Original Research Article

An Analysis of Thyroid Function among Beta-Major Thalassemia Patients using Deferiprone in Ulin Banjarmasin General Hospital

.

ABSTRACT

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| **Aims:** This study aims to analyze thyroid function in beta-thalassemia major patients receiving transfusions at Ulin Regional General Hospital, Banjarmasin, based on the duration of deferiprone therapy and the patients' age.**Study design:** This is an analytical observational research with a cross-sectional design.**Place and Duration of Study:** Pediatric patients diagnosed with beta-thalassemia major who received oral deferiprone iron chelation for for at least one yearat the Department of Child Health, Ulin Banjarmasin General Hospital, during the period from January 2022 to July 2024.**Methodology:** The study samples were collected using total population sampling, with a total of 37 participants. Bivariate analysis was performed using the Fisher's Exact test with a 95% confidence level.**Results:** The mean age of the total 37 samples was 11.12 ± 4.61 years, with a predominance of male patients at 64%.The average levels of ferritin and hemoglobin were 4990.07 ± 2856.37 ng/mL and 8.42 ± 1.35 g/dL, respectively. A total of 36 samples were in a euthyroid state and 1 sample was in a hypothyroid state. Bivariate analysis using Fisher's Exact test showed no significant association between age, the duration of deferiprone therapy, and thyroid function in beta-thalassemia major patients at Ulin Regional General Hospital, with p-values of 1.00 and 0.378, respectively.**Conclusion:** Most beta-thalassemia major patients at Ulin Regional General Hospital receiving deferiprone iron chelation therapy exhibited normal thyroid function, with only 1 patient found to be hypothyroid. There is no significant relationship between age or the duration of deferiprone therapy and thyroid function in beta-thalassemia major patients at Ulin Regional General Hospital. |

*Keywords: Thyroid function, Beta major thalassemia transfusion dependent, Deferiprone*

1. INTRODUCTION

Blood transfusion therapy plays an important role in thalassemia patients to treat anemia, but iron deposition as a side effect of transfusion can trigger problems in the body's endocrine and metabolic processes.[1] The pathomechanism of endocrine gland damage is triggered by iron deposition directly in the endocrine gland itself as primary hypothyroidism or through the hypothalamic-pituitary axis resulting in central hypothyroidism.[2] Both primary and central hypothyroidism are affected by iron deposition. High ferritin levels, non-compliance with iron chelation therapy, and splenectomy increase the risk of endocrine disease in patients with thalassemia.[3] Iron's direct cytotoxicity to the thyroid gland is primarily responsible for thyroid dysfunction in patients with thalassemia.[3,4]

Besides blood transfusion, iron chelation is the standard therapy for thalassemia beta major. A lower prevalence of hypothyroidism is reported in patients with lower iron levels as assessed by ferritin levels.[3] Deferiprone (DFP) is an oral iron chelation that has better compliance than desferioxamine. It is able to mobilize iron from tissues into the circulation for excretion, mainly through urine (DFP). However, various clinical studies have shown a decrease in thyroid levels in pediatric patients receiving oral iron chelation. Therefore, this study aims to analyze thyroid function in beta-thalassemia major patients receiving transfusions at Ulin Regional General Hospital, Banjarmasin, based on the duration of deferiprone therapy and the patients' age.

2. METHODOLOGY

This study was an analytical observational study with a cross sectional research design in pediatric patients with a diagnosis of thalassemia beta major who received Deferiprone oral iron chelation for at least 1 year. Then laboratory examinations (pre-transfusion hemoglobin, ferritin, TSH and fT4) were conducted based on the Schwartz method. The study was conducted at the Department of Pediatrics (IKA) of Ulin Regional General Hospital Banjarmasin, Department of Clinical Pathology of Ulin Regional General Hospital Banjarmasin. Basic patient data was obtained by taking data from medical records. Laboratory examination data (pre-transfusion hemoglobin, ferritin, fT4 and TSH) were obtained from the outpatient and inpatient units of the IKA Department of Ulin Hospital, in collaboration with the Clinical Pathology Department of Ulin Hospital Banjarmasin from January 2022 to July 2024.

