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Review Article

Efficacy of bicyclol combined with berberine on hyperthyroidism patients and analysis of related factors inducing the disease

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Abstract: Objective: This paper aimed to explore the efficacy of bicyclol combined with berberine on hyperthyroidism patients and investigate related factors inducing the disease. Methods: Altogether 134 hyperthyroidism patients treated in Xintai People's Hospital (May 2017-December 2018) were enrolled, in which 71 cases were treated by bicyclol combined with berberine (an observation group), while the other 63 cases were treated by bicyclol alone (a control group). They were compared with respect to disease treatment, adverse reactions, levels of thyroid hormones (FT_3, FT_4, TSH), and levels of liver function indices (ALT, AST, TBIL) before and after treatment. Risk factors inducing the disease were analyzed through Logistics regression. Results: Efficacy was significantly better in the observation group. The differences in adverse reactions were not significant between the two groups. Post-treatment levels of FT_3, FT_4, ALT, AST, and TBIL were significantly lower, while TSH level was significantly higher in the observation group. Hyperthyroidism family history, TSH, FT_3, and FT_4 were risk factors for inducing hyperthyroidism. Conclusion: Bicyclol combined with berberine has good efficacy on hyperthyroidism patients. Hyperthyroidism family history, low TSH, high FT_3, and high FT_4 are risk factors for inducing the disease.

Keywords: Bicyclol, berberine, hyperthyroidism, risk factors

Introduction

As a common endocrine system disease, hyperthyroidism refers to thyroid function enhancement and abnormal thyroid hormone secretion as a result of a variety of factors [1]. Its most common causes are Graves' disease and toxic nodular goiter [2]. The abnormal endocrine system of hyperthyroidism patients further affects their nervous system, digestive system, and other systems, thereby leading to a series of complications (including abnormal liver function and heart failure) [3]. Hyperthyroidism also increases the risk of cancers in patients [4]. The disease is currently treated by surgery, radioiodine, and drugs in clinical practice [5, 6], which, however, are possibly complicated with complications. Surgical treatment may give rise to hypothyrea and paralysis. Radioiodine treatment results in cytotoxicity, possibly causing genetic damage to patients and increasing the incidence of cerebrovascular diseases. Drug treatment may lead to agranulocytosis and affect liver function [7-9]. Therefore, therapeutic methods with better efficacy and fewer complications should be found to better improve the treatment of patients.

As a common adverse reaction of thyroid drugs for treating hyperthyroidism, liver function damage is also caused by thyroid hormone abnormalities, which limits drug treatment [10-12], so improving the liver function is likely to better improve the clinical efficacy on patients. Bicyclol, a novel chemical drug with a good liver-protection effect, can improve the patients' liver function and reduce their liver injury caused by some drugs, so it is used as a hepatoprotective agent in many areas [13, 14]. A common complication of hyperthyroidism is cardiovascular diseases, whose incidence and mortality rates greatly increase due to thyroid dysfunction, and which are an important cause of death for hyperthyroidism patients [15, 16]. Berberine is an isoquinoline alkaloid extracted from Chinese goldthread rhizome. It is found to relieve arrhythmia, prevent myocardial injury, and regulate and protect patients' immune,

hepatic, and renal functions [17, 18]. The specific efficacy of bicyclol combined with berberine on treating hyperthyroidism remains unclear, and included risk factors inducing the disease are also poorly understood.

Therefore, in this study, the therapeutic effect of the combination on hyperthyroidism patients was observed, and related factors inducing the disease were explored, so as to provide direction and basis for clinical research.

