Thyrotoxicosis in Children: Treatment and Outcome

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Objectives: *To study the treatment modalities and the outcome of treatments of children with thyrotoxicosis or Graves' disease.*
Material and Method: *A retrospective study of 56 patients diagnosed with thyrotoxicosis from January 1992 to December 2004 was conducted. There were 44 girls and 12 boys (female to male ratio 3.7:1). The average age at diagnosis was 11.9 3.4 years.*
Results: *All patients were initially treated with antithyroid drugs, either propylthiouracil (n = 53) or methimazole (n = 3). All patients achieved euthyroidism within 8.4 3.3 weeks. Eleven patients are still on the treatment, and 45 patients have completed the treatment. Of these 45 patients, 38 (84.4%) remitted after antithyroid drug treatment of an average duration of 37.4 16.5 months (range 12-90), 4 patients (8.9%) chose radioactive iodine treatment and three patients (6.7%) underwent thyroidectomy. Of the 38 patients remitted with antithyroid drugs, eleven (28.9%) relapsed within 4-24 months. The relapsed patients remitted with a second course of antithyroid drugs in three patients, underwent radioactive iodine in seven patients, and thyroidectomy in one patient. Therefore, of the total 45 patients who had completed the treatment, 30 patients (66.7%) remitted with antithyroid drugs, eleven patients (24.4%) received radioactive iodine, and four patients (8.9%) underwent thyroidectomy. Using stepwise multivariate logistic regression, the authors could not identify any factors (including age, gender, family history of thyroid diseases, size of goiter, level of free T_4, dosage and duration of antithyroid drugs) that would predict the remission of thyrotoxicosis with antithyroid drugs.*
Conclusion: *Antithyroid drugs should remain the first-line therapy for treatment of thyrotoxicosis in children with a remission rate of 66.7%. The patients who are noncompliant or relapse after treatment with antithyroid drugs should be treated with radioactive iodine.*

Keywords: *Graves' disease, Hyperthyroidism, Thyrotoxicosis*

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Thyrotoxicosis or Graves' disease is rare in childhood and adolescence with an overall incidence in the general population of 0.1-3.0/100,000. It accounts for 10-15% of all childhood thyroid diseases[1-3]. In a survey of goiter in southern Thailand, thyrotoxicosis accounted for only 0.45% of goiter in schoolchildren aged 9-16 years[4]. Children affected with thyrotoxicosis suffer from sympathetic over activity such as palpitation, irritability, emotional lability and weight loss for a period of time before the diagnosis is made. The aim of management is to restore euthyroidism with a safe, quick, convenient, effective, and least complication method. To date, the best, most optimal method for treatment of thyrotoxicosis in children remains controversial. The three traditional methods, long term antithyroid drugs, thyroidectomy, and radioactive iodine, all have inherent advantages and disadvantages. Most pediatric endocrinologists advocate antithyroid drug treatment as the first-line treatment in children[5-10]. However, the proper dosage and optimal duration of

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antithyroid drug to achieve long term remission has not been clearly defined, and has varied from 0.5-7 years[5-11]. Further controversy arises when euthyroidism is not achieved after the first course of antithyroid drug treatment.

Songklanagarind Hospital is the major referral center in southern Thailand and most children with endocrinological problems are referred to this institute. From January 1992 to December 2004, 56 pediatric patients with thyrotoxicosis were treated and followed-up. The purpose of the present study was to evaluate the authors' treatment modalities in patients with thyrotoxicosis, the outcome of the treatments, and also the prognostic factors for the outcome of medical therapy.

Material and Method

The medical records of pediatric patients with a diagnosis of thyrotoxicosis or Graves' disease who attended Songklanagarind Hospital from January 1992 to December 2004 were reviewed. The diagnosis of thyrotoxicosis was made on the basis of the clinical criteria and confirmed by elevated serum Free Thyroxine (FT_4), suppressed thyrotropin (TSH), and the presence of thyroid antibodies (either anti-thyroglobulin > 1:10, or anti-microsomal antibody > 1:100, or both). The method of measurement of FT_4 was Radio Immuno Assay (RIA), of TSH was Immuno Radio Metric Assay (IRMA), and of thyroid antibodies was the hemagglutination agglutination method. Radioactive iodine uptake and thyroid ultrasonography were performed only in patients suspected of having a functional thyroid nodule. A Thyroid Stimulating Immunoglobulin (TSI) test was not available in the authors' institute.