The sampling of this study was conducted using the total population sampling method, in which the entire sample population that met the inclusion criteria was included without randomization. The study sample consisted of subjects who fit the inclusion criteria, namely: pediatric patients aged 2 to 18 years; pediatric patients with thalassemia beta major who had received oral iron chelation therapy using deferiprone for at least one year at the Department of Pediatrics of Ulin Hospital Banjarmasin in the period January 2022 to July 2024; and patients who agreed to participate and signed informed consent. Meanwhile, the exclusion criteria included: patients with incomplete medical record data; patients who were non-compliant or irregularly taking deferiprone (less than 75 mg/kgBB/day); patients with a history of thyroid dysfunction before deferiprone therapy; patients with other hematologic or oncologic comorbidities; patients who had undergone splenectomy; and patients with acute infections.

Data were collected from the study subject population by considering the inclusion and exclusion criteria. Data were collected from the hematology clinic of Ulin Hospital Banjarmasin and inpatients diagnosed with transfusion-dependent Beta Major Thalassemia. The characteristics of the study subjects were then taken in the form of age, gender, and treatment received. Patients had been given iron chelation therapy for at least 1 year. Patients were then subjected to ferritin examination and fT4 and TSH examination.

The statistical program used to process the data was SPSS version 23.0. Sample data in each study group were presented in tabular form and statistically tested to determine whether there was a relationship between variables. To analyze the relationship between the duration of deferiprone administration and thyroid function, the Fischer exact test was performed. All analyses were performed at the 95% confidence level.

3. results and discussion

**3.1 Subject characteristics**

 The number of research subjects obtained were 59 subjects, of which 37 subjects used deferiprone iron flat and 22 subjects used desferasirox iron flat. The results of the analysis can be seen in the table below, table 1.

**Table 1. Subject characteristics**

|  |  |  |
| --- | --- | --- |
| Variable | Mean | N (%) |
| Age (years) $\pm $ SD | 11.12 $\pm $ 4.61 |  |
| Sex |  |  |
| * Male
 |  | 24 (64.9) |
| * Female
 |  | 13 (35.1) |
| Ferritin Serum (ng/mL) | 4990.07 $\pm $ 2856.37 |  |
| Hemoglobin (g/dL) | 8.42 $\pm $ 1.35 |  |
| Iron Chelation Duration |  |  |
| * 1-10 years
 |  | 23 (62.2) |
| * >10 years
 |  | 14 (37.8) |
| FT4 level (pmol/L) |  |  |
| * Low (<10.6 pmol/L)
 |  | 4 (10.8) |
| * Normal (10.6-19.4 pmol/L)
 |  | 32 (86.5) |
| * High (>19.4 pmol/L)
 |  | 1 (2.7) |
| TSH level (uIU/mL) |  |  |
| * Low (<0.25 uIU/L)
 |  | 0 (0) |
| * Normal (0.25-5 uIU/L)
 |  | 35 (94.6) |
| * High (>5 uIU/L)
 |  | 2 (5.4) |
| Thyroid function |  |  |
| * Hypothyroidism
 |  | 1 (2.7) |
| * Euthyroid
 |  | 36 (97.3) |

**3.2 Relationship between Duration of Iron Chelation Deferiprone and Thyroid Function**

**Table 2. Relationship between the duration of iron chelation deferiprone administration and thyroid function**

|  |  |  |
| --- | --- | --- |
| Deferiprone iron chelation duration | Thyroid function | *P* |
| Euthyroid | Hypothyroidism |
| 1-10 years | 23 | 0 | 0.38 |
| >10 years |  13 | 1 |

*\*Fischer exact test*

Tables 2 and 3 are 2x2 tables of Fischer exact test results that combine the cell values of subclinical hypothyroidism and primary hypothyroidism into “hypothyroidism”. Based on table 2, in the study sample given deferiprone iron chelation for 1-10 years, it is known that none of them had impaired thyroid function (euthyroid). In the study samples given deferiprone iron chelation for >10 years, 13 samples were in normal condition (euthyroid) and only 1 sample experienced hypothyroidism. Therefore, it can be concluded that there is no relationship between deferiprone chelation and thyroid function in the 1-10 years and >10 years groups. This was further proven by the results of the Fischer exact test, which showed a *P* value of 0.38.