Materials and methods

One hundred and thirty-four hyperthyroidism patients treated in Xintai People's Hospital (May 2017-December 2018) were enrolled. Seventy-one cases in the observation group were treated by bicyclol combined with berberine, including 40 males and 31 females, with an average age of 48.7±8.0 years. Sixty-three cases in the control group were treated by bicyclol alone, including 34 males and 29 females, with an average age of 47.6±7.3 years. Sixty-nine healthy subjects undergoing physical examinations in Xintai People's Hospital during the same period were enrolled in the normal group. This study was approved by the Medical Ethics Committee. All patients were informed in advance of the study and signed the informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: Patients confirmed with hyperthyroidism, with diagnostic criteria based on the 2016 edition of *Guidelines for Diagnosis and Management of Hyperthyroidism* from the America Thyroid Association [19]; patients who had not received anti-hyperthyroidism therapy before; patients with complete clinical data; patients cooperated in treatment and follow-up.

Exclusion criteria: Patients complicated with hepatic diseases (such as alcoholic liver injury, steatohepatitis, viral hepatitis) or renal insufficiency; patients with allergies to the drugs used in this study; patients complicated with other cardiovascular diseases; pregnant or lactating women.

Main reagents and instruments

A fully-automated biochemical analyzer (AU5800) was purchased from Beckman Coulter, USA. Bicyclol was purchased from Beijing Union Pharmaceutical Factory, China. Berberine was purchased from Shaanxi Ark Pharmaceutical Co., Ltd., China. Methimazole was purchased from Beijing Taiyang Pharmaceutical Industry Co., Ltd., China.

Therapeutic schemes

All patients were treated with conventional anti-hyperthyroidism drugs. Methimazole (15 mg) was orally administrated once a day. On this basis, those in the control group were orally administrated with bicyclol (25 mg) three times a day, and those in the observation group were additionally and orally administrated with berberine (1 g) twice a day. The patients were treated for 1 month.

Detection methods

Venous blood (5 mL) at 6 hours after fasting was collected from all patients on admission and after treatment, placed in coagulation promoting tubes, and then centrifuged (3000 g at 4°C for 10 min) in a centrifuge, so as to collect the serum that was stored at -80°C for later use. After the serum of all subjects was taken out, the fully-automated biochemical analyzer was used to detect levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), free triiodothyronine (FT_3), free thyroxine (FT_4), and thyroid stimulating hormone (TSH) after treatment. Three repeated measurements were conducted.

Efficacy evaluation

Post-treatment clinical efficacy was divided into markedly effective, effective, and ineffective. Markedly effective indicated that levels of FT_3, FT_4, and TSH returned to normal range or their recovery range was >50%, and patients' clinical signs and symptoms basically disappeared. Effective indicated that the recovery range of the levels was 50-25%, and the clinical signs and symptoms were relieved. Ineffective indicated that the recovery range of the levels was <25%, and the clinical signs and symptoms were not improved or even aggravated.

Outcome measures

Major outcome measures: The efficacy after treatment, levels of thyroid hormones (FT_3, FT_4,

Table 1. Clinical data table

	Observation group (n=71)	Control group (n=63)	X^2/t	P
Age (Years)	48.7±8.0	47.6±7.3	0.828	0.409
Gender			0.076	0.783
Male	40 (56.34)	34 (53.97)		
Female	31 (43.66)	29 (46.03)		
BMI (kg/m^2)	21.23±2.03	21.16±1.98	0.201	0.841
Place of residence			0.318	0.573
City	58 (81.69)	49 (77.78)		
Countryside	13 (18.31)	14 (22.22)		
History of smoking	16 (22.54)	12 (19.05)	0.246	0.620
History of alcoholism	11 (15.49)	12 (19.05)	0.297	0.586
Hyperthyroidism family history	12 (16.90)	9 (14.29)	0.173	0.678
History of thyroid hypofunction	3 (4.23)	4 (6.35)	0.304	0.581
History of traumatic infection	5 (7.01)	7 (11.11)	0.678	0.410

Table 2. Clinical efficacy

	Observation group (n=71)	Control group (n=63)	X^2	P
Markedly effective	15 (21.13)	10 (15.87)		
Effective	49 (69.01)	39 (61.90)		
Ineffective	7 (9.86)	14 (22.23)	3.861	0.049
Total effective rate of treatment	64 (90.14)	49 (77.77)		

Table 3. Adverse reactions

	Observation group (n=71)	Control group (n=63)	X^2	P
Leukopenia	1 (1.41)	2 (3.18)		
Thyroid hypofunction	0 (0)	2 (3.18)		
Rash	2 (2.82)	1 (1.59)		
Gastrointestinal discomfort	0 (0)	3 (4.76)		
Total incidence	3 (4.23)	8 (12.71)	3.180	0.075

TSH) before and after treatment, and risk factors inducing hyperthyroidism.

