin and thyroid function. Gaya et al. found no significant difference in serum ferritin levels between hypothyroid and euthyroid thalassemia patients (p = 0.432), suggesting other contributing factors like chronic hypoxia and differential iron distribution. Conversely, Yassouf et al. reported a correlation between higher ferritin and TSH levels in hypothyroid patients (p < 0.001), indicating iron overload’s role in thyroid dysfunction. Sharmin et al. also found no significant correlation between ferritin and hypothyroidism (p = 0.279) but observed a significant association with lower pre-transfusion hemoglobin levels (p = 0.02), suggesting anemia as a key factor in thyroid dysfunction. [1,6,11]

For thyroid function, 6 respondents (10%) had low FT4, 53 (88.3%) had normal levels, and 1 (1.7%) had high FT4. TSH levels were normal in 57 respondents (95%), while 3 (5%) had high levels; none had low TSH. Overall, 58 respondents (96.6%) were euthyroid, while 2 (3.4%) had subclinical hypothyroidism.

**Table 1. Subject characteristics**

|  |  |  |
| --- | --- | --- |
| Variable | Mean | N (%) |
| Age (years) | 7.9 4.1 |  |
| Gender |  |  |
| * Male |  | 37 (61.7) |
| * Female |  | 23 (38.3) |
| Serum Ferritin Level (ng/mL) | 5291.86 2664.37 |  |
| Hemoglobin Level (g/dL) | 8.39 1.32 |  |
| Iron Chelation Duration |  |  |
| * 1-10 years |  | 41 (68.3) |
| * >10 years |  | 19 (31.7) |
| Iron Chelation Type |  |  |
| * Deferiprone |  | 37 (61.7) |
| * Deferasirox |  | 23 (38.3) |
| FT4 Level (pmol/L) |  |  |
| * Low |  | 6 (10) |
| * Normal |  | 53 (88.3) |
| * High |  | 1 (1.7) |
| TSH Level (uIU/mL) |  |  |
| * Low |  | 0 (0) |
| * Normal |  | 57 (95) |
| * High |  | 3 (5) |
| Thyroid Dysfunction |  |  |
| * Primary hypothyroidism |  | 0 |
| * Subclinical hypothyroidism |  | 2 (3.4) |
| * Euthyroid |  | 58 (96.6) |

In this study, 58 out of 60 thalassemia patients (96.6%) were euthyroid, while only 2 (3.4%) had subclinical hypothyroidism. This aligns with findings from Gaya et al., Yassouf et al., and Basher et al., all of whom reported a higher prevalence of euthyroid status in thalassemia patients.[1,5,6] Yassouf et al. found hypothyroidism in only 30.5% of cases, while Basher et al. reported 89.5% of patients as euthyroid.[1,5] Similarly, Upadya et al. found only 4 out of 83 patients had subclinical hypothyroidism, further supporting that subclinical hypothyroidism is the most common thyroid dysfunction in thalassemia.[7] Factors influencing thyroid dysfunction may include age, iron levels, duration of transfusions, and chelation therapy adherence. Studies show older patients have a higher risk, as seen in Gaya et al., where hypothyroidism was more frequent in patients >10 years old.[6]

In contrast, Ansaf et al. reported a higher prevalence of hypothyroidism (47%) among thalassemia patients in southern Iraq, with 53% being euthyroid, 24.2% having subclinical hypothyroidism, 12.1% central hypothyroidism, and 10.6% primary hypothyroidism. The high prevalence was attributed to the lack of mandatory Hb electrophoresis screening, inadequate maintenance of diagnostic equipment, and poor availability and quality of iron chelation therapy. Economic constraints and low socioeconomic status further contributed to poor adherence to treatment and follow-up. Overall, this may indicate a lack of concern with no clear plan for primary prevention by the government and health authorities about this genetic blood disease and the problems associated with this disease that can affect multisystem throughout life.[9]

In contrast to the study conducted by Asad et al, where 105 patients with thalassemia major as cases were compared in terms of thyroid gland function with 105 healthy subjects as controls, and it was found that FT4 levels in the case group were lower than those in the control group, while TSH levels were higher. These results indicate obvious hypothyroidism in patients with thalassemia. Logistic regression analysis showed that FT4 levels in the case group were 0.58, compared to the control group, and serum TSH levels in the case group were 1.57 times higher than those in the control group. The differences in these studies occur because the prevalence of hypothyroidism varies greatly, depending on age, region, and type of treatment, including the rate of blood sampling in a month, iron chelation therapy, and the follow-up interval of the patients studied.[10]

**3.2 Relationship Between Age and Thyroid Function**

Analysis of the relationship between age and thyroid function in this study is depicted in Table 2. The table shows no significant differences in FT4 and TSH levels between thalassemia patients aged 2-10 years and those aged >10-18 years (FT4: *P* = .22, TSH: *P* = .26). In the 2-10 year group, mean FT4 was 12.82 ± 2.12 pmol/L, and mean TSH was 2.40 ± 0.92 uIU/mL, both within the normal range. Similarly, in the >10-18 year group, mean FT4 was 12.27 ± 1.35 pmol/L, and mean TSH was 2.56 ± 1.86 uIU/mL, also within normal limits.

