Factors Influencing the Early Remission of Pediatric Thyrotoxicosis Within Two Years of Propylthiouracil Medication

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Abstract

Background : Propylthiouracil (PTU) is the anti-thyroid medication commonly used as a first-line therapy for pediatric thyrotoxicosis in Thailand. Because of low remission rate and long periods of medical therapy, several studies were attempted to identify factors associated with remission outcomes. These predicting factors remain controversial.

Objective : To evaluate predicting factors of early remission in pediatric thyrotoxicosis treated with PTU in Lampang Hospital.

Material and method : A cross-sectional analytical study was conducted on the patients age under 16 years who were diagnosed with thyrotoxicosis and treated with PTU at outpatient department of Lampang Hospital between 1st January 2002 and 28th February 2010. The general data, clinical findings, laboratory and treatment outcomes were retrospectively reviewed. The data was analyzed by descriptive statistics. Comparison between patients who achieved early remission within 2 years and who were treated for more than 2 years but did not achieve remission was analyzed by using student t-test and Fisher exact test. Odds ratio (OR) was calculated to identify predicting factors by logistic regression analysis.

Results : Fifty-three patients enrolled the study (F:M = 43:10). The mean age was 11.1 ± 2.0 years. Twenty patients achieved remission with PTU within 2 years but thirty-three did not. Univariate analysis showed significantly less pulse pressure ($p<0.001$) and heart rate ($p=0.04$) in the remission group. Logistic regression analysis identified 4 predictors of early remission; smaller goiter size (OR=0.03, 95%CI 0.002-0.52, $p=0.01$), older age (OR=2.84, 95%CI 1.23-6.54, $p=0.01$), narrow pulse pressure (OR=0.64, 95%CI 0.50-0.82, $p<0.001$) and low heart rate (OR=0.74, 95%CI 0.58-0.91, $p=0.03$). Adverse drug reactions of PTU were arthralgia (5%) and skin rash (3%). No patient had major side effect.

Conclusion : Small goiter size, older age, narrow pulse pressure and low heart rate were predicting factors for remission of pediatric thyrotoxicosis within 2 years of PTU medication.

Keywords: Thyrotoxicosis, Early remission, Anti-thyroid medication, Propylthiouracil, PTU

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Introduction

Thyrotoxicosis accounts for 10-15% of all childhood thyroid disease and increases to 60% in children aged 10 to 15 year.[1-4] The presenting signs and symptoms are goiter, exophthalmos, nervousness, tremor, weight loss, tachycardia, increase appetite and hyperactivity. Classical laboratory tests include elevated serum free T4 and T3 with suppressed TSH. The optional treatment of thyrotoxicosis in children is controversial. The three therapeutic options include anti-thyroid drug (ATD), radioactive iodide (RAI) and subtotal thyroidectomy. RAI is highly effective treatment in toxic goiter. Concerning about the potential long-term consequences of thyroid cancer and leukemia, many physicians avoid RAI. Meanwhile, subtotal thyroidectomy yields high remission rates but many complications and requires highly experienced surgeon. ATD is chosen as the most common first-line therapy. The available ATD in Thailand are propylthiouracil (PTU) and methimazole. Because of low remission rate and prolonged course of drug intake, the prognostic outcome of ATD is the common question that patients want to know. Few previous reports in Thailand showed treatment outcomes in drug-treated Graves' disease[5,6], but none studied about prognostic factors for remission.

The purpose of this study was to evaluate the predictors of early remission of hyperthyroidism in children treated with PTU in Lampang Hospital.

Material and method

A cross-sectional analytical study was conducted on 61 patients aged less than 16 years old who were diagnosed Graves' disease or thyrotoxicosis between 1st January 2002 and 28th February 2010 at outpatient department of Lampang Hospital. All of them were treated with PTU medication and divided into 2 groups. The patients who achieved remission within 2 years of medication were categorized as remission group. The patients who continued medical therapy for more than 2 years and did not achieve remission were categorized as non-remission group. Patients were excluded from the study if they were subsequently treated with alternative method, subtotal thyroidectomy, lost to follow-up or referred to other hospital.