Secondary outcome measures: Clinical data, adverse reactions after treatment, and changes in liver function indices (ALT, AST, TBIL) before and after treatment.

Statistical analysis

In this study, SPSS20.0 (SPSS Inc., Chicago, IL, USA) medical statistical analysis software was used to statistically analyze the collected data. GraphPad Prism 7 (GraphPad Software, Inc., San Diego CA, USA) was used to plot figures. Count data were expressed by rate (%), conducted by chi-square test, and represented by X^2. The data were conducted by Fisher's test when the sample number was ≥40 and the theoretical frequency was <1. Measurement data, which conformed to normal distribution, were expressed in the form of mean ± standard deviation (Mean ± SD). Independent samples t test was used for their comparison between two groups, while paired t test for the comparison within groups which was represented by t. Multivariate Logistics regression test was used for the multivariate analysis of risk factors inducing hyperthyroidism. The difference was statistically significant when $P<0.05$.

Results

Comparison of clinical data

The differences were not significant between the observation and control groups with respect to their age, gender, body mass index (BMI), place of residence, history of smoking, history of alcoholism, hyperthyroidism family history, history of thyroid hypofunction, and history of traumatic infection. See **Table 1**.

Better efficacy in the observation group

Patients in the observation group had a significantly higher total effective rate of treatment. See **Table 2**.

Adverse reactions with no significant difference between the observation and control groups

Adverse reactions occurred in the observation group such as leukopenia and rash, while those in the control group experienced leuko-

