EFFECTS OF METHIMAZOLE AND PROPYLTHIOURACIL ON GLUCOSE AND LIPID METABOLISM, SERUM THYROXINE, CYSTATIN C AND B2-MICROGLOBULIN IN PATIENTS WITH HYPERTHYROIDISM

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ABSTRACT

Objective: *To investigate the effects of methimazole and propylthiouracil on glucose and lipid metabolism, serum thyroxine, cystatin C and β2-microglobulin in patients with hyperthyroidism.*

Methods: *100 patients with hyperthyroidism diagnosed and treated in general surgical thyrid department in our hospital from September 2017 to September 2018 were divided into the control group and the observation group according to different treatment regimens, each 50 cases. Patients in the control group were treated with propylthiouracil, and those in the observation group treated with methimazole. Both groups were treated for consecutive 1 year. The clinical effects and adverse reactions of patients in the two groups were observed. [Low-density lipoprotein cholesterol LDL-C, total cholesterol (TC), triglyceride (TG), postprandial 2 h blood glucose (2 hPG), fasting blood glucose (FPG).)], serum thyroxine [high-sensitivity thyroid stimulating hormone (S-TSH), free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), total thyroxine (TT4)], Cystatin C (CysC) and β2-microglobulin (β2- MG) level changes of patients in two groups were compared.*

Results: *The total effective rate of the observation group was 88.00% significantly higher than that of the control group (76.00%) (P<0.05). The levels of LDL-C, TC and TG of patients in the two groups were significantly higher than those before treatment, and the levels of 2hPG and FPG were significantly lower than those before treatment (P<0.05). The levels of LDL-C, TC and TG in the control group were significantly increased (P<0.05). After treatment, the levels of S-TSH in the two groups were significantly higher than those before treatment, and the levels of FT3, FT4, TT3 and TT4 were significantly lower than those before treatment (P<0.05). The levels of CysC andβ2-MG in the two groups were significantly lower than those before treatment (P<0.05). The levels of CysC and β2-MG of patients in the observation group were significantly lower than those in the control group (P<0.05). There was no significant difference between the two groups with respect to the incidence rate of adverse reactions (P>0.05).*

Conclusion: *Methimazole is effective in the treatment of hyperthyroidism, which can effectively improve serum thyroxine, β2-MG and CysC levels, and has little effect on glycolipid metabolism.*

Keywords: *Methimazole, propylthiouracil, hyperthyroidism, glucose and lipid metabolism index, cystatin C, β2-microglobulin.*

DOI: 10.19193/0393-6384_2019_6_477

Received *November 30, 2018;* ***Accepted*** *February 20, 2019*

Introduction

Hyperthyroidism (hyperthyroidism) is a group of clinical syndromes caused by hypermetabolism or excessive secretion of thyroid hormones, causing hyperactivity and sympathetic excitation, thus leading to palpitations, sweating, eating, increased stools, and weight loss, which belongs to multiple diseases in endocrine system[(1)]. Clinically, 80% of hyperthyroidism is caused by diffuse toxic goiter (also known as Graves' disease). It is affected by factors such as iodized salt and accelerated life rhythm. Its incidence rate is increasing year by year[(2)]. Most hyperthyroidism patients are often accompanied by high metabolic syndromes of eye processes, eyelid edema, visial deterioration, diffuse goiter and skin lesions, etc and even by syndromes in respiratory, circulatory, cardiac and digestive systems and physiological disorders[(3)].At present, there are many methods for the treatment of hyperthyroidism in clinical practice, mainly anti-thyroid drugs, 131I and surgical treatment[(4)]. Imidazole drugs and thiourea drugs are commonly used anti-thyroid drugs. Methimazole and propylthiouracil are their representative drugs respectively. Clinical studies have shown that patients have a treatment remission rate of 40% to 50%, and which can lead to permanent decreased thyroid function. However, the drug treatment regimen has a high recurrence rate, and there are many adverse reactions such as rash,

joint pain, liver injury, etc and even liver damage and death[5]. Therefore, it provides a reference for the clinical treatment of hyperthyroidism patients. This study used methimazole and propylthiouracil to treat hyperthyroidism patients, aiming at exploring effects of them on glucose and lipid metabolism indicators [Low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), postprandial 2 h blood glucose (2hPG), fasting blood glucose (FPG)], serum thyroxine [High sensitivity thyrotropin (S-TSH), free Triiodothyronine (FT3), free thyroxine (FT4), total triiodide Total Triiodothyronine (TT3), Total Thyroxine (TT4), Cystatinc (CysC) and β2-microglobulin (β2-MG).

