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Retrospective Study

Clinical effect of methimazole combined with selenium in the treatment of toxic diffuse goiter in children

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Author contributions: Zhang XH, Yuan GP, and Chen TL designed and performed the study; Zhang XH, Yuan GP, and Chen TL analyzed the data; all authors contributed to the writing and revising of the manuscript.

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Abstract

BACKGROUND

The incidence of toxic diffuse goiter (Graves' disease) is higher in adolescents and preschool-aged children, with an upward trend. The incidence at 6–13 years of age is approximately 11.0%, and the incidences in men and women are 7.8% and 14.3%, respectively.

AIM

To explore the clinical effect of methimazole combined with selenium in the treatment of toxic diffuse goiter (Graves' disease) in children and its effect on serum anti-thyroglobulin antibody (TRAb) and anti-thyroid peroxidase antibody (TPOAb).

METHODS

A total of 103 children with Graves' disease treated in our hospital from January 2018 to June 2021 were divided into a traditional group and a combined group (15-20 mg methimazole orally given to children) and a combined group (50 µg selenium added on the basis of traditional treatment) according to different treatment methods to explore the therapeutic effects of the two methods and to observe the changes in thyroid volume and serum TRAb, TPOAb, free thyroxine (FT4) and inflammatory factor levels before and after treatment. The time taken for FT4 to return to normal was compared between the two groups.

RESULTS

Treatment was significantly more effective in the combined group than in the traditional group ($P < 0.05$). The thyroid volumes of the children in the two groups was measured before and after treatment. Thyroid volume decreased significantly after treatment in both groups, and the thyroid volume was significantly lower in the combined group than in the traditional group ($P < 0.05$). The serum levels of interleukin-6 (IL-6), IL-8, TRAb, TPOAb and FT4 in the two groups were detected before and after treatment. The levels of IL-6, IL-8, TRAb,

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TPOAb and FT4 were significantly lower in the combined group than in the traditional group ($P < 0.05$). Follow-up of the children in the two groups showed that compared with the traditional group, it took less time for children in the combined group to return to the normal level ($P < 0.05$).

CONCLUSION

Methimazole combined with selenium can effectively treat Graves' disease in children, reduce the expression of TRAb, TPOAb, FT4 and inflammatory factors, and improve the curative effect. Thus, the combined treatment warrants further clinical research.

Key Words: Methimazole; Selenium; Children; Antithyroid globulin; Anti-thyroid peroxidase antibody

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Core Tip: Anti-thyroglobulin (thyroglobulin antibody, TRAb) is a common antibody in the sera of children with autoimmune thyroid disease, and anti-thyroid peroxidase antibody (thyroid peroxidase antibody, TPOAb) is an indicator closely related to thyroid immune damage. In this study, 103 children with Graves' disease treated in our hospital were selected and divided into a traditional group and a combined group according to treatment method to explore the therapeutic effects of the two methods and to detect changes in serum TRAb and TPOAb levels of the two groups of children before and after treatment. The clinical efficacy of the combined treatment provides a solid theoretical foundation for the clinical diagnosis and treatment of Graves.

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INTRODUCTION

Toxic diffuse goiter (Graves) is an organ-specific autoimmune disease accompanied by increased secretion of thyroid hormone. It is the most common autoimmune thyroid disease in children. The main clinical symptoms are goiter, pain, and emotional agitation[1]. The enlarged thyroid gland is symmetrical and has a lobulated appearance. The texture of the enlarged gland is as tough as rubber. Some children will have symptoms of hyperthyroidism, and later symptoms of hypothyroidism may seriously affect the child's physical and mental health. Therefore, timely and effective diagnosis and treatment are important for the child's condition and prognosis[2,3]. In recent years, methimazole has been widely used in the clinical treatment of Graves. Methimazole is a thyroid disease drug that inhibits the synthesis of thyroxine and improves thyroid function. However, due to children's physique and drug control problems[4], side effects of methimazole occur frequently in children. Selenium is an essential trace element for the human body. Selenium is closely related to thyroid gland function and can improve the antioxidant capacity of the thyroid gland and curb hypothyroidism. Selenium can inhibit the activity of thyroid hormone receptors, reduce the probability of thyroid hormone binding, reduce the basal metabolic rate, and inhibit the occurrence and development of thyroid diseases[5].