**Table 2. Relationship between age and thyroid function**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Age | Mean SD | MD | 95% CI | *P* |
| FT4 | 2-10 years | 12.82 2.12 | 0.54 | -0.34 - 1.44 | .22 |
|  | >10-18 years | 12.27 1.35 |
| TSH | 2-10 years | 2.40 0.92 | -0.15 | -0.98 - 0.66 | .26 |
|  | >10-18 years | 2.56 1.86 |

In this study, the mean patient age was 7.9 ± 4.1 years, with no significant association between age and thyroid function. This aligns with Basher et al., who reported no significant age-thyroid function correlation in thalassemia patients (*P* = .25). Iron overload-related thyroid dysfunction typically emerges in the second decade and worsens in later decades.[5] Similarly, Ansaf et al. found no significant correlation (*P* = .89), with comparable hypothyroidism distribution across age groups.[8] Bordbar et al. (2019) also reported no statistical significance (*P* = 0.22), despite higher hypothyroidism prevalence in older patients (<18 years: 12.2%, 18–30 years: 63.5%, >30 years: 24.3%).[11]

**3.3 Relationship between Duration of Deferiprone and Deferasirox Iron Chelation with Thyroid Function**

Iron chelation therapy has become one of the basics in the management of thalassemia patients. The human body does not have a physiological mechanism to remove excess iron and each blood bag transfused contains about 200 mg of iron, transfusion-dependent beta thalassemia patients have a constant positive iron balance. Iron chelation therapy will remove excess iron from the body by forming a non-toxic, stable, and water-soluble complex. The most commonly used types of iron chelation therapy are deferiprone and deferasirox, both of which are given orally. [4,12] Table 3 shows no significant differences in FT4 and TSH levels between thalassemia patients receiving deferiprone iron chelation for ≤10 years or >10 years (FT4: *P* = .22; TSH: *P* = .76). In both groups, average FT4 and TSH levels remain within the normal (euthyroid) range.

**Table 3. Relationship between Duration of Deferiprone Iron Chelation and Thyroid Function**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Deferiprone Iron Chelation Therapy Duration | Mean SD | MD | 95% CI | *P* |
| FT4 | 10 years | 12.74 1.92 | 0.71 | -0.47 – 1.90 | .22 |
|  | >10 years | 12.02 1.32 |
| TSH | 10 years | 2.61 1.91 | 0.17 | -1.0 – 1.35 | .76 |
|  | >10 years | 2.43 1.30 |

Table 4 shows no significant differences in FT4 and TSH levels between thalassemia patients receiving deferasirox iron chelation for ≤10 years or >10 years (FT4: *P*= .32; TSH: *P* = .47). In both groups, average FT4 and TSH levels remain within the normal (euthyroid) range.

**Table 4. Relationship between Duration of Deferasirox Iron Chelation and Thyroid Function**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Deferasirox Iron Chelation Therapy Duration | Mean SD | MD | 95% CI | *P* |
| FT4 | 10 years | 12.71 1.73 | 0.86 | -0.91 – 2.65 | 0.32 |
|  | >10 years | 11.84 1.50 |
| TSH | 10 years | 2.54 1.38 | 0.49 | -0.91 – 1.90 | 0.47 |
|  | >10 years | 2.04 1.15 |

| *Mann-Whitney U test* | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | U | | df | | p | |
| FT4 |  | 321.50 |  |  |  | 0.10 |  |
| TSH |  | 376.00 |  |  |  | 0.40 |  |
|  | | | | | | | |

This study found no significant differences in thyroid function (TSH and FT4 levels) among thalassemia patients receiving iron chelation therapy for ≤10 or >10 years, regardless of whether they were treated with deferiprone or deferasirox. This study also found no difference in median FT4 or TSH levels between patients receiving deferiprone and deferasirox. This aligns with findings from Krisbiyantoro et al., who also reported no significant differences in TSH and FT4 levels between patients on deferasirox and deferiprone (p > 0.05). Several factors may contribute to variations in thyroid function, including TSH and FT4 concentrations, study design, transfusion volume, and chelation dosage. Moreover, TRH (Thyrotropin Releasing Hormone) testing is considered more sensitive than TSH and FT4 in detecting thyroid abnormalities. Other studies have also found no significant association between gender, chelation duration, transfusion history, ferritin levels, and hypothyroidism in thalassemia patients.[4] On the other hand, a systematic Yassouf et al. reported that non-compliance with iron-chelation therapy increased the risk of thyroid dysfunction by 6.38 times. Sanctis et al. also reported delayed initiation of iron chelation therapy and noncompliance to therapy resulted in earlier onset of thyroid failure in homozygous β-thalassemia patients. Hence, compliance to iron chelation, therapy regardless of the type of iron chelating agent, is paramount in disability prevention.

