

The effects of levothyroxine combined with methimazole on the clinical efficacy of hyperthyroidism treatment

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Abstract: To investigate the effects of levothyroxine combined with methimazole on the clinical efficacy of hyperthyroidism treatment. A total of 102 patients with hyperthyroidism admitted to our hospital from January 2018 to June 2020 were selected and randomly assigned into the combination group (levothyroxine combined with methimazole) and the control group (methimazole treatment alone). 3 months after treatment, the two groups were compared with regard to clinical efficacy, changes in ultrasound findings, the thyroid hormones, and serum indexes and the adverse reactions rate. The combination group (98.04%) outperformed the control group (86.27%) in total effective rate, and the overall efficacy garnered the similar result. After treatment, the combination group showed advantages in thyroid hormone level, serum index level, thyroid volume, superior thyroid artery diameter, and maximum blood flow rate when compared with those of the control group ($P < 0.05$). As for the adverse reactions rate, the combination group was superior to the control group (3.92% vs 15.69%) ($P < 0.05$). Levothyroxine combined with methimazole promotes the clinical efficacy of hyperthyroidism treating, reduces thyroid volume and the diameter of superior thyroid artery, enhances the patient's thyroid function and serum index, with higher safety profile.

Keywords: Hyperthyroidism, thyroid volume, levothyroxine, methimazole, serum index.

INTRODUCTION

Hyperthyroidism, also known as *JiaKang* in Chinese, is a common clinical disease of the thyroid system demonstrating a rising trend worldwide in recent years (Hongling, 2017; Min *et al.*, 2019; Yingping *et al.*, 2019). Hyperthyroidism is a kind of disease induced by hyperthyroidism and sympathetic hyperactivity caused by excessive release of thyroid hormone in the body (Jianlong *et al.*, 2020; Menglei *et al.*, 2019). Hyperthyroidism can affect the nervous system, circulatory system, metabolic system, digestive system, etc., and it takes a toll on the work, study and life of patients.

To date, conservative drug treatment remains the mainstay of hyperthyroidism (Hong, 2020; Xinyu, 2020; Yu *et al.*, 2020). Methimazole, a conventional anti-hyperthyroidism drug, is recognized as a drug against hyperthyroidism. However, due to the complexity of the disease, the outcome of single administration of methimazole was not desirable, which is prone to adverse reactions such as secondary hypothyroidism. Levothyroxine, as a main medicine used against thyroid hypofunction, can alternatively play a role in the treatment of hyperthyroidism and when it combined with methimazole, they can improve the clinical efficacy and the safety of treatment, lower adverse reactions. This study was being conducted with the aim to examine the specific efficacy of this combined treatment and its

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impact on correlative indexes and safety.

MATERIALS AND METHODS

General Information

This study enrolled a sample of 102 patients with hyperthyroidism admitted to our hospital between January 2018 and June 2020. They were assigned into the control group and the combination group using random number table, with 51 cases in each group. The diagnostic criteria were in line with Guidelines for the Diagnosis and Treatment of Thyroid Diseases in China Hyperthyroidism (2007).

Inclusion criteria

- Patients met the diagnosis criteria listed in the above guidelines;
- Patients ≥ 18 years old;
- Patients had no previous treatment of anti-hyperthyroidism;
- Patients informed consent were obtained from patients and their families.
- Exclusion criteria:
- With hyperthyroidism atrial fibrillation, arrhythmia and other heart diseases;
- With myasthenia gravis or hyperthyroidism crisis;
- History of allergy to the drugs involved in this study;
- In gestation, preparation of pregnancy, lactation or any other special physiological periods;
- With psychiatric diseases, cognitive impairment, unconsciousness and communication barriers;

- With thyroid anatomy abnormalities;
- With thyroid cancer and other malignant tumors;
- In acute stage of infectious diseases, cardiovascular and cerebrovascular adverse events, within 14 days after surgery or trauma.