The medical records were retrospectively reviewed. The collecting data included demographic data, clinical signs and symptoms, WHO stages of goiter size, laboratory results, dosage, duration and side effects of PTU treatment.

Outcome definition

Remission : maintenance of normal serum FT3, FT4 , TSH without medication for more than 6 months.

Early remission : remission within 2 years of starting medical treatment.

Statistical analysis

Univariate analysis was used to detect

differences between 2 study groups. Normally distributed continuous variables were analyzed by using student t-test. Categorical variables were analyzed with Fisher's exact test. All statistical tests were conducted based on two tailed alternative. P-values <0.05 were considered significant difference.

Age, gender and variables retaining a significant association with early remission ($p< 0.05$) were considered independent predictors of early remission and eligible into logistic regression analysis.

Results

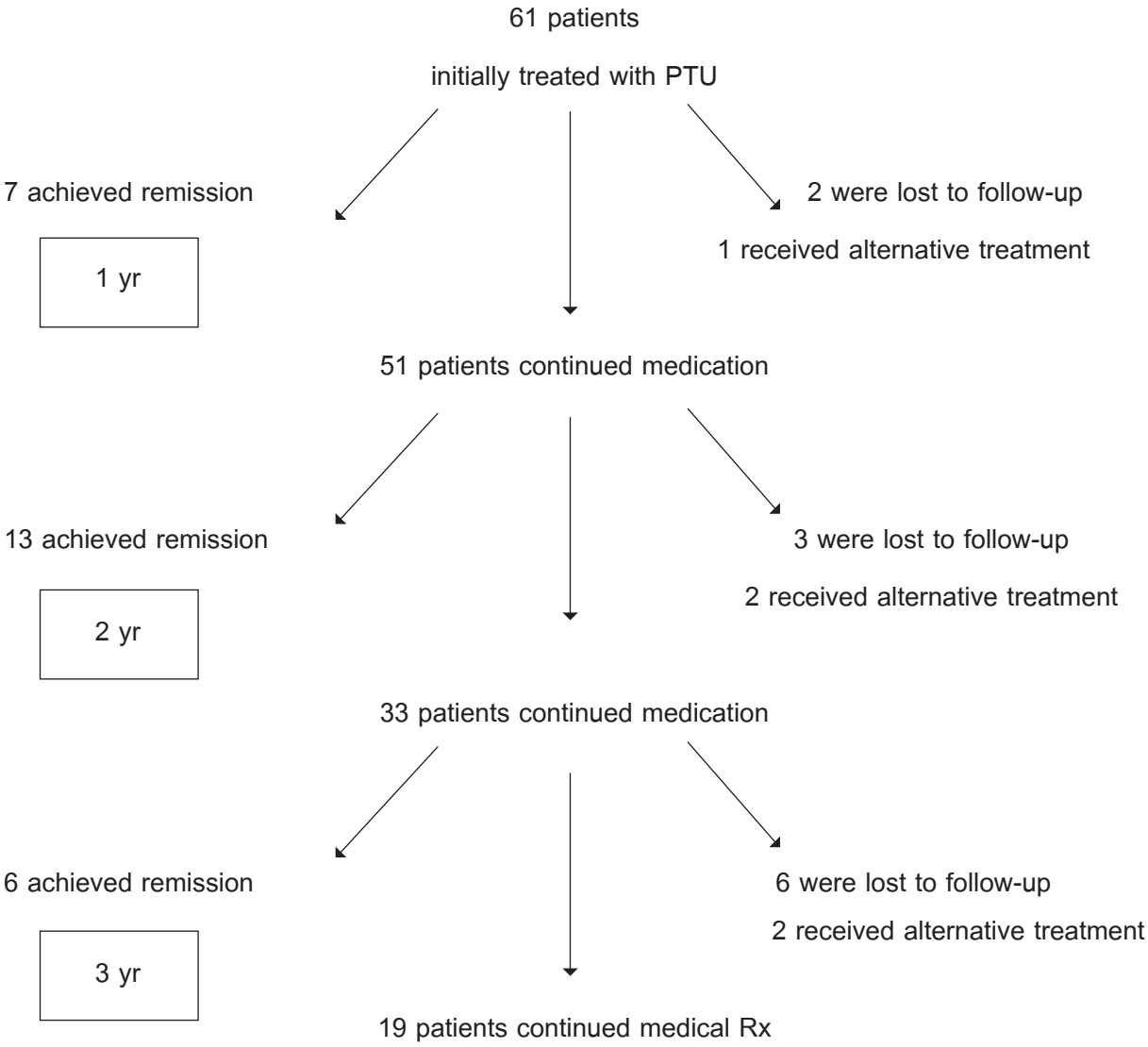
All of the 61 patients had clinical presentation with goiter. Exophthalmos was found in 55% of cases. Tachycardia, wide pulse pressure, nervousness and fine tremor were presented in about two-third of the patients (Table 1).