MATERIALS AND METHODS**General information**

A total of 103 children with Graves' disease who were treated in our hospital from January 2018 to June 2021 were selected and divided into a traditional group and a

combined group according to their different treatment methods. There were 50 children in the traditional group, including 28 males and 22 females, with an average age of 7.85 ± 1.23 years, a course of 2 to 4 years, and an average course of 2.84 ± 0.31 years. There were 53 children in the combined group, including 26 males and 27 females, with an average age of 7.49 ± 1.21 years, a course of 2 to 4 years, and an average course of 2.91 ± 0.35 years. The inclusion criteria were as follows[7]: (1) Meet the standards in "Internal Medicine. Endocrinology Division": (a) Clinical manifestations of thyrotoxicosis; (b) B-ultrasound of the thyroid gland suggesting diffuse thyroid enlargement; (c) Thyroid stimulating hormone is reduced, and free triiodothyronine and free thyroxine (FT4) are elevated; (d) Exophthalmos and other infiltrating eye signs; (e) Anterior tibial mucinous edema; and (f) Positive for thyroglobulin antibody (TRAb) or thyroid stimulating antibody. Criteria (a), (b), and (c) are a necessary diagnosis, and criteria (d), (e), and (f) are an auxiliary diagnosis; (2) First treatment; (3) Age 4-13 years; and (4) Complete information. The exclusion criteria were as follows: (1) Thyroid hyperfunctioning adenoma; (2) Toxic nodular goiter; (3) Transient hyperthyroidism such as subacute thyroiditis, Hashimoto's disease, painless thyroiditis, *etc.*; (4) Medical history of malignant thyroid tumor; (5) Previous thyroid surgery or 131 iodine therapy; (6) Reduced white blood cells and impaired liver function; and (7) Other autoimmune diseases.

Treatment and testing methods

Children in the traditional group received 15–20 mg of methimazole (Merck Pharmaceuticals (Jiangsu) Co., Ltd., National Medicine Standard: J20171078), 1 time/d, 7 d/course, for 4–5 courses. If the dose calculated based on the weight of the child exceeded the adult level, the adult dose was usually used. After the clinical symptoms of the child were relieved, the dosage of the drug was reduced.

Children in the combined group received methimazole on the same basis as in the traditional group in combination with 50 μ g of selenium (Guangzhou Shanyuantang Health Technology Co., Ltd., approval number: Shijianbei 201744000090) orally, 2 times/d, 7 d/course, lasting 4–5 courses.

Blood was collected from all children before and after treatment for 6 mo. Three milliliters of peripheral venous blood was centrifuged in a KH19A centrifuge (Hunan Kaida Scientific Instrument Co., Ltd.) at 4000 r/min with a radius of 5 cm for 10 min, and serum was collected. The chemiluminescence method was used to detect the expression levels of TRAb and anti-thyroid peroxidase antibody (TPOAb) in children using a kit provided by Mingde Biotechnology Co., Ltd according to the manufacturer's instructions. The reference range for normal TRAb was 0–1.75 mIU/L; the reference range for normal TPOAb was 3.0–6.0 pmol/L; and the levels of IL-6, IL-8 and FT4 were determined by an enzyme-linked immunosorbent assay kit (Shanghai Enzyme United Biotechnology Co., Ltd.). The reference range for normal FT4 was 10–31 pmol/L.

Evaluation criteria for effects and indicators

The efficacy evaluation criteria were as follows: markedly effective: disappearance of symptoms, weight gain, normal pulse rate, and normal thyroid function; effective: improved symptoms, weight gain, improved pulse rate, and improved thyroid function; invalid: failure to meet the above criteria.

Statistical analysis

Statistical analysis uses SPSS22.0 software, measurement data uses mean \pm SD, multi-group comparison uses analysis of variance, pairwise comparison uses LSD-*t* test; count data comparison uses χ^2 test. Inspection level = 0.05.

RESULTS

Comparison of the treatment effect of the two groups of children

Comparing the treatment effect of the two groups of children, it was found that the treatment efficiency of the children in the combination group was significantly higher than that of the control group. In the combination group, 25 children had a significant therapeutic effect, 20 children had an effective value, and the total effective rate was 84.9%. In the traditional group, 16 cases were markedly effective, 14 cases were effective, the total effective rate was 60.0%, and the difference was statistically significant ($P < 0.05$) (Table 1).

Table 1 Comparison of therapeutic effects between the two groups, *n* (%)

Group	Cases	Markedly effective	Efficient	Invalid	Total effective rate
Joint group	53	25	20	8	45 (84.9)
Traditional group	50	16	14	20	30 (60.0)
χ^2					8.062
<i>P</i> value					0.005

Comparison of thyroid volume between the two groups of children before and after treatment

The thyroid volume of the two groups of children before and after treatment showed that the volumes of both groups of children decreased significantly after treatment, and the thyroid volume of the children in the combination group (6.37 ± 1.06) was significantly lower than that of the traditional group (6.92 ± 1.03) ($P < 0.05$) (Table 2).