Basher et al. similarly reported no significant correlation between chelation type, duration, and thyroid function (p = 0.179). Hypothyroidism in thalassemia may result from chronic anaemia and hypoxia rather than iron overload alone. [5] Bilgin’s study further suggests that aggressive combination chelation therapy (deferoxamine + deferiprone) is more effective in managing endocrine complications than single-agent therapy.[12]

The availability of iron chelation therapy allows personalized treatment for patients, but it is important to look for its impact on different organs. Chirico et al. demonstrated that combined deferoxamine and deferiprone therapy effectively reduces iron overload and endocrine complications like thyroid dysfunction. This suggests that iron-induced tissue damage is reversible, but without intensive chelation, the risk of primary hypothyroidism remains. Older thalassemia patients with delayed chelation and high ferritin levels often exhibit permanent thyroid dysfunction, highlighting the time-dependent nature of iron toxicity.[13]

Several studies (Upadya et al., Krisbiyantoro et al., Bordbar et al.) found no significant correlation between iron chelation type/duration and thyroid dysfunction.[4,7,14] Research by Karadag et al. indicated that deferasirox monotherapy reduces cardiac iron overload more effectively than deferiprone.[3] Meanwhile, Maggio et al. and Bollig et al. found deferiprone and deferasirox similarly effective in chelating iron without a significant impact on thyroid function.[14,15] Research conducted by Sharma et al also showed that the incidence of thyroid dysfunction in thalassemia patients was not related to the type of iron chelation therapy given, because both the sample group given deferiprone and the group given deferasirox both had a tendency to develop hypothyroidism.[16] Research conducted by Chow et al also showed a statistically insignificant relationship between the type and duration of iron chelation therapy and the incidence of hypothyroidism in thalassemia patients.[17]

Despite guidelines recommending monotherapy, iron overload remains a concern, leading to the recommendation of combination therapy. This approach enhances iron removal, improves compliance, and reduces complications like cardiomyopathy. Moreover, combination therapy is beneficial when toxicity and side effects happen.[18] In addition to its benefits for the removal of excess iron, various side effects related to the use of iron chelation therapy have also been widely reported. Side effects vary: deferoxamine can cause eye, hearing, bone, and neurological issues; deferiprone is linked to agranulocytosis and gastrointestinal problems; deferasirox may cause GI issues and increased serum creatinine. Poor adherence to chelation therapy significantly increases thyroid dysfunction risk.[19]

One of the things that plays an important role in the effect of iron chelation on thyroid function in thalassemia patients is patient compliance in consuming it. Research by Yassouf et al. confirms that iron chelation therapy, particularly when adhered to, can prevent or reverse thyroid dysfunction.[1] However, not all studies agree on its impact. While some show a correlation between ferritin levels, adherence, and endocrine disorders, others suggest a central mechanism involving the pituitary gland. [20] Nonetheless, chelation therapy remains essential in managing iron overload and reducing complications in thalassemia patients.[21]

**3.4 Strength and Limitations**

One of the main strengths of this study is its focus on the relationship between age and the duration of deferiprone and deferasirox iron chelation therapy on thyroid function in patients with beta-thalassemia major, a topic that has been rarely explored. Additionally, data collection was conducted using medical records and laboratory examinations, including pre-transfusion hemoglobin, ferritin, FT4, and TSH levels. These data were obtained from both outpatient and inpatient units of the Department of Pediatrics at Ulin General Hospital, in collaboration with the Department of Clinical Pathology at Ulin General Hospital and the Biochemistry Laboratory of the Faculty of Medicine, Universitas Lambung Mangkurat. This multidisciplinary approach enhances data accuracy and reliability. Furthermore, this study does not focus solely on deferiprone but also includes deferasirox, allowing for a comparative analysis of different iron chelation therapies and their potential impact on thyroid function in patients with beta-thalassemia major.

Despite its strengths, this study has certain limitations. It does not account for potential confounding variables that may influence thyroid function, which could affect the accuracy of the findings. Additionally, other risk factors for thyroid dysfunction in beta-thalassemia major patients were not assessed, including nutritional status, frequency and duration of transfusions, iron chelation therapy dosage, and patient adherence to treatment, whether as monotherapy or combination therapy. The exclusion of these factors may limit the study’s ability to fully capture the complexity of thyroid dysfunction in this patient population.

4. Conclusion

This study examined the relationship between age, duration of deferiprone and deferasirox iron chelation, and thyroid function (FT4 and TSH levels) in beta-thalassemia major patients at RSUD Ulin Banjarmasin. The findings indicate that most patients had normal FT4 (88.3%) and TSH (95%) levels, with only a small proportion experiencing thyroid dysfunction (3.4%), specifically subclinical hypothyroidism. No significant association was found between age or duration of deferiprone and deferasirox therapy and thyroid function. Further research with larger sample sizes and improved study designs is recommended to explore additional risk factors affecting thyroid function in beta-thalassemia major. Additionally, further studies and education on optimal iron chelation regimens, including drug type, dosage, and combination therapy, are essential for both clinicians and patients.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Consent AND ETHICAL APPROVAL

The study was non-invasive. All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The written informed consent was obtained from the study participants and their parents after the purpose of the study was explained. Participants were informed that the data obtained from them would be kept confidential.

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