Table 1. Clinical characteristics of children with thyrotoxicosis at initial visit (n=61)

	Symptoms and signs	Number	%
Major	Goiter	61	100.0
	Tachycardia	44	72.1
	Wide pulse pressure	43	70.5
	Nervousness	37	60.7
	Exophthalmos	34	55.7
	Palpitation	30	49.2
	Psychosis (auditory & visual hallucination)	2	3.3
Minor	Fine tremor	43	70.5
	Weight loss	34	55.7
	Increased appetite	30	49.2
	Heat intolerance	18	29.5

Starting with 61 patients initially treated with PTU medication, 5 cases were lost to follow-up and 3 cases received alternative treatment within 2 years. There were 53 patients enrolled the study. Among these, twenty achieved remission within 2 years but thirty-three did not (Figure 1).

Figure 1. Overview of medical treatment for thyrotoxicosis



Univariate analysis of clinical characteristics showed that the remission group had significantly less pulse pressure and heart rate than the non-remission group ($p<0.001$ and $p=0.04$ respectively). More percentage of goiter size WHO stage I was found in the remission group than the non-remission group (35.0 % *vs* 12.1%) but not significantly different ($p=0.07$). Other clinical findings, laboratory and treatment data were not significantly different between two groups (Table 2).

Table 2. Univariate analysis of clinical characteristics comparing between remission group and non-remission group

Variables	Remission group (n =20) mean ± SD	Non-remission group (n =33) mean ± SD	p-value
Demographic information			
Age (years)	11 ± 0.4	11.2 ± 0.4	0.71
< 11 years (school age)	12 (60.0%)	12 (36.4%)	0.15
> 11 years (adolescent)	8 (40.0%)	21 (63.6%)	
Gender (female)	17 (85.0%)	26 (78.8%)	0.72
Duration of illness (months)	1.85 ± 1.0	1.9 ± 0.9	0.82
Physical examination			
Body mass index, BMI (kg/m^2)	16.8 ± 3.9	16.7 ± 3.2	0.93
Heart rate (beat/min)	106.8 ± 16.5	116.3 ± 20.4	**0.04**
Pulse pressure (mmHg)	35 ± 8.9	45.3 ± 6.1	**<0.001**
Goiter size: WHO stage I	7 (35%)	4 (12.1%)	0.07
WHO stage II & III	13 (65%)	29 (87.9%)	
Presence of exophthalmos	10 (50%)	19 (57.6%)	0.77
Treatment data			
Duration Rx to euthyroid (months)	4.5 ± 2.4	5.3 ± 2.7	0.28
Maximal dose PTU used (mg/kg/d)	7.5 ± 3.0	9.0 ± 4.4	0.17
Laboratory data			
FT3 (pg/ml)	13.6 ± 8.3	13.5 ± 6.2	0.96
FT4 (ng/dl)	3.57 ± 2.4	3.65 ± 1.6	0.89
TSH (mu/L)	0.04 ± 0.01	0.028 ± 0.01	0.25
FT3 / FT4 ratio	4.62 ± 3.4	3.89 ± 1.6	0.30
FT4 / FT3 ratio	0.27 ± 0.11	0.28 ± 0.09	0.65

The variables eligible into logistic regression analysis were age, gender, heart rate, pulse pressure and stage of goiter size (Table 3). Age was an independent predictor of early remission (OR=2.84, 95%CI 1.23-6.54). Pulse pressure and heart rate were significant preventive factors of early remission (OR=0.64 and 0.74 respectively). Goiter size stage II and III decreased chance of early remission comparing with goiter size stage I (OR=0.03).

