Effects of Thiamazole Administration on Weight Changes in Children with Graves' Disease at H. Adam Malik General Hospital Medan, Indonesia

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ABSTRACT

Background: Graves' disease is the most common cause of hyperthyroidism in children. Delay in the diagnosis and treatment of hyperthyroidism in children is associated with neurodevelopmental disorders, changes in bone maturation, decreased school performance, drastic weight loss. Three treatment options include antithyroid drugs, surgery, and radiation. The initial treatment regimen is the use of the antithyroid drug thiamazole subtype.

Objective: The aim of this study was to determine the effect of tiamazol administration on changes in body weight in children with Graves' disease

Methode: This study is a retrospective cohort analytic using medical record data on all children aged 1–18 years according to the inclusion criteria. The subject's medical record data was requested from the Medical Record Installation by showing the research permit. Subject data, namely characteristics including gender, child's age, year of arrival, nutritional status (weight, height) and thyroid profile (T4, TSH). Data analysis was carried out using the SPSS version 20.0 program with dependent t test and wilcoxon test. The difference was considered significant if $p < 0.05$

Result : A total of 32 subjects in this study according to the inclusion criteria. There were significant differences in weight, height and mass index at the first and second visits with $p<0.05$. There was a significant change in baseline T4 levels compared to visit I and visit II with $p<0.05$, while the difference in the mean change in baseline TSH levels at visits I and II was not significant ($p>0.05$).

Conclusion : Tiamazole administration caused changes in free T4 levels in the blood in the third and sixth months, but changes in TSH levels were not significant at the sixth month.

Keywords: *Graves'* Disease, Thiamazole, Nutritional Status, Children

Introduction

Graves' disease is the most common cause of hyperthyroidism in children (John M, et al., 2015). The prevalence is about 0.1–3 per 100,000 children worldwide and increases during puberty to about 1 per 1,000,000 children under 4 years of age and 8 per 1,000,000 children younger than 15 years (Hanley P, et al., 2016). The incidence ratio in black ethnicity is 1.92–2.53, and in Asia-Pacific it is around 1.78–3,36 (McLeod, et al., 2014). The prevalence of hyperthyroidism over the age of 15 years in Indonesia reaches 0.4% according to 2013 Basic Health Research data,[4] but it does not yet exist in children (Riset Kesehatan Dasar, 2013).

Delay in diagnosis and treatment of hyperthyroidism in children is associated with neurodevelopmental disorders, changes in bone maturation, decreased school performance, and drastic weight loss. Therefore, appropriate treatment must be carried out immediately. Three treatment options that can be done, including antithyroid drugs, surgery, and radiation. The initial treatment regimen commonly used is antithyroid drugs, particularly the thiamazole subtypes, namely methimazole and carbimazole (Lee HS, et al., 2014). This subtype has fewer hepatotoxic side effects than other antithyroid drugs, namely propylthiouracil (PTU) (Akmal A, et al., 2014). A decrease in thyroid hormone levels in the body results in the accumulation of body fat, decreases basal energy requirements and physical activity, and increases body water content resulting in an increase in body weight. In a study of 57 hyperthyroid children, there was weight gain at a duration of 2–6 months after starting antithyroid medication (Crocker MK, et al., 2010). Monitoring of weight and height during drug consumption should be done regularly. Based on the above review, a study was conducted to monitor body weight while taking antithyroid drugs in children with Graves' disease.

Methode

This study is an analytic study with a retrospective cohort design using medical records at H. Adam Malik Central General Hospital Medan. The study was conducted based on patient data from the endocrinology unit from January 2018 to December 2020. Inclusion criteria were children aged 1-18 years who had just been diagnosed with hyperthyroidism, thiamazole therapy, visited the endocrine unit for a period of 3 months and 6 months after starting treatment and there were data on weight, height, T4 and TSH levels. Sample collection is done by consecutive sampling.