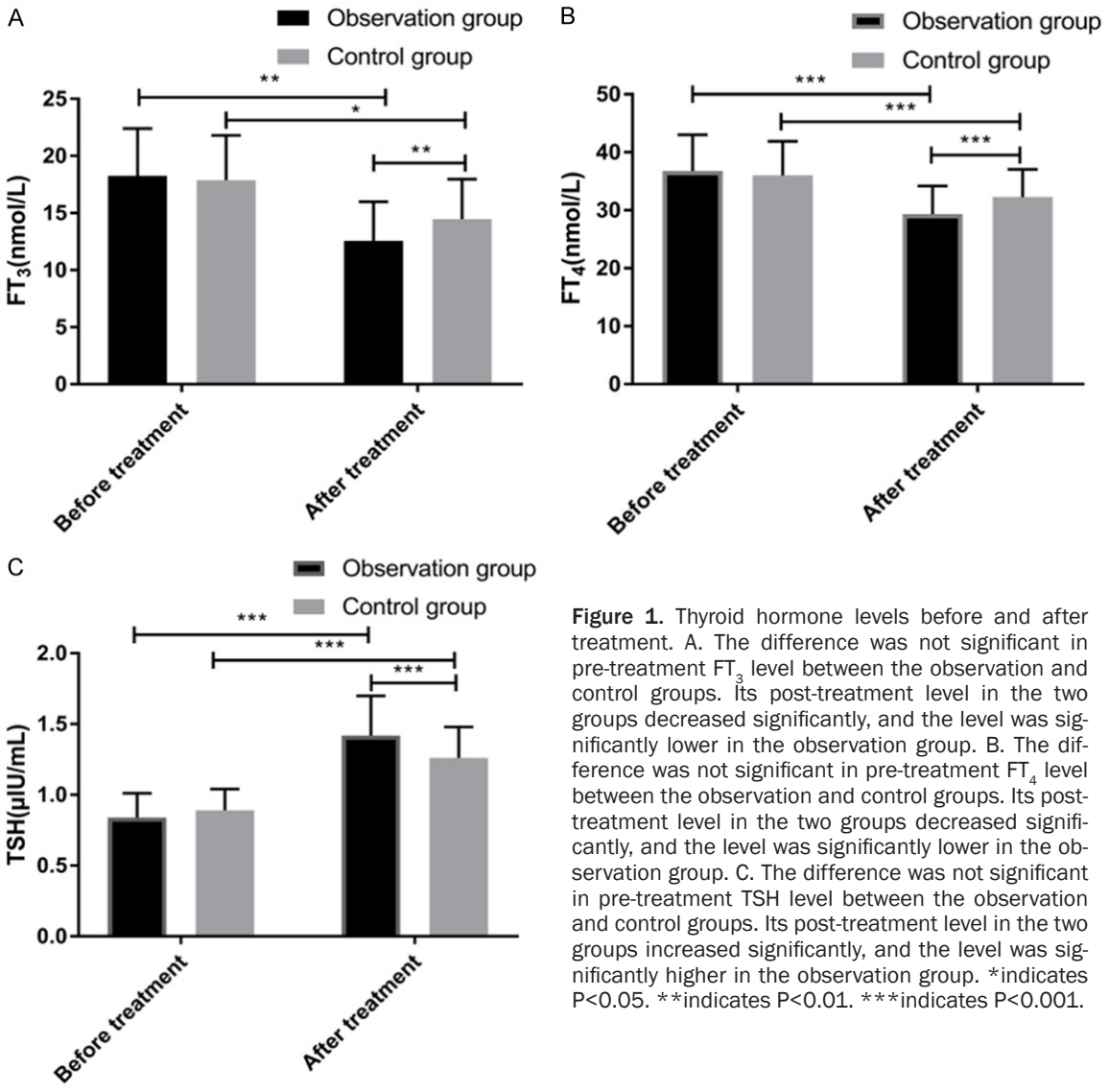

Figure 1. Thyroid hormone levels before and after treatment. A. The difference was not significant in pre-treatment FT_3 level between the observation and control groups. Its post-treatment level in the two groups decreased significantly, and the level was significantly lower in the observation group. B. The difference was not significant in pre-treatment FT_4 level between the observation and control groups. Its post-treatment level in the two groups decreased significantly, and the level was significantly lower in the observation group. C. The difference was not significant in pre-treatment TSH level between the observation and control groups. Its post-treatment level in the two groups increased significantly, and the level was significantly higher in the observation group. *indicates P<0.05. **indicates P<0.01. ***indicates P<0.001.

Table 4. Thyroid hormone levels before and after treatment

		Observation group (n=71)	Control group (n=63)	t	P
FT_3 (nmol/L)	Before treatment	18.26±4.15	17.88±3.92	0.543	0.588
	After treatment	12.57±3.41*	14.46±3.50*	3.163	0.002
FT_4 (nmol/L)	Before treatment	36.75±6.27	36.04±5.86	0.645	0.501
	After treatment	29.36±4.84*	32.27±4.78*	3.494	<0.001
TSH (μS/mL)	Before treatment	0.84±0.17	0.89±0.15	1.795	0.075
	After treatment	1.42±0.28*	1.26±0.22*	3.645	<0.001

Note: *indicates a statistically significant difference between before and after treatment.

penia, thyroid hypofunction, rash, and gastrointestinal discomfort. The total incidence of adverse reactions was not different between the observation and control groups. See **Table 3**.

Greater differences of thyroid hormones before and after treatment in the observation group

The differences were not significant in pre-treatment levels of FT_3, FT_4, and TSH between the observation group and the control group. Post-treatment FT_3 and FT_4 levels in the two groups reduced significantly, while post-treatment TSH level increased significantly. The FT_3 and FT_4 levels in the observation group (12.57±3.41, 29.36±4.84) were significantly lower than those in the con-