In this study, there was no statistically significant relationship between the duration of deferiprone iron chelation and thyroid function, as shown by the *P* value of 0.42 in thalassemia patients who were given deferiprone iron chelation therapy. Research conducted by Basher et al also showed no significant relationship between the duration of iron chelation therapy and the type of iron chelation therapy given to thyroid function. In the study, 43 samples received deferiprone iron chelation therapy (70.5%), 8 samples received deferasirox iron chelation therapy (13.1%), 2 samples received a combination of deferiprone and deferoxamine iron chelation therapy (3.3%), and 8 samples received a combination of deferiprone and deferasirox iron chelation therapy (13.1%). The mean duration of iron chelation therapy was 17.93 ± 15.52 months, and the *P* value was 0.18, which is not statistically significant. The most likely explanation for this is thought to be because hypothyroidism may occur due to several other factors such as anemia and chronic hypoxia in patients with thalassemia.3 Bilgin mentioned in his study that the administration of iron chelation therapy with deferoxamine showed little impact on the course of progressive endocrine dysfunction and only aggressive iron chelation therapy with a combination of two drugs, deferoxamine and deferiprone, achieved better results regarding endocrine complications.[5]

**3.3 Relationship between Age and Thyroid Function**

**Table 3. Relationship between age and thyroid function**

|  |  |  |
| --- | --- | --- |
| Age | Thyroid function | *P* |
| Euthyroid | Hypothyroidism |
| 2-10 years |  14 | 0 | 1.00 |
| >10-18 years | 22 | 1 |

*\*Fischer exact test*

Among 59 subjects, 1 subject was identified with hypothyroidism. The patient is a 15-year-old female presenting with a body weight of 29 kg, height of 145 cm, and arm circumference of 17 cm. The patient was diagnosed with Thalassemia Beta in 2013 and has taken long-term iron chelation therapy with Deferiprone for a duration of 11 years and 6 months. Lab results shown a hemoglobin level of 10.8 g/dL, with levels consistent for transfusion-dependent thalassemia patients, and a ferritin level of 5005.74, indicating a severe iron overload despite an evidently adequate hemoglobin level. Additionally, during the observed time, her hypothyroidism markers show a low FT4 of 9.47mIU/L and a normal TSH of 2.309mIU/L, which may suggest the presence of subclinical hypothyroidism and the need for additional attention.

Based on Table 3, all samples in the 2-10 years age group had no thyroid dysfunction (euthyroid). In the study samples who were in the age group >10-18 years, it was found that 22 of them did not have any thyroid dysfunction (euthyroid), and only 1 sample had hypothyroidism. Therefore, it can be concluded that there is no relationship between the patient's age at the time of the study and thyroid function in the 2-10 years and >10-18 years age groups. This was further proven by the results of the Fischer exact test, which showed a *P* value of 1.00.

This is in line with research conducted by Basher et al. The study states that there is no relationship between age and thyroid function among thalassemia patients. The mean age of euthyroid patients in the study was 12.28 ± 3.95 and the mean age of patients experiencing hypothyroidism was 13.89 ± 3.48 with a *P* value of 0.25. This is because based on theory, complications from iron overload in the form of thyroid dysfunction will usually only appear in the second decade of life so it will be less significant, and its severity will increase gradually in the third and fourth decades of life of thalassemia patients who receive transfusion and iron chelation therapy.[3] Another study conducted by Ansaf et al also showed no relationship between age and thyroid function in thalassemia patients (*P=* 0.89). Of all thalassemia patients in the age group ≤15 years, 7 patients were euthyroid (53.8%), 2 patients had primary hypothyroidism (15.4%), 3 patients had subclinical hypothyroidism (23.1%), and 1 patient had central hypothyroidism (7.7%). Of all thalassemia patients in the age group >15 years, 28 patients were euthyroid (532.8%), 5 patients with primary hypothyroidism (9.4%), 13 patients with subclinical hypothyroidism (24.5%), and 7 patients with central hypothyroidism (13.2%).[6] This is also in line with a study conducted by Bordbar et al in 2019 in Iran. The study found that the incidence of hypothyroidism in thalassemia patients aged <18 years was 12.2% (2 people), age 18-30 years was 63.5% (47 people), age >30 years was 24.3% (18 people), with a *P* value of 0.22 which also showed that age was not statistically significant to thyroid function.[7]