Fifty-six patients were diagnosed with thyrotoxicosis during the studied period. There were 12 boys and 44 girls, giving a ratio of female to male of 3.7:1 The average age at diagnosis was 11.9 $\pm$ 3.4 years (range 3.1-17.0), 10 prepuberty and the rest already in puberty. There were seven patients (12.5%) who had associated diseases: three with Down's syndrome, two with myasthenia gravis, and two with Systemic Lupus Erythematosus (SLE). The clinical and laboratory characteristics at the time of diagnosis are shown in Table 1. All patients presented with increased appetite and palpitation with an average duration of 4.0 $\pm$ 2.5 months (range1-12). Goiter was detected in all patients with the average longest diameter of the thyroid lobe of 5.9 $\pm$ 1.0 cm (range 4.0-8.5). Because there was no standardization of goiter size, thyroid enlargement was graded by a pediatric endocrinologist (S.J.) as grade I, II, or III according to the WHO classification[12].

All patients were initially treated with Propyl Thio Uracil (PTU) and propranolol, and scheduled for follow-up regularly every 6-10 weeks in the first 6 months, then every 3-4 months. At each visit, the patients were evaluated for signs and symptoms of thyrotoxicosis, goiter size, height, weight, and pubertal status. FT_4 and TSH were measured every 6-8 weeks until euthyroidism was achieved, then every 3-6 months. A complete blood count was performed usually at the time of the thyroid function test. After euthyroidism was achieved, the parents and the patients were asked to maintain euthyroidism by either titration regimen or block-replacement regimen. All parents and patients preferred the titration method because of the convenience of taking fewer tablets. This also led to better compliance.

Statistical analysis

Descriptive statistics: range, mean $\pm$ SD and percentage were presented to describe the characteristics of data. Stepwise multivariage logistic regression was used to identify the factors correlated to the remission of thyrotoxicosis with antithyroid drugs. A p-value of less than 0.05 was considered significant.

Results

All patients were treated with PTU with an average initial dosage of 7.0 $\pm$ 2.1 mg/kg/d (range 3.6-13), divided into 2-3 times daily. The average dosage of propranolol was 1.0 $\pm$ 0.5 mg/kg/day (range 0.2-2.2). All patients achieved a euthyroid state within a mean duration of 8.4 $\pm$ 3.3 weeks (range 4-16) after PTU was started. Although the euthyroid state was achieved within 8.4 weeks, the initial dosage of PTU was continued for an average duration of 18.4 $\pm$ 4.3 months. After 16 weeks, PTU was titrated to maintain the euthyroid state. There were three patients who developed a skin rash after treatment with PTU and treatment was switched to methimazole of 0.5 mg/kg/d. The skin rashes subsided after 12 weeks without other adverse effects. Of the 56 patients, eleven were diagnosed within 2 years and continued on PTU or methimazole treatment. Altogether, 45 patients completed the treatment. The average duration of antithyroid drug use was 37.4 $\pm$ 16.5 months (range 12-90).

Outcome

There were 38 patients (84.4%) who achieved remission with the antithyroid drugs alone, including one patient with Down's syndrome and one patient with SLE. Of the seven patients who failed to remit with

Table 1. Clinical and laboratory characteristics of children with thyrotoxicosis at the time of diagnosis (n = 56)

Girls : boys	44:12 (3.7:1)
Age at diagnosis (years)	
Median	12.7
Mean ± SD	11.9 ± 3.4
Range	3.0-17.0
Weight SDS	-0.10 ± 1.24
Height SDS	-0.06 ± 1.26
Symptoms and signs	
Goiter	100%
Grade 1 (n = 12)	21.4%
Grade 2 (n = 41)	73.2%
Grade 3 (n = 3)	5.4%
Longest diameter of thyroid lobe	5.9±1.0 cm (range 4-8.5)
Tachycardia (56/56)	100%
Palpitation (50/56)	89.3%
Tremor (48/56)	85.7%
Increased appetite (42/56)	75.0%
Weight loss (34/56)	60.7%
Exophthalmos (20/56)	35.7%
Family history of thyroid diseases (16/56)	28.6%
Maternal side (13/56	23.2%
Paternal side (3/56)	5.4%
Laboratory studies	
Free T_4 (ng/dL)	
Mean ± SD	5.97 ± 2.48
Range	2.1-10.3
T_3 (ng/mL)	
Mean ± SD	4.45 ± 2.05
Range	2.6-9.55
TSH (mU/L)	0.01 ± 0.01 (0.00-0.04)
Anti-microsomal antibody > 1:100 (48/56)	85.7%
Anti-thyroglobulin antibody > 1:10 (40/56)	71.4%
Positive either anti-thyroglubulin or anti-microsomal antibody (53/56)	94.6%
Associated diseases (7/56)	12.5%
Down's syndrome (n = 3)	5.4%
Systemic lupus erythematosus (n = 2)	3.6%
Myasthenia gravis (n = 2)	3.6%