The patient's medical record is taken at the Medical Record Installation by showing a research permit. Furthermore, a selection was made to take the research subjects by taking into account the inclusion criteria. Subject data was collected through analysis of medical records to obtain characteristic data including gender, child's age, year of arrival, nutritional status and thyroid profile. Data on weight, height, T4 and TSH levels were taken every time the control was taken for at least 6 months in the medical record. Data analysis was carried out using the Statistical Package for Social Science version 20.0 program. The Saphiro-Wilk test was used to determine whether the data were normally distributed or not. Dependent t test if both data are normally distributed, Wilcoxon test if the distribution is not normal. The difference was considered significant if $p < 0.05$.

Results

A total of 52 subjects with a diagnosis of hyperthyroidism were obtained and then analyzed based on inclusion and exclusion criteria. There were 5 subjects with duplicate data, 3 subjects who were not diagnosed with Graves' disease based on laboratory tests, and 5 subjects visited before 2008 and after 2020. Furthermore, from 39 subjects, there were 7 subjects with incomplete study variables, which are then presented in figure 1 and demographic data are presented in table 1.

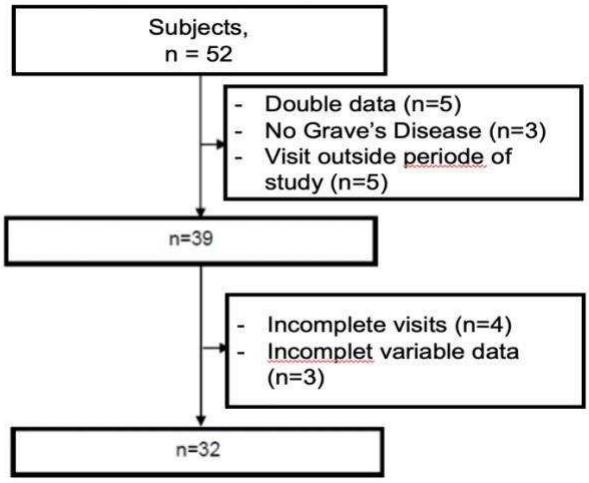

Figure 1. Flowchart of Patient Inclusion

There was a significant difference in body weight (1.6, 95% CI 1.2 – 2 kg), height (0.3, 95% CI 0.1 – 0.4 cm), and body mass index (0. 7, 95% CI 0.5 – 0.9 kg/m2) at the first and second visits with $p < 0.05$ can be seen in table 2.

Tabel. 1. Characteristics of Subjects

Characteristics	n = 32
Sex, n (%)	
Boys	2 (6,3)
Girls	30 (93,8)
Age, year	13,4 ± 3,0
Age Groups, n (%)	
Child (<10 years)	6 (18,8%)
Adolescent (10 – 18 years)	26 (81,3%)
Year of visit, n (%)	
2018	15 (46,9)
2019	13 (40,6)
2020	4 (12,5)
Weight, kg	40,5 ± 12,9
Height, cm	145,5 ± 11,9
Body Mass Index, kg/m^2	18,6 ± 3,8
Nutritional Status, n (%)	
Severe Malnutrition	1 (3,1)
Mild Malnutrition	7 (21,9)
Normal	11(34,4)
Overweight	5 (15,6)
Obesity	8 (25)
Thyroid profile	
TSH (µIU/mL)	0.01 (0 – 19,1)
T4 (µg/dL)	3.1 ± 1,3

Tabel. 2.Changes in Nutritional Status Indicator

	Baseline	Visit I (1-3 Months)	ΔBB1	p[a]	Visit II (4-6 Months)	ΔBB2	p[b]
Weight	40,5 ± 12,9	42,2 ± 12,7	1,6	0,000**	43,8 ± 13,2	3,7	0,000**
Height	145,5 ± 11,9	145,8 ± 11,8	0,3	0,001**	145,7± 11,8	0,5	0,001**
BMI	18,6 ± 3,8	19,4 ± 3,6	0,7	0,000**	20,2 ± 3,7	1,6	0,000**

[a]Baseline dependent t-test and 1 visit
[b]Baseline dependent t-test and 2 visit
**Significant p< 0.01
ΔBB1: difference between BB visit 1 and the beginning
ΔBB2: difference between BB visit 2 and the beginning

Based on the results of the analysis using repeated annova showed that there was a significant increase in body weight, height, initial body mass index, first and second visits for all subjects (p<0.01). This change can be seen in figure 2.