This study was approved by our hospital ethics committee. The control group included 18 males and 33 females aged from 21 to 68 years (mean age, 45.84±6.98); course of disease ranged from 1 to 12 months, with an average of (6.21±1.04) months. The combination group was composed of 17 males and 34 females aged between 22 and 69 years old (mean age, 46.03±7.07), and the course of disease was from 1 to 14 months, with an average of (6.25±1.06) months. No significant gaps between the two groups were exhibited in the above-mentioned information (P>0.05).

Methods

The control group was given the initial dose of methimazole (SFDA approval number: H11020440) 10 mg/time orally, 3 times a day; After the condition was stable, thyroid function was detected, according to the test results and symptoms, the dose could be gradually reduced to 5-10mg / D and maintained and the treatment was continued for 3 months as a course of treatment.

The combination group was additionally given levothyroxine (SFDA approval number: H20010008) orally, 50-100µg/time, once a day and the methimazole was administered the same as the control group, and continued for 3 months.

Outcome measurements

After 3 months of treatment, the clinical efficacy of the two groups was compared, including thyroid volume, superior thyroid artery diameter, maximum blood velocity, blood flow resistance index, as well as thyroid hormone levels [serum thyroid stimulating hormone (TSH) level, free thyroxine (FT4) level, free triiodothyronine (FT3) level and serum indexes drawing on changes in interleukin-2 (IL-2) and transforming growth factor-β (TGF-β)]. What's more, adverse reactions rate were also recorded.

The clinical efficacy was assessed by referring to relevant literature standards (Xiaowu, 2020). Markedly effective: clinical symptoms disappeared and thyroid hormone level reached the normal scale. Effective: The symptoms improved, the thyroid hormone level was enhanced, but is still lower or above the normal range. Ineffective: symptoms were not improved or aggravated. The total effective rate is the sum of markedly effective rate and effective rate.

3ml of fasting peripheral elbow vein blood samples was drew from all patients before and after treatment, and were placed in the dark sterile room for 20min,

centrifuged at the speed of 3000r / min for 10min, and the serum was obtained for detection; the levels of thyroid hormones were detected by immunochemiluminescence method, and the serum index levels were detected by enzyme-linked immunosorbent assay. The ultrasound indexes were measured and calculated by Doppler ultrasound diagnostic instrument.

STATISTICAL ANALYSIS

All data of this study were processed and analyzed by SPSS 23.0, among which ordinal data were examined using rank-sum test and counting data were examined using X² test, all expressed in [n(%)]; the measurement data were given as ($\bar{x} \pm s$) and t test was employed to examine the difference. Significance was claimed at a P value of <0.05.

RESULTS

Clinical efficacy

The total effective rate in the combination group was 98.04%, which was higher than 86.27% in the control group (P<0.05). See table 1.

Thyroid hormone levels

No significant difference was observed in all thyroid hormone levels between the two groups before treatment (P>0.05). After treatment, the combination group demonstrated lower levels of FT3 and FT4, higher level of TSH when compared against the control group (P<0.05). See table 2.

Thyroid ultrasound indexes

Before treatment, there was no significant difference in thyroid volume, diameter of superior thyroid artery, maximum blood flow velocity and blood flow resistance between the two groups (P>0.05); After treatment, significant difference was revealed in blood flow resistance between the two groups (P>0.05), while thyroid volume, diameter of superior thyroid artery and maximum blood flow velocity in the combination group were found to be remarkably lower than the control group (P<0.05, table 3).

Serum indexes

Table 4 and fig. 4 demonstrates that serum indexes in the two groups were basically the same prior treatment (P>0.05); After treatment, a notable lower expression levels of IL-2 and TGF-β in the combination group was identified when compared to the control group (P<0.05).

Adverse reactions

Regarding the adverse reaction rate, the combination group was superior to the control group (3.92%vs 15.69%) (P<0.05), as shown in table 5.