Materials and methods

Genenral data

100 patients with hyperthyroidism diagnosed and treated in general surgical thyrid department in our hospital from September 2017 to September 2018 were enrolled in the study.

The inclusive criteria were:

- all met the criteria for the diagnosis of hyperthyroidism;
- all patients were newly diagnosed with hyperthyroidism;
- hyperthyroidism had been diagnosed by B-ultrasound and X-ray;
- TT4, TT3> normal value and FT3, FT4 were normal or slightly larger than normal;
- no relevant treatment was taken;
- patients were aware of the study medication regimen and signed the informed consent form.

Exclusion criteria:

- patients with diabetes, liver and kidney dysfunction, hyperlipidemia;
- patients who were had hepatosplenomegaly, mental disorders, blood system diseases excluded;
- patients who were allergic to methimidazole and propylthiouracil-related drugs excluded;
- patients whose clinical data is insufficient;
- patients who had systemic infectious diseases;
- patients who were pregnant and lactating women excluded.

Patients were divided into the control group and the observation group following different treatment regimens, among which, 50 patients in the control group, consiting of 25 males and 25 females. Mean age was (52.31±2.31) years. Mean disease duration was (4.32±0.85) months; 45 patients in the observation group, consisting of 30 males and 20 females. Mean age was (51.98±2.45) years. Mean disease duration was (4.56±0.69) months. There was no significant difference in general data between the two groups (P>0.05).

Methods

The patients in the control group were treated with propylthiouracil (specification: 50mg/piece approval number: H31021082 Shanghai Zhaohui Pharmaceutical Co., Ltd.), the initial dose was 250mg daily, and reduced until to the gradual improvenment of patient's clinical symptoms and thyroid function indicators. Then the dose of 40~90mg was continued for treatment for consecutive 1 year. The patients in the observation group were treated with methimazole (specification: 5mg/piece approval number: H11022440 produced by Beijing Yanjing Pharmaceutical Co., Ltd.), the initial dose was 30mg daily, and reduced until to the gradual improvenment of patient's clinical symptoms and thyroid function indicators. Then the dose of 5-10 mg per day was continued for treatment for consecutive 1 year.

Observation indicators:

- The clinical effects of patients in two groups were compared, significantly effective: clinical symptoms disappeared, TT3, TT4, FT3, FT4 basically returned to normal; effective: clinical symptoms improved, TT3, TT4, FT3, FT4 decreased; invalid: clinical symptoms improved or even worsen, the levels of TT3, TT4, FT3, and FT4 did not change significantly. Total effective rate = (number of significant effective cases + number of effective cases) / total number of cases × 100%.
- Changes in LDL-CTC, triglyceride (TG), 2 h postprandial 2 hPG, and FPG levels before and after treatment were measured using automatic biochemical analyzer.
- Radioimmunoassay Changes in S-TSH, FT3, FT4, TT3, and TT4 levels before and after treatment were detected using radioimmunoassay.
- CysC and β2-MG levels before and af-

ter treatment were detected using enzyme-linked immunosorbent assay.

- The incidence of adverse reactions was compared between the two groups.

Statistical method

The data were analyzed by SPSS23.0. The measurement data were represented by ($\bar{x}\pm s$). The t test was used for comparison between groups. The enumeration data was represented by [n (%)], and the $\chi 2$ test was used. P<0.05 was considered as statistically significant.

Results

Comparison of clinical effects between the two groups

The total effective rate of the observation group was 88.00% significantly higher than that of the control group (76.00%) (P<0.05). Seen in Table 1.

Group	n	Significant effective	Effective	Invalid	The total effective rate
Control	50	18(36.00)	20(40.00)	12(24.00)	38(76.00)
Observation	50	29(58.00)	15(30.00)	6(12.00)	44(88.00)
χ^2					2.439
P					0.462

Table 1: Comparison of clinical effects in two groups [n (%)].