the antithyroid drugs, five were poor compliant. Of those who failed to remit, the parents decided on further treatment with radioactive iodine in four patients (aged > 14 years) and thyroidectomy in three patients (1 patient aged 4 years). Of the 38 patients who achieved remission with the antithyroid drugs, 27 continued in remission after a mean follow-up time of 40.7 ± 18.2 months (range 12-108), and 11 relapsed within 4-24 months after discontinuation of the antithyroid drugs. Of those eleven patients who relapsed, three remitted after the second course of PTU with the duration of treatment of 18-24 months. Of the eight patients who failed to remit after the second course of PTU, seven patients decided to change treatment to radioactive iodine and one underwent a thyroidectomy. The duration of remission after the second course of PTU was 12-60 months. Therefore, of the total 45 patients who had completed the treatment, 30 patients (66.7%) responded to antithyroid drugs, eleven patients (24.4%) received radioiodine therapy, and four patients (8.9%) underwent thyroidectomy. Permanent hypothyroidism developed in 3 of 4 patients (75%) after thyroidectomy,

and in 8 of 11 patients (72.7%) after radioiodine therapy. All hypothyroid patients were in a euthyroid state after thyroxine was administered.

Predictors of remission with ATD

The authors defined remission as maintenance of normal levels of FT_4 and TSH without medication for more than 12 months. For purposes of analysis, the patients were divided into 2 groups: patients who achieved remission with antithyroid drugs and those who did not achieve remission. There were 30 patients in the remission group and 15 patients in the non-remission group. Using stepwise multivariate logistic regression, the authors could not identify any factors (including age, gender, family history of thyroid diseases, weight SDS, height SDS, size of goiter, levels of FT_4, T_3, TSH, the presence of thyroid antibodies, dosage and duration of antithyroid drugs, and weight gain after 6 months of treatment) that would predict the remission of thyrotoxicosis with antithyroid drugs.

Discussion

The clinical characteristics of the presented patients agree with the previous findings reported in the literature[3-7,9]. Most patients were female and were in puberty with an average age at presentation of 12 years. The major symptom was palpitation with an average duration of 4 months. A history of weight loss despite increased appetite was common and helpful for investigation of thyrotoxicosis. At the time of presentation, tachycardia and thyroid enlargement were found in all patients. The average longest diameter of the thyroid lobe was 5.9 cm. Exophthalmos was less common and found in only 35.7% of the presented patients. The majority of the presented patients (94.6%) had positive thyroid antibodies, either anti-thyroglobulin or anti-microsomal antibody or both. The diseases associated with thyrotoxicosis in the presented patients confirm the findings as reported in previous studies such as Down's syndrome[13,14], myasthenia gravis[15,16], and systemic lupus erythematosus[17].

To date, the best method of treatment for thyrotoxicosis in children is controversial. The three most common methods are antithyroid drugs, thyroidectomy and radioactive iodine. Each method has distinct advantages as well as disadvantages. However, antithyroid drugs have been advocated as the first-line treatment in children[18]. The duration of treatment with antithyroid drugs from various studies were different ranging from 1 year to as long as 10.9 years, with a remission rate of 25-53%[5-11]. In the present study, antithyroid drugs, particularly propylthiouracil, were the first-line treatment with an average initial dosage of 7.0 mg/kg/day, and euthyroidism was achieved with a mean duration of initial treatment of 8.4 weeks. All the presented patients and their parents preferred the titration method due to the convenience of taking fewer tablets and the patients' feeling of getting better with time. The average duration of antithyroid drug treatment in the present study was 37.4 months, with the highest remission rate of up to 84%. However, the relapse rate was also high, up to 28.9% with relapse within 24 months after discontinuation of medication. The relapsed patients received a second course of antithyroid drugs with a remission rate of only 27.3%. The overall remission rate with antithyroid drugs was 66.7%. The greater remission rate in the present study compared to other studies is probably explained by the longer duration of high dose antithyroid drug treatment (18 weeks), the longer duration of the course of the antithyroid drugs (37 months), and probably an ethnic difference in response to antithyroid drugs. An adverse reaction to the antithyroid drug occurred in only three patients and was only minor (skin rash and transient neutropenia). The incidence of adverse effects in the present study was very low (only 5.4%) compared to 5-32% as reported in other studies[1,3,5-8,10,11,18-20]. Serious adverse effects such as agranulocytosis, hepatotoxicity, and lupus-like reaction were not found in the presented patients.

In the present study, the patients who failed to remit after long term medication or who were non-compliant were switched to the alternative treatment, either thyroidectomy or radioactive iodine therapy. The use of radioactive iodine for the treatment of Graves' disease in children is still a subject of concern. Known carcinogenic effects of external thyroid irradiation[21] and radioisotope fallout[22] have been the cause of fear of developing thyroid cancer after I^{131} therapy, particularly in children younger than 10 years of age. However, several epidemiological studies have failed to demonstrate an increased incidence of thyroid cancer or other malignancies following I^{131} therapy in adults[23-25]. The risk of thyroid cancer, leukemia, genetic damage and reproduction problems in children treated with radioactive iodine is still uncertain. Several studies of long term follow-up in children with Graves' disease have not shown an increased risk of thyroid neoplasia or other malignancies[26-28]. However, it has been suggested that radioactive iodine should be avoided in children less than 5 years of age[29]. The efficacy of radioiodine therapy is very high with a remission rate

> 90%[3,5,10,19,28]. Permanent hypothyroidism after radioiodine treatment has been reported to be 60-90%[1-3,5,9,10,19], requiring thyroxine replacement therapy. In the present study, radioiodine therapy was used in patients older than 10 years of age who did not benefit from the antithyroid drugs due to noncompliance (4 patients), and those who relapsed after discontinuation of antithyroid drugs (7 patients). The remission rate in the presented patients was 100% and permanent hypothyroidism developed in 72.7%.

Thyroidectomy is preferred by some patients with thyrotoxicosis and their parents, particularly those who are concerned about the possible increased risk of carcinogenic effects from the radioiodine in later life. In the present study, only four patients (8.9%) underwent near-total thyroidectomy. No complications of vagus nerve injury or hypocalcemia were found after surgery. The remission rate was 100% and postprocedural hypothyroidism developed in three patients (75%)

The predicting factors of remission with medical therapy have been studied in children with thyrotoxicosis, and yielded variable results[6,7,11,20,29]. Some studies have demonstrated that initial goiter size and a reduction in goiter size during antithyroid treatment are of prognostic importance[11,20,29]. On the other hand, other studies have shown no prognostic factors to predict remission[6,7]. The present study could not identify any factors to predict remission.

In summary, the results of the present study have shown that antithyroid drugs should still be used as first-line management in children with thyrotoxicosis, with a remission rate of 66.7%. Radioactive iodine or thyroidectomy should be performed in patients who are noncompliant or relapse after discontinuation of medication. Permanent hypothyroidism was found in 60-75% of patients who were treated with radioactive iodine or thyroidectomy.

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ไทรอยด์เป็นพิษในผู้ป่วยเด็ก: วิธีการรักษาและผลการรักษา

สมจิตร์ จารุรัตนศิริกุล, กัลยา ลีธนาภรณ์, หัชชา ศรีปลั่ง

วัตถุประสงค์: *เพื่อศึกษาถึงวิธีการรักษาและผลการรักษาผู้ป่วยเด็กไทรอยด์เป็นพิษ*

วัสดุและวิธีการ: *การศึกษาย้อนหลังผู้ป่วยเด็กที่ได้รับการวินิจฉัยเป็นไทรอยด์เป็นพิษตั้งแต่มกราคม พ.ศ. 2535 ถึงธันวาคม พ.ศ. 2547 พบว่ามีผู้ป่วยทั้งหมด 56 คน เพศหญิง 44 คน เพศชาย 12 คน (หญิง: ชาย 3.7: 1) อายุเฉลี่ยขณะได้รับการวินิจฉัย 11.9 $\pm$ 3.4 ปี*

ผลการศึกษา: *ผู้ป่วยทุกรายได้รับการรักษาเบื้องต้นด้วยยาต้านไทรอยด์ โดยเป็นยา propylthiouracil (PTU) ในผู้ป่วย 53 ราย และ methimazole ในผู้ป่วย 3 ราย ผู้ป่วยทุกรายเข้าสู่ภาวะ euthyroidism ภายในเวลา 8.4 $\pm$ 3.3 สัปดาห์ ในจำนวนผู้ป่วยทั้งหมด 56 ราย มีผู้ป่วยจำนวน 45 รายที่การรักษาเสร็จสิ้นไปแล้ว ผู้ป่วย 38 ราย (ร้อยละ 84.4) มีโรคสงบหลังที่ให้การรักษาด้วยยาต้านไทรอยด์เป็นระยะเวลาเฉลี่ย 37.4 $\pm$ 16.5 เดือน (พิสัย 12-19) ผู้ป่วย 4 ราย (ร้อยละ 8.9) ที่ได้รับการรักษาด้วยไอโอดีนกัมมันตรังสี และผู้ป่วย 3 ราย (ร้อยละ 6.7) ที่ได้รับการผ่าตัดเอาต่อมไทรอยด์ออก ในผู้ป่วย 38 รายที่มีระยะโรคสงบด้วยยาต้านไทรอยด์ มีผู้ป่วยจำนวน 11 ราย (ร้อยละ 28.9) ที่มีการเกิดโรคกลับในเวลา 4-24 เดือนหลังหยุดยาต้านไทรอยด์ ในผู้ป่วยที่มีการเกิดโรคกลับ 11 รายนั้นมีผู้ป่วยเพียง 3 รายที่มีระยะโรคสงบหลังจากได้ยาต้านไทรอยด์ครั้งที่สอง ผู้ป่วย 7 รายเลือกวิธีการรักษาด้วยไอโอดีนกัมมันตรังสี และ 1 รายเลือกการรักษาด้วยการผ่าตัดเอาต่อมไทรอยด์ออก ฉะนั้น ในจำนวนผู้ป่วยไทรอยด์เป็นพิษทั้งหมด 45 รายที่การรักษาเสร็จสมบูรณ์ พบว่าผู้ป่วย 30 ราย (ร้อยละ 66.7) ที่สามารถมีระยะโรคสงบด้วยยาต้านไทรอยด์ ผู้ป่วย 11 ราย (ร้อยละ 24.4) รักษาด้วยไอโอดีนกัมมันตรังสีและ 4 ราย (ร้อยละ 8.9) ที่รักษาด้วยการผ่าตัดเอาต่อม ไทรอยด์ออก ภาวะขาดไทรอยด์ฮอร์โมนพบในผู้ป่วย 8 ราย (ร้อยละ 72.7) หลังการรักษาด้วยไอโอดีนกัมมันตรังสี และพบในผู้ป่วย 3 ราย (ร้อยละ 75) หลังการรักษาด้วยการผ่าตัดต่อมไทรอยด์ออก*

การคำนวณทางสถิติโดยวิธี multiple logistic regression ไม่พบปัจจัยที่ใช้ทำนายการมีระยะโรคสงบหลังการรักษาด้วยยาต้านไทรอยด์ ไม่ว่าจะเป็นอายุ เพศ ประวัติครอบครัวที่มีโรคไทรอยด์ ขนาดคอพอก ระดับไทรอยด์ฮอร์โมน ขนาดยาต้านไทรอยด์ และระยะเวลาของการรักษาด้วยยาต้านไทรอยด์

สรุป: *ยาต้านไทรอยด์น่าจะยังเป็นการรักษาเริ่มต้นในผู้ป่วยเด็กไทรอยด์เป็นพิษ โดยทำให้มีระยะโรคสงบได้ร้อยละ 66.7 ผู้ป่วยที่มีการเกิดโรคกลับหลังหยุดยาต้านไทรอยด์ ควรเลือกการรักษาโดยไอโอดีนกัมมันตรังสี*