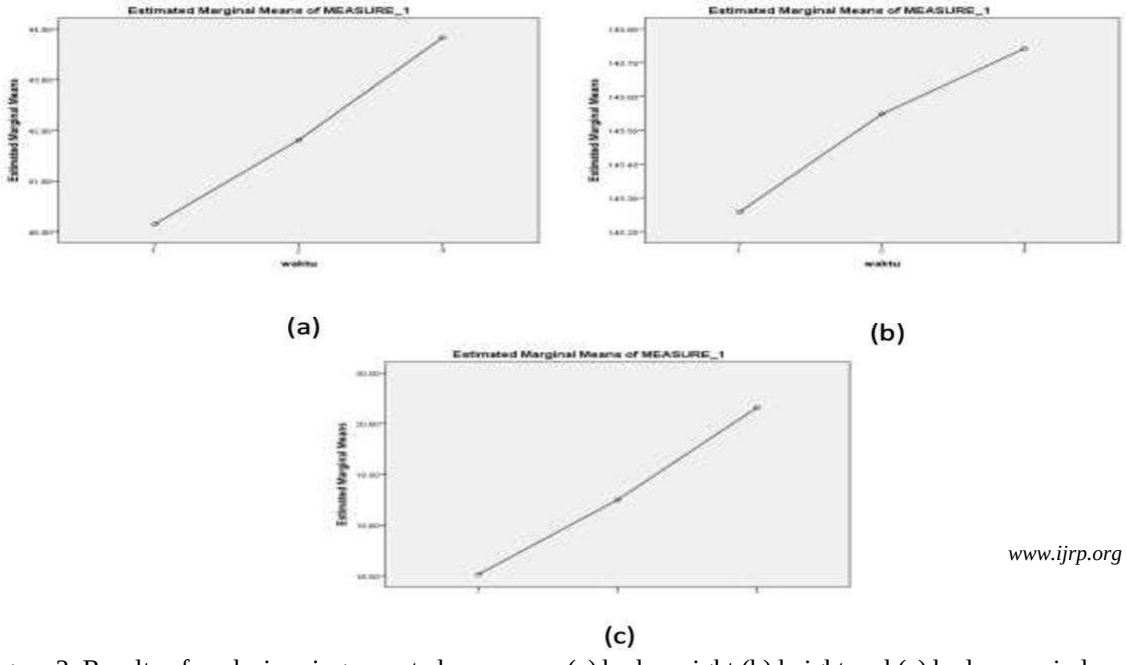

Figure 2. Results of analysis using repeated annova on (a) body weight (b) height and (c) body mass index (p<0.01)

Thyroid profile assessment carried out during control to the unit was TSH and T4 levels. Based on this analysis, there was a significant change in baseline T4 levels compared to visit I (1.6, 95% CI 1.1 – 2.1) and baseline T4 levels compared to visit II (1.9, 95% CI 1.4 – 2 ,4). The difference in the mean changes in TSH levels at baseline, visits I and II was not significant (p>0.05), they can be seen in table 3. The correlation between changes in weight and changes in T4 in table 4.

Table 3. Changes in Thyroid Profile Indicators

	Baseline	Visit I (1-3 Months)	p[a]	Visit II (4-6 Months)	p[b]
Weight	40,5 ± 12,9	42,2 ± 12,7	0,000**	43,8 ± 13,2	0,000**
Height	145,5 ± 11,9	145,8 ± 11,8	0,001**	145,7± 11,8	0,001**
BMI	18,6 ± 3,8	19,4 ± 3,6	0,000**	20,2 ± 3,7	0,000**

[a]baseline Wilcoxon test and visit 1
[b]wilcoxon baseline test and visit 2
**Significant p<0.01

Tabel 4. Correlation between changes in weight and changes in T4

ΔBB	ΔT4	P[a]
-1,6 ± 1,3	1,6 ± 1,1	0,133

[a]pearson correlation test

Discussion

The results of this study indicate that the prevalence of Graves' disease is more in women (93.8%) than men. This is in line with a study in France where the incidence of hyperthyroidism in children was 76.6% in women and 23.4% in men (Simon M, et al., 2018). The mean age of the subjects was 13.4 years with a range of 6.6 – 17.4 years. The incidence in adolescents aged 10-18 years was higher at 81.3% (n=26) and <10 years 18.8% (n=6). Another study reported that the incidence of hyperthyroidism in women was higher than in men, especially in the early teenage age group of 10-14 years (Srinivasan S, et al., 2015). Thyroid hormone is essential for normal growth, sexual development and reproductive function. During puberty, changes in thyroid function and an increase in thyroid volume occur due to adaptations to sexual growth and development (Marwaha RK, et al., 2012).