Comparison of glucose and lipid metabolism indexes between the two groups

The levels of LDL-C, TC and TG of patients in the two groups were significantly higher than those before treatment, and the levels of 2hPG and FPG were significantly lower than those before treatment (P<0.05). The levels of LDL-C, TC and TG of patients in the control group significantly increased. (P<0.05). Seen in Table 2.

Group		LDL-C (mmol/L)	TC (mmol/L)	TG (mmol/L)	2Hpg (mmol/L)	FPG (mmol/L)
Control group	Before treatment	1.40±0.56	3.54±0.54	1.13±0.35	7.22±1.12	5.89±0.62
	After treatment	3.25±0.43^{ab}	4.89±0.73^{ab}	1.62±0.43^{ab}	5.81±0.60^{ab}	5.07±0.58^{ab}
Observation group	Before treatment	1.53±0.58	3.52±0.51	1.07±0.29	7.19±1.15	5.92±0.64
	After treatment	2.29±0.45^{a}	4.08±1.15^{a}	1.32±0.34^{a}	5.77±0.63^{a}	5.13±0.55^{a}

Table 2: Comparison of glucose and lipid metabolism indexes between the two groups ($\bar{x}\pm s$).

Note: compared with before treatment, $^{a}P<0.05$;compared with the control group, $^{b}P<0.05$.

Comparison of serum thyroxine levels between the two groups

After treatment, the levels of S-TSH of patients in the two groups were significantly higher than those before treatment, and the levels of FT3, FT4, TT3 and TT4 were significantly lower than those before treatment (P<0.05). The level of S-TSH of patients in the observation group was significantly higher than that in the control group, FT3, and the levels of FT4, TT3 and TT4 were significantly lower than those of the control group (P<0.05). Seen in Table 3.

Group		S-TSH (UIV/ml)	FT3 (pmol/L)	FT4 (pmol/L)	TT3 (pmol/L)	TT4 (pmol/L)
Control group	Before treatment	0.44±0.31	12.08±6.07	28.92±7.98	4.07±3.20	250.52±112.57
	After treatment	3.89±1.21^{a}	7.28±1.17^{a}	18.90±3.62^{a}	2.46±0.87^{a}	113.21±20.24^{a}
Observation group	Before treatment	0.53±0.30	12.12±6.15	29.12±8.73	4.21±3.15	249.82±113.42
	After treatment	5.25±0.89^{ab}	5.77±2.15^{ab}	16.69±4.15^{ab}	1.24±0.63^{ab}	97.23±21.12^{ab}

Table 3: Comparison of serum thyroxine levels between the two groups ($\bar{x}\pm s$).

Note: compared with before treatment, $^{a}P<0.05$; compared with the control group, $^{b}P<0.05$.

Comparison of CysC and β2- MG levels in two groups

The levels of CysC and β2-MG of patients in the two groups were significantly lower than those before treatment (P<0.05). The levels of CysC and β2-MG in the observation group were significantly lower than those in the control group (P<0.05). Seen in Table 4.

Group	CysC (mg/L)		*t*	*P*	β-MG (mg/L)		*t*	*P*
	Before treatment	After treatment			Before treatment	After treatment		
Control group	10.51±1.42	6.52±1.13	15.547	P<0.001	9.39±0.91	7.28±0.86	11.916	P<0.001
Observation group	10.45±1.36	3.13±0.79	32.910	P<0.001	9.44±0.89	3.52±0.73	36.366	P<0.001
t	0.216	17.356			0.278	23.569		
P	0.830	P<0.001			0.782	P<0.001		

Table 4: Comparison of serum thyroxine levels between the two groups ($\bar{x}\pm s$).

Note: compared with before treatment, $^{a}P<0.05$; compared with the control group, $^{b}P<0.05$.

Comparison of adverse reactions between the two groups

There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). Seen in Table 5.

Group	n	Itching	Leukocyte abnormalities	Rash	Adverse reaction rate
Control group	50	0	2(4.00)	2(4.00)	4(8.00)
Observation group	50	1(2.00)	2(4.00)	2(4.00)	5(10.00)
χ^2					0.122
P					0.727

Table 5: Comparison of adverse reactions between the two groups [n (%)].