Adverse drug reactions of PTU found in this study were arthralgia (5%) and skin rash (3%). No patient had major side effect.

Table 3. Logistic regression analysis to identify independent predictors of early remission

Variables	Odds Ratio	95% CI	p-value
Pulse pressure	0.64	0.50-0.82	**<0.001**
Age	2.84	1.23-6.54	**0.01**
Goiter size: WHO stage II and III compare with stage I	0.03	0.002-0.52	**0.01**
Heart rate	0.74	0.58-0.91	**0.03**
Gender (female)	1.78	0.15-21.1	0.65

Discussion

Thyrotoxicosis is an autoimmune disease characterized by a course of remission and relapse. To avoid serious side effects of thyroidectomy and radioactive iodide treatment in children, anti-thyroid drugs are frequently used as the first-line therapy in many institutions. Because of low remission rate, approximately 25% every 2 years, and long period of medical therapy, many previous studies attempted to identify factors associated with remission outcomes.[7,8]

According to the univariate and logistic regression analysis in this study, variables with prognostic value for determining early remission were goiter size, age, pulse pressure and heart rate.

Glaser and Styne[9] found that factors determined early remission included age, BMI, heart rate, goiter size, serum T4 and T3 concentrations, platelet count, thyroid stimulating immunoglobulin, change in goiter size and time required to normalize serum T4 and T3. However, in this study BMI, serum T4 and T3 level and treated duration to euthyroid were not found to be prognostic factors. Similarly to Garton et al[10] who found no significant differences in serum T4 and T3 concentrations, T3/T4 ratio among the patients

who did and did not achieve remission on medical therapy.

Concordance with the present study, several literatures demonstrated that initial goiter size had prognostic importance.[10-12] Buckingham et al found that patients with goiter less than two times of normal size at the conclusion of therapy were more likely to achieve remission.[11] Likewise, the study of Winsa et al supported that larger goiter size was a poor prognostic sign.[13] Although Garton et al[10] did not find a significant correlation between initial goiter size and ability to achieve remission, 67% of the patients with small goiters achieved remission within 2 years and 65.5% of those with large goiters required longer than 2 years to achieve remission.

Collen et al[7] found a tendency toward earlier remission in patients older than 13 years and in males. The present study showed older age as a predicting factor of early remission. Although Graves' disease was more common in girls than boys,[14] but gender was not a predicting factor in this study.

For ophthalmopathy, some study found to be poor prognostic sign for remission.[1,3] Nevertheless, Schleusener et al [15] did not find a significant correlation with early remission, as same as this study. Goiter was the most common clinical presentation, similar to the study of Somnuke et al [5] in Thai children. It has been reported to be presented in 97-100% of cases.[1-4] Exophthalmos was presented in only 55% of cases in this study comparing with up to 70% of children with Graves' disease in other reports.[12]

Wide pulse pressure is a major sign of thyrotoxicosis.[1-4] The present study showed pulse pressure as a factor influencing the early remission. This finding indicated the severity of disease at diagnosis as an important determinant for early remission.

PTU and methimazole are the anti-thyroid drugs available in Thailand. In the present study, minor side effects of PTU were found only 8% of treated patients. This incidence was less than previously reported. This could be due to small numbers of presented subjects. In other studies, side effects occurred in 20-30% of children during medical therapy.[11,16] Therefore, PTU is still a safe anti-thyroid drug used in children with thyrotoxicosis.

This study had some limitations. Firstly, because of its retrospective nature, the follow-up period was limited. Patients who were euthyroid for longer than 6 months after medical discontinuation were considered to achieve remission. Some of them experienced relapse later. Secondly, the sample size was small, so the detection of significant differences at smaller magnitude may not be allowed. Lastly, it was unable to study some variables with theoretical interest, such as immunological study, because of the limitation of laboratory capability.

Conclusion

Small goiter size, older age, narrow pulse pressure and low heart rate were predicting factors to favor remission within 2 years of PTU therapy in pediatric thyrotoxicosis. These factors provided useful information for patient counseling and decision for alternative treatment.