Comparison of inflammatory indexes between the two groups of children before and after treatment

The levels of interleukin-6 (IL-6), IL-8 in the serum of the two groups of children were detected before and after treatment, and it was found that the levels of IL-6, IL-8 in the two groups of children were significantly decreased after treatment, and the levels of inflammatory indexes in the serum of the children in the combination group (6.19 ± 1.26 pg/mL, 293.62 ± 20.93 pg/mL) significantly lower than the traditional group (7.61 ± 1.13 pg/mL, 332.78 ± 87.07 pg/mL) ($P < 0.05$, Table 3).

Comparison of serum TRAb, TPOAb and FT4 before and after treatment in the two groups of children

The serum levels of serum TRAb, TPOAb, FT4 in the two groups of children before and after treatment were detected. It was found that serum TRAb, TPOAb, FT4 in the two groups were significantly decreased after treatment, and the TRAb, TPOAb, FT4 levels in the combined group (312.77 ± 44.73 μ/mL, 238.42 ± 83.08 μ/mL, 28.39 ± 4.57 pmol/L) were significantly lower the traditional group (617.61 ± 104.05 μ/mL, 332.78 ± 87.07 μ/mL, 24.63 ± 3.96 pmol/L) ($P < 0.05$, Table 4).

Comparison of the time taken for FT4 to return to normal in the two groups

Follow-up of the two groups of children found that, compared with the traditional group, it took less time for the FT4 of the combined group to return to the normal level ($P < 0.05$) (Table 5).

DISCUSSION

The clinical cause of Graves' disease has not yet been clarified, but recent studies have reported obvious family clustering phenomena[8,9], suggesting genetic or related factors. In addition, children with the disease often have autoimmune diseases such as anemia, diabetes, and reduced adrenal function. Therefore, it is speculated that environmental factors such as infection and excessive intake of iodide in the diet may also be related to the disease[10].

Very young children with this type of thyroiditis have obvious symptoms of hyperthyroidism. Commonly used medications for children include thyroid hormone preparations, antithyroid drugs, and adrenal cortex hormones[11,12]. In the present study, the effect of the combined treatment was significantly better than that of the traditional treatment, indicating that methimazole + selenium regimen is an effective treatment regimen for Graves' disease. Methimazole is an antithyroid drug that inhibits the expression of peroxidase in the thyroid, thereby blocking the coupling of the iodide oxidant to tyrosine in the gland and ultimately inhibiting the production of thyroxine and triiodothyronine[13]. Selenium is an electron donor for glutathione peroxidase, which can induce the conversion of oxidized glutathione to reduced glutathione. Supplementing selenium can effectively enhance the antioxidant capacity of the thyroid, remove reactive oxygen intermediates, and reduce oxidative damage to thyroid cells, preventing hypothyroidism and playing a balancing role[14]. In addition,

Table 2 Comparison of thyroid volume between the two groups before and after treatment (mean ± SD)

Group	Cases	Thyroid volume		t value	P value
		Before treatment	After treatment		
Joint group	53	10.25 ± 3.21	6.37 ± 1.06	8.142	0.000
Traditional group	50	10.87 ± 3.15	6.92 ± 1.03	8.449	0.000
t value		0.981	2.693		
P value		0.162	0.004		

Table 3 Comparison of inflammatory indexes between the two groups before and after treatment (mean ± SD)

Group	Cases	IL-6 (pg/mL)		IL-8 (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Joint group	53	13.62 ± 3.56	6.19 ± 1.26 ^a	351.47 ± 23.89	293.62 ± 20.93 ^a
Traditional group	50	12.93 ± 3.17	7.61 ± 1.13 ^a	353.69 ± 23.12	332.78 ± 87.07 ^a
t value		1.03	6.08	0.478	3.179
P value		0.15	0.000	0.316	0.000

^aP < 0.05 vs before treatment.

IL-6: Interleukin-6; IL-8: Interleukin-8.