The number of subjects who came in 2019 and 2020 decreased in relation to the state of the COVID-19 pandemic in Indonesia. Subjects with normal nutritional status had the largest percentage. However, there were 13 subjects with overweight and obesity status (40.5%). In theory, hyperthyroidism will lead to weight loss due to increased basal energy requirements and lipolysis (Cicatiello AG, et al., 2018). However, this study lacked data on weight loss before the diagnosis was made. All subjects used methimazole after the diagnosis was made. No drug side effects were reported. A study in 43 pediatric hyperthyroidism patients where two children using PTU and 38 children using methimazole reported a hypersensitivity reaction so that they were changed to PTU (Van Veenendaal NR, et al., 2011).

Subjects experienced a significant increase in body weight, height, and body mass index for 6 months after administration of Thiamazole. The average weight gain was 1.6 kg in the first 3 months and 3.7 kg in the following 6 months. This may be due to a decrease in basal energy requirements after thiamazole administration. This decrease was positively correlated with a decrease in T3 and T4 levels (Kim MJ, et al., 2018). The study by Krocker and Caplowitz et al showed a mean weight gain of 3.4 kg at the first follow-up (mean duration 2 months) and 7.1 kg (14.3%) at the second follow-up (mean duration 6 months) after starting treatment in 57 children with a mean age of 14.1 years.

In this study, changes in body weight in the initial phase of the first 3 months were not significantly different from the following 3 months (p>0.05). Other studies suggest that weight gain is greatest in the first 3 months after the onset of treatment and continues for up to 6 months (Van Veenendaal NR, et al., 2011). The increase in weight, height and body mass index will contribute to the category of nutritional status of the subject. In this study, there was also a significant increase in the nutritional status category in the subjects at 3 months and 6 months duration compared to baseline (p<0.01). In addition, the increase in body weight was also associated with the subject's adherence to medication and medication dosage. However, data on the subject's drug consumption compliance were not obtained. The Thiamazole group has a better advantage over PTU regarding drug adherence due to its long and effective half-life. Subjects in this study received Thiamazole at a dose according to the guidelines of the Indonesian Pediatrician Association, namely the initial dose starting from 0.25-1 mg/kg/BW/day with a maximum dose of 30 mg/day.

T4 levels were significantly different at 3 months and 6 months (p<0.01). The pattern of weight gain is proportional to the correction of the hyperthyroid state. Other studies have reported a positive correlation between decreased T4 levels and decreased basal energy requirements associated with increased body weight (Kim MJ, et al., 2018). However, in this study there was no significant correlation between weight gain and changes in thyroid levels. Changes in TSH levels were not significantly different during 6 months of monitoring. The literature indicates that TSH is often suppressed for long enough that 6 months of follow-up may not be sufficient for significant changes (Yati N, et al., 2017). The weakness of this study was that it did not analyze changes in the subject's caloric intake and had a limited number of samples. The study design of a cohort without a control group

as a comparison is also a limitation of the study. In addition, data on Thiamazole dosages were not available in full in the medical records so that the researcher could not see the effect of dose adjustment on changes in the nutritional status and thyroid profile of the subjects.

Conclusion

Giving Thiamazole to children with Graves' Disease caused weight gain with a mean of 1.6 kg in the third month and 3.7 kg in the sixth month, 0.3 cm in height in the third month and 0.5 cm in the sixth month, and mass index. body 0.7 kg/m2 in the third month and 1.6 kg/m2 in the sixth month with the third p value <0.05. The administration of tiamazole to children with Graves' disease caused a significant change in the free T4 level in the blood at the third and sixth months, but the change in TSH levels was not significant at the sixth month

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