Table 1: Comparison of clinical efficacy evaluation [n (%)]

Group	N	Markedly effective	Effective	ineffective	Total effective rate
Control group	51	33(64.71)	11(21.57)	7(13.73)	44(86.27)
Combination group	51	41(80.39)	9(17.65)	1(1.96)	50(98.04)
Z/x ²			-1.971		4.883
P			0.049		0.027

Table 2: Comparison of thyroid hormone levels before and after therapy ($\bar{x}\pm s$)

Group	N	Time	FT ₃ (pg/ml)	FT ₄ (pg/ml)	TSH(ml/L)
Control group	51	Before treatment	15.19±3.00	70.71±17.22	0.22±0.11
		After treatment	6.15±1.70	16.63±6.10	2.45±0.98
Combination group	51	Before treatment	15.28±3.22	70.74±18.22	0.21±0.10
		After treatment	4.08±1.24	11.06±4.25	3.94±1.11
Before treatment		t	0.153	0.010	0.262
		p	0.879	0.992	0.794
After treatment		t	7.032	5.347	7.214
		p	0.000	0.000	0.000

Table 3: Thyroid ultrasound indexes before and after therapy ($\bar{x}\pm s$)

Group	N	Time	Thyroid volume (cm ³)	Artery diameter (mm)	Maximum blood flow rate (cm/s)	Blood flow resistance index (value)
Control group	51	Before treatment	22.49±6.29	3.67±0.22	112.15±12.68	0.58±0.17
		After treatment	10.41±2.41	2.09±0.19	41.56±8.19	0.56±0.10
Combination group	51	Before treatment	22.61±6.09	3.68±0.22	113.03±11.83	0.60±0.18
		After treatment	8.42±1.91	1.69±0.12	32.76±5.46	0.54±0.11
Before treatment		t	0.095	0.283	0.362	0.548
		p	0.924	0.778	0.718	0.585
After treatment		t	4.627	12.686	6.383	1.046
		p	0.000	0.000	0.000	0.298

Table 4: Serum indicators before and after treatment ($\bar{x}\pm s$)

Group	N	Time	IL-2(pg/L)	TGF-β(ng/ml)
Control group	51	Before treatment	2.96±0.35	63.86±6.31
		After treatment	2.05±0.37	37.20±5.27
Combination group	51	before treatment	2.98±0.39	64.07±6.21
		After treatment	1.47±0.31	19.16±4.43
Before treatment		t	0.257	0.166
		p	0.798	0.868
After treatment		t	8.526	18.707
		p	0.000	0.000

Table 5: Comparison of the incidence rate of adverse reactions [n(%)]

Group	N	Slight skin rashes	Leukopenia	Thyroid dysfunction (hypothyroidism)	Total incidence
Control group	51	2(3.92)	3(5.88)	3(5.88)	8(15.69)
Combination group	51	1(1.96)	0(0)	1(1.96)	2(3.92)
x ²		0.343	3.091	1.041	3.991
P		0.558	0.079	0.308	0.046

DISCUSSION

It is well known that the mechanism of hyperthyroidism is complex, and it is attributable to excessive secretion of thyroid hormone, which in turn results in hyperthyroidism and sympathetic hyperactivity and further lead to abnormal physiological changes in tissues and organs (Bo, 2020; Guodan, 2020; Jie, 2020). Hyperthyroidism patients often exhibit diffuse goiter, metabolic dysfunction and other manifestations (Huihui *et al.*, 2020; Yibing, 2020). Using Doppler ultrasound to measure and analyze the thyroid of patients with hyperthyroidism can quantitatively observe the thyroid lesions of patients and provide accurate reference for follow-up treatment and efficacy evaluation. TSH can improve human thyroid function, enhances the synthesis and release of thyroid hormone, and promotes the growth and reproduction of thyroid cells. FT3 and FT4 can directly reflect the level of thyroid function. Therefore, FT3, FT4 and TSH are commonly used indicators for clinical diagnosis, curative effect observation and thyroid function evaluation of thyroid diseases. IL-2 is a kind of cell growth factor synthesized by T lymphocytes. It directly acts on human B cells and promotes the proliferation, differentiation and immunoglobulin secretion of B cells. TGF- β can regulate the growth and differentiation of cells and play an important role in the immune regulation mechanism. It is noted that serum IL-2 and TGF- β have important value in evaluating the condition and prognosis of patients with hyperthyroidism.