In thalassemia patients under the age of 5 years, growth retardation is usually caused because they do not receive regular blood transfusions, while in thalassemia patients aged 5-10 years, growth retardation is often caused by inadequate iron chelation therapy and as a result of iron accumulation due to blood transfusions which disrupts the IGF-1 growth hormone axis and consequently affects linear growth. The most commonly used types of iron chelation therapy are deferiprone and deferasirox, both given orally, and deferoxamine. One study showed that deferiprone had a favorable effect on serum ferritin concentrations and had an acceptable safety profile for children[8-10]

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. Side effects that arise are known to affect patient compliance with the use of iron chelation therapy.[11] In a study conducted by Yassouf et al in 2019, it was found that among 45 patients who were compliant with taking iron chelation (23 men and 22 women), only 4 patients (8.89%) had subclinical hypothyroidism, and 41 other patients (91.11%) had normal thyroid function levels. The study also found that the risk of thyroid dysfunction in patients who were not compliant with iron chelation was 6.38x greater than in patients who were compliant with iron chelation [risk ratio (RR) = 6.385; 95%CI, 2.40-16.95]. This was a result of excessive iron overload which was associated with increased serum ferritin levels in the iron chelation non-compliant group compared to the iron chelation compliant group (ferritin 6953±2690ng/mL, 3970±1524ng/mL, respectively, *P*<0.0001). Better thyroid function was more associated with adherence to iron chelation therapy. These results emphasize the importance of adherence to iron chelation therapy to minimize the risk of thyroid dysfunction, rather than focusing on the relationship between the type and duration of iron chelation therapy.[12] Faranoush in his study also mentioned that the level of adherence of thalassemia patients to iron chelation therapy varies widely. This level of adherence may affect the outcome of thyroid function, regardless of the type or duration of iron chelation therapy.[13]

In the literature, it is stated that the incidence of hypothyroidism arising from endocrine abnormalities in patients with thalassemia (whether clinically or subclinically manifested, whether primary or secondary) depends on the study, criteria, population, disease control, and therapy applied for beta thalassemia. Risk factors include: high ferritin levels (OR 0.98; 95% CI 0.96-0.99, *P*= 0.003), poor adherence to thalassemia beta major therapy (OR 0.38; 95% CI 0.16-093, *P*= 0.03), and use of combination iron chelation therapy as combination therapy is known to reduce the risk of endocrinopathies compared to monotherapy (*P=* .04). However, not all studies agree on the effect of iron chelation therapy on the incidence of thyroid dysfunction. FT4 and TSH did not correlate with serum ferritin levels, nor with the type and duration of oral iron chelation therapy and transfusion. The presumed mechanism that dominates this is a central process, i.e. mostly related to the pituitary.[14] However, one thing that is known for sure is that the administration of iron chelation therapy will help balance the amount of iron accumulated in blood transfusions by increasing iron removal in urine and/or feces with chelation. Due to the promising results of using iron chelation both monotherapy and in combination for the treatment of iron overload, research on iron-specific chelators including deferiprone (DFP), deferoxamine (DFO), and deferasirox (DFX) continues to grow.[15]

**3.4 Strengths and limitations**

This study addresses the rare investigation of the relationship between age, duration of deferiprone iron chelation therapy, and thyroid function in patients with beta-thalassemia major. Data collection involved comprehensive records, including medical records and laboratory results (pre-transfusion hemoglobin, ferritin, FT4, and TSH), from both inpatient and outpatient services at the Pediatric Department of RSUD Ulin, in collaboration with the Clinical Pathology Department. This approach enhances data accuracy. Additionally, the study focuses on deferiprone, the most commonly used iron chelation regimen, providing insights into its mechanism of action, efficacy, side effects, and recommended dosage.

However, this study does not account for confounding variables and fails to identify other risk factors for thyroid dysfunction in patients with beta-thalassemia major undergoing iron chelation therapy. These include nutritional status, monthly transfusion frequency, transfusion duration, age at first transfusion and iron chelation therapy, iron chelation regimen dosage, patient compliance, and whether monotherapy or combination therapy was used.

4. Conclusion

The conclusion of this study is that neither the duration of deferiprone iron chelation therapy nor age is associated with thyroid function (euthyroid or hypothyroidism) in beta-thalassemia major patients at Ulin Regional General Hospital, Banjarmasin.