Acknowledgment

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ปัจจัยที่มีผลต่อการสงบของโรคธัยรอยด์เป็นพิษในผู้ป่วยเด็ก ภายในระยะเวลา 2 ปี ของการรักษาด้วยยาโปรปิลไธโอยูราซิล

พัฒนพงศ์ เส็งพานิช พบ.
กลุ่มงานกุมารเวชกรรม โรงพยาบาลลำปาง

ลำปางเวชสาร 2554; 32(1): 1-10

บทคัดย่อ

ภูมิหลัง: โปรปิลไธโอยูราซิล (propylthiouracil, PTU) เป็นยาต้านธัยรอยด์ที่นิยมใช้เป็นทางเลือกลำดับแรกของการรักษาโรคธัยรอยด์เป็นพิษในผู้ป่วยเด็กไทย แต่ใช้ระยะเวลารักษานานและมีอัตราการสงบของโรคต่ำ มีงานวิจัยหลายฉบับที่พยายามค้นหาปัจจัยที่มีผลต่อการสงบของโรคแต่ยังไม่มีข้อสรุป
วัตถุประสงค์: เพื่อค้นหาปัจจัยที่มีผลต่อการสงบของโรคภายในระยะเวลา 2 ปี ของการรักษาผู้ป่วยเด็กโรคธัยรอยด์เป็นพิษด้วยยา PTU
วัสดุและวิธีการ: เป็นการศึกษาเชิงวิเคราะห์แบบตัดขวางในผู้ป่วยโรคธัยรอยด์เป็นพิษที่อายุน้อยกว่า 16 ปี และได้รับการรักษาด้วยยา PTU ที่ห้องตรวจกุมารเวชกรรม โรงพยาบาลลำปาง ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2545 ถึง 28 กุมภาพันธ์ พ.ศ. 2553 เก็บข้อมูลย้อนหลังจากเวชระเบียน วิเคราะห์ข้อมูลด้วยสถิติเชิงพรรณนา เปรียบเทียบผู้ป่วย 2 กลุ่ม คือ กลุ่มที่มีโรคสงบภายในเวลา 2 ปีของการรักษาและกลุ่มที่ไม่มีการสงบของโรค ต้องกินยานานกว่า 2 ปี โดยใช้ student t-test และ Fisher's exact test คำนวณ odds ratio (OR) ของปัจจัยเสี่ยงด้วยการวิเคราะห์ logistic regression
ผลการศึกษา: มีผู้ป่วยจำนวน 53 คน (ชาย:หญิง = 43:10) อายุเฉลี่ย 11.1 ± 2.0 ปี กลุ่มที่มีโรคสงบภายในเวลา 2 ปี (n=20) มี pulse pressure และอัตราการเต้นหัวใจต่ำกว่ากลุ่มที่ไม่มีการสงบของโรค (n=33) อย่างมีนัยสำคัญทางสถิติ (p<0.001 และ p=0.04 ตามลำดับ) เมื่อวิเคราะห์ logistic regression พบว่ามี 4 ปัจจัยที่มีผลต่อการสงบของโรค คือ ขนาดต่อมธัยรอยด์ที่เล็ก (OR=0.03, 95% CI 0.002-0.52, p=0.01), อายุที่มาก (OR=2.84, 95% CI 1.23-6.54, p=0.01), pulse pressure ที่แคบ (OR=0.64, 95% CI 0.50-0.82, p<0.001) และอัตราการเต้นหัวใจที่ช้า (OR=0.74, 95% CI 0.58-0.91, p=0.03) อาการไม่พึงประสงค์ของยา PTU ได้แก่ ปวดข้อ (ร้อยละ 5) และผื่นผิวหนัง (ร้อยละ 3)
สรุป: ขนาดต่อมธัยรอยด์ที่เล็ก, อายุที่มาก, pulse pressure ที่แคบและอัตราการเต้นหัวใจที่ช้าเป็นปัจจัยทำนายที่มีผลต่อการสงบของโรคธัยรอยด์เป็นพิษในเด็ก ภายในเวลา 2 ปีของการรักษาด้วยยา PTU

คำสำคัญ: โรคธัยรอยด์เป็นพิษ, การสงบของโรค, ยาต้านธัยรอยด์, โปรปิลไธโอยูราซิล, PTU