To our best knowledge, methimazole is a conventional drug in the treatment of hyperthyroidism (Linrong and Ailing, 2021), which can inhibit the activities of peroxidase and iodine in thyroid, interfere with the tyrosine coupling process, and finally reduce the synthesis of FT3 and FT4. Despite methimazole shows definite efficacy in the treatment of hyperthyroidism, it is easy to induce secondary hypothyroidism by increasing TSH secretion under feedback stimulation. Levothyroxine is an oral thyroid hormone, mostly used in the clinical treatment of hypothyroidism (Hongmei and Feixuan, 2020), and characterized by stable efficacy and strong drug activity, which can maintain the normal development of the body, keep the metabolic balance, and enhance the sensitivity of sympathetic adrenal system. Moreover, levothyroxine can regulate the balance of thyroid pituitary endocrine axis, improve the synthesis and secretion of thyroid hormone, thus reduce or antagonize goiter.

In this study, the authors found that the combination group excelled in the clinical efficacy beyond the control group. Furthermore, after treatment, the levels of FT3, FT4 and TSH the combination group were higher than those in the control group, suggesting that the combined treatment can further regulate the level of thyroid hormone and maintain its stability. Besides, we observed

that the expression levels of serum TGF- β and IL-2 in the combination group were lower, indicating that the combined treatment can improve the expression level of serum indicators in patients with hyperthyroidism, enhance thyroid function and prevent or reduce goiter. Fortunately, the combination group outperformed the control group in the diameter of superior thyroid artery and the maximum blood flow velocity after treatment. It is suggested that the combined medication can effectively reduce the thyroid volume of patients with hyperthyroidism and the abnormally larger diameter of superior thyroid artery, so as to effectively reduce the thyroid blood flow velocity and fundamentally improve the organic lesions. Subsequently, the authors found that the adverse reactions rate in the combination group was lower and it is presumably due to that when methimazole maintained the drug concentration required for the treatment of hyperthyroidism, it could continuously suppress the secretion of thyroid hormones, which led to an increased risk of secondary hypothyroidism. It is suggested that the application of methimazole alone has many adverse reactions and the combined application of levothyroxine can reduce the risk of secondary hypothyroidism and various adverse reactions caused by alternative treatment mechanisms, maintain stable thyroid hormone levels.

The aforementioned strength of the combination regimen is attributable to that methimazole is a thyroid depressant, with a goal to reduce the secretion of thyroid hormone and decrease the level of thyroid hormone secretion, and finally in favor of clinical symptoms of patients with hyperthyroidism. However, the abnormal increase in TSH levels caused by the drug feedback mechanism can induce thyroid hyperplasia, further increase the patient's thyroid volume, and compromise the clinical efficacy. Levothyroxine has played the role of thyroxine replacement therapy in the combination medication, which can remarkably diminish the volume of the thyroid, regulate the level of thyroid hormone, and reduce the blood flow velocity of the thyroid body, thereby assisting in improving the clinical efficacy. Moreover, the sodium salt of tetraiodothyronine in levothyroxine can be converted into tetraiodothyronine after oral absorption, which can regulate the basic metabolic balance. Therefore, when the two drugs are used together, a complementary effect will be yielded to further improve the thyroid function of patients with hyperthyroidism, and they can regulate the secretion of various thyroid hormones and improve serum cytokine levels.

CONCLUSION

In conclusion, levothyroxine combined with methimazole is a preferred option for hyperthyroidism, and it can reduce the patient's thyroid volume and artery diameter, slow down the thyroid blood flow rate, regulate the

patient's thyroid hormone secretion level, and improve the patient's serum indicators.

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