**Recommendations:** Further research with a better study design, a larger sample size, and longer patient follow-up is needed to identify other risk factors affecting thyroid function in beta-thalassemia major patients undergoing iron chelation therapy. Additionally, more research and educational initiatives are required to establish and disseminate optimal iron chelation regimens, including type, formulation, dosage, and the use of monotherapy or combination therapy, for both physicians and patients.

CONSENT AND ETHICAL APPROVAL

The study was non-invasive. The prior written permission of the institutional authority was taken. 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.

References

1. Ibrahim AS, El-Fatah AHA, El-Halim AFA, Mohamed FF. Assessment of hypothyroidism among adult patients suffering from beta thalassemia major. Mansoura Medical Journal. 2023;52(1).

2. Haghpanah S, Hosseini-Bensenjan M, Sayadi M, Karimi M, de Sanctis V, Ramzi M, et al. The Prevalence of Hypothyroidism among Patients With β-Thalassemia: A Systematic Review and Meta-Analysis of Cross-Sectional Studies. Vol. 45, Hemoglobin. 2021.

3. De Sanctis V, Soliman A, Candini G, Campisi S, Anastasi S, Iassin M. High prevalence of central hypothyroidism in adult patients with β-thalassemia major. Georgian Med News. 2013;(222).

4. Singhal A, Goyal H. Thyroid dysfunction in beta thalassemia major patients. Thyroid Research and Practice. 2020;17(2).

5. Bilgin BK, Yozgat AK, Isik P, Çulha V, Kacar D, Kara A, et al. The effect of deferasirox on endocrine complications in children with thalassemia. Pediatr Hematol Oncol. 2020;37(6).

6. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet [Internet]. 2017 Sep 23 [cited 2024 Dec 2];390(10101):1550–62. Available from: https://pubmed.ncbi.nlm.nih.gov/28336049/

7. Bordbar M, Bozorgi H, Saki F, Haghpanah S, Karimi M, Bazrafshan A, et al. Prevalence of endocrine disorders and their associated factors in transfusion-dependent thalassemia patients: a historical cohort study in Southern Iran. J Endocrinol Invest. 2019;42(12).

8. Rindang C, Batubara JRL, Amalia P, Satari H. Some aspects of thyroid dysfunction in thalassemia major patients with severe iron overload. Paediatr Indones. 2011;51(2).

9. Maggio A, Kattamis A, Felisi M, Reggiardo G, El-Beshlawy A, Bejaoui M, et al. Evaluation of the efficacy and safety of deferiprone compared with deferasirox in paediatric patients with transfusion-dependent haemoglobinopathies (DEEP-2): a multicentre, randomised, open-label, non-inferiority, phase 3 trial. Lancet Haematol. 2020;7(6).

10. Gaya ML, Rini EA, Izzah AZ. Hubungan Kadar Ferritin Serum dengan Fungsi Tiroid pada Anak dengan Thalassemia beta Mayor. Sari Pediatri. 2023;25(1).

11. Lee WJ, Mohd Tahir NA, Chun GY, Li SC. The impact of chelation compliance in health outcome and health related quality of life in thalassaemia patients: a systematic review. Vol. 22, Health and Quality of Life Outcomes. 2024.

12. Yassouf MY, Alquobaili F, Kabalan Y, Mukhalalaty Y. Compliance with Deferoxamine Therapy and Thyroid Dysfunction of Patients with β-Thalassemia Major in Syria. Hemoglobin. 2019;43(3).

13. Faranoush M, Faranoush P, Heydari I, Foroughi-Gilvaee MR, Azarkeivan A, Parsai Kia A, et al. Complications in patients with transfusion dependent thalassemia: A descriptive cross-sectional study. Health Sci Rep. 2023;6(10).

14. Carsote M, Vasiliu C, Trandafir AI, Albu SE, Dumitrascu MC, Popa A, et al. New Entity—Thalassemic Endocrine Disease: Major Beta-Thalassemia and Endocrine Involvement. Vol. 12, Diagnostics. 2022.

15. Entezari S, Haghi SM, Norouzkhani N, Sahebnazar B, Vosoughian F, Akbarzadeh D, et al. Iron Chelators in Treatment of Iron Overload. Vol. 2022, Journal of Toxicology. 2022.