Discussion

Hyperthyroidism is the excessive secretion of thyroid hormone into the blood circulation and transported to the entire body caused by a variety of reasons, which in turn has a certain impact on the body's multiple organs[6]. At present, the pathogenesis of hyperthyroidism has not been fully elucidated. Most clinical researchers believe that it is caused by various factors such as mental stimulation and infection on the basis of genetic defects, and is closely related to various factors such as age, gender and environment[7]. Improving the clinical symptoms of patients and reducing the recurrence rate of diseases is the purpose of clinical treatment for hyperthyroidism. Methimazole and propylthiouracil are first-line drugs for the treatment of hyperthyroidism. Their efficacy, comparative study and safety analysis had become hot topics in clinical research before[8]. The action mechanism of the two drugs is basically the same, which can inhibit the activity of thyroid catalase, inhibit the oxidation of ionic iodine accumulated in the thyroid to be transformed into activity iodine, thus protecting the tyrosine, and interfering with the condensation of iodinated tyrosine, hindering the production of FT3 and FT4, then ultimately playing a role in improving the clinical symptoms of patients[9]. Propylthiouracil inhibits the conversion of FT4 into FT3 by inhibiting thyroid peroxidase[10].

Clinical studies have shown that the same dose of methimazole in the treatment of hyperthyroidism patients with clinical effects significantly higher than that of the control group, and the absorption rate and plasma half-life are higher, which is basically consistent with our findings[11]. The results of this study showed that the total effective rate in the observation group was 88.00% significantly higher than that of the control group (76.00%) ($P<0.05$). There was no significant difference in the incidence of adverse reactions of patients between the two groups ($P>0.05$). The level of S-TSH in the observation group was significantly higher than that in the control group, and the levels of FT3, FT4, TT3 and TT4 were significantly lower than those in the control group ($P<0.05$). The level of S-TSH in the observation group was significantly higher than that in the control group, and the levels of FT3, FT4, TT3 and TT4 were significantly lower than those in the control group ($P<0.05$), showing methimazole is more effective than propylthiouracil and can effectively improve serum thyroid hormone levels.

In recent years, clinical studies have shown that hyperthyroidism is closely related to glucose metabolism[12]. Some patients with hyperthyroidism may have a decrease in impaired glucose tolerance, and even lead to secondary diabetes. Lipid metabolism disorder is common in patients with hyperthyroidism. Excessive secretion of thyroid hormone can promote protein and fat breakdown. Increased protein and fat consumption is an important factor leading to emaciation in patients with hyperthyroidism. Therefore, the selected drugs should have no effect on glucose and lipid metabolism in patients[13]. High levels of thyroid hormone can enhance the function of the adenylyl cyclase system, interfere with the action of tissue on auxin, catecholamine and other lipid mobilizing hormones, further promote fat breakdown, and increase the activity of lipoprotein lipase in skeletal muscle. ultimately affecting blood lipid levels[14]. The results of this study showed that the levels of LDL-C, TC and TG in the two groups were significantly higher than those before treatment, and the levels of 2hPG and FPG were significantly lower than those before treatment ($P<0.05$). LDL-C, TC and TG levels of patients in the control group significantly increased ($P<0.05$), indicating methimazole has little effect on glycolipid metabolism. Serum β2-MG and CysC concentrations are closely related to the degree of cell secretion.

When hyperthyroidism occurs, the level of thyroid hormone in the blood rises, the body's metabolism accelerates, and it has a certain influence on cell metabolism, which raises serum β2-MG and CysC levels[15]. Studies have shown that levels of β2-MG and CysC in patients with hyperthyroidism are positively correlated with disease severity. The results of this study showed that the levels of CysC and β2-MG of patients in the observation group were significantly lower than those in the control group ($P<0.05$), indicating that methimazole can effectively reduce the levels of CysC and β2- MG. In conclusion, metformin is effective in the treatment of hyperthyroidism, which can effectively improve serum thyroxine, β2-MG and CysC levels, and has little effect on glycolipid metabolism and a certain significance for clinical medication.

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