Table 4 Comparison of Serum anti-thyroglobulin, anti-thyroid peroxidase antibody, free thyroxine between the two groups before and after treatment (mean ± SD)

Group	Cases	TRAb (μ/mL)		TPOAb (μ/mL)		FT4 (pmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Joint group	53	723.62 ± 124.6	312.77 ± 44.73 ^a	429.48 ± 93.89	238.42 ± 83.08 ^a	56.54 ± 5.56	28.39 ± 4.57 ^a
Traditional group	50	722.93 ± 123.2	617.61 ± 104.05 ^a	429.74 ± 93.97	332.78 ± 87.07 ^a	56.38 ± 5.07	24.63 ± 3.96 ^a
t value		0.028	19.51	1.984	5.63	0.152	4.451
P value		0.488	0.000	0.494	0.000	0.879	0.000

^aP < 0.05 vs before treatment.

TRAb: Serum anti-thyroglobulin; TPOAb: Anti-thyroid peroxidase antibody; FT4: Free thyroxine.

Table 5 Comparison of time taken for free thyroxine to return to normal between the two groups (mean ± SD)

Group	Cases	Time to return to normal (d)
Joint group	53	90.67 ± 8.54
Traditional group	50	123.5 ± 15.14
t value		13.65
P value		0.000

the addition of selenium can also reduce the amount of hyperthyroidism medication, avoid excessive treatment and cause hypothyroidism.

TRAb is a thyroglobulin-specific antibody synthesized by the human immune system, and TPOAb is an autoantibody mediated by thyroid peroxidase. Abnormal expression of TRAb and TPOAb is closely related to the occurrence and development of autoimmune thyroid diseases. TRAb and TPOAb are commonly used as clinical markers for the detection of immune disorders[15].

In the present study, serum TRAb and TPOAb levels decreased in both groups of children after treatment but were significantly higher in the combined treatment group than in the traditional treatment group, indicating that the combined regimen is more advantageous in terms of immune balance than methimazole alone. One possible reason is that methimazole has antioxidant and immunoregulatory functions[16]. Animal experiments show that methimazole inhibits the synthesis of antibodies by B lymphocytes and induces the expression of thyroid-stimulating antibodies in the blood, thereby maintaining suppressor T cells. Selenium deficiency inhibits the expression of CD8+ T cells, enhances the function of helper T cells, causes B lymphocytes to synthesize a large number of antithyroid antibodies, promotes the activation of thyroid peroxidase, and ultimately damages thyroid tissue. Selenium supplementation can effectively improve these pathological and physiological changes [17,18]. In addition, selenium supplementation can effectively enhance the antioxidant capacity of the thyroid gland, reduce thyroid cell damage, inhibit the expression of thyroglobulin and thyroid peroxidase, and improve the immune status of children.

FT4 is commonly used as an indicator of thyroid function in *in vitro* tests[19]. In the present study, the time for FT4 to return to normal levels was shorter in the combined group than in the traditional group, indicating that the combined dosing regimen can effectively restore children's thyroid function. Although eye improvement was observed in both groups of children after treatment, eye protrusion was significantly lower in the combined group than in the traditional group, indicating that the combined drug regimen also effectively improved the symptoms of hyperthyroidism in the children. Studies have shown that selenium supplementation plays an important role in the treatment of thyroiditis in children. On this basis, we found that methimazole + selenium has a significantly higher therapeutic effect than simple selenium supplementation in children to restore immune balance, improve the symptoms of hyperthyroidism, and restore thyroid function[20].

CONCLUSION

In summary, methimazole combined with selenium can effectively treat Graves' disease, reduce the expression levels of TRAb and TPOAb, and improve thyroid function in children. This regimen warrants further clinical research.

ARTICLE HIGHLIGHTS

Research background

Thyroglobulin antibody is a common antibody in the serum of children with autoimmune thyroid disease. Anti-thyroid peroxidase antibody (TPOAb) is an indicator closely related to thyroid immune damage.

Research motivation

This study explored the therapeutic effects of the two methods, and to detect the changes in serum anti-thyroglobulin antibody (TRAb) and TPOAb levels of the two groups of children before and after treatment.

Research objectives

This study aimed to explore the clinical efficacy of methimazole combined with selenium in the treatment of toxic diffuse goiter (Graves' disease) in children.

Research methods

In this study, 103 children with Graves' disease treated in our hospital were selected and divided into traditional group and combination group according to the treatment method.

Research results

The levels of interleukin (IL)-6, IL-8, TRAb, TPOAb and free thyroxine were significantly lower in the combined group than in the traditional group.

Research conclusions

The clinical efficacy of combined therapy provides a solid theoretical basis for Graves'

clinical diagnosis and treatment.

Research perspectives

This regimen warrants further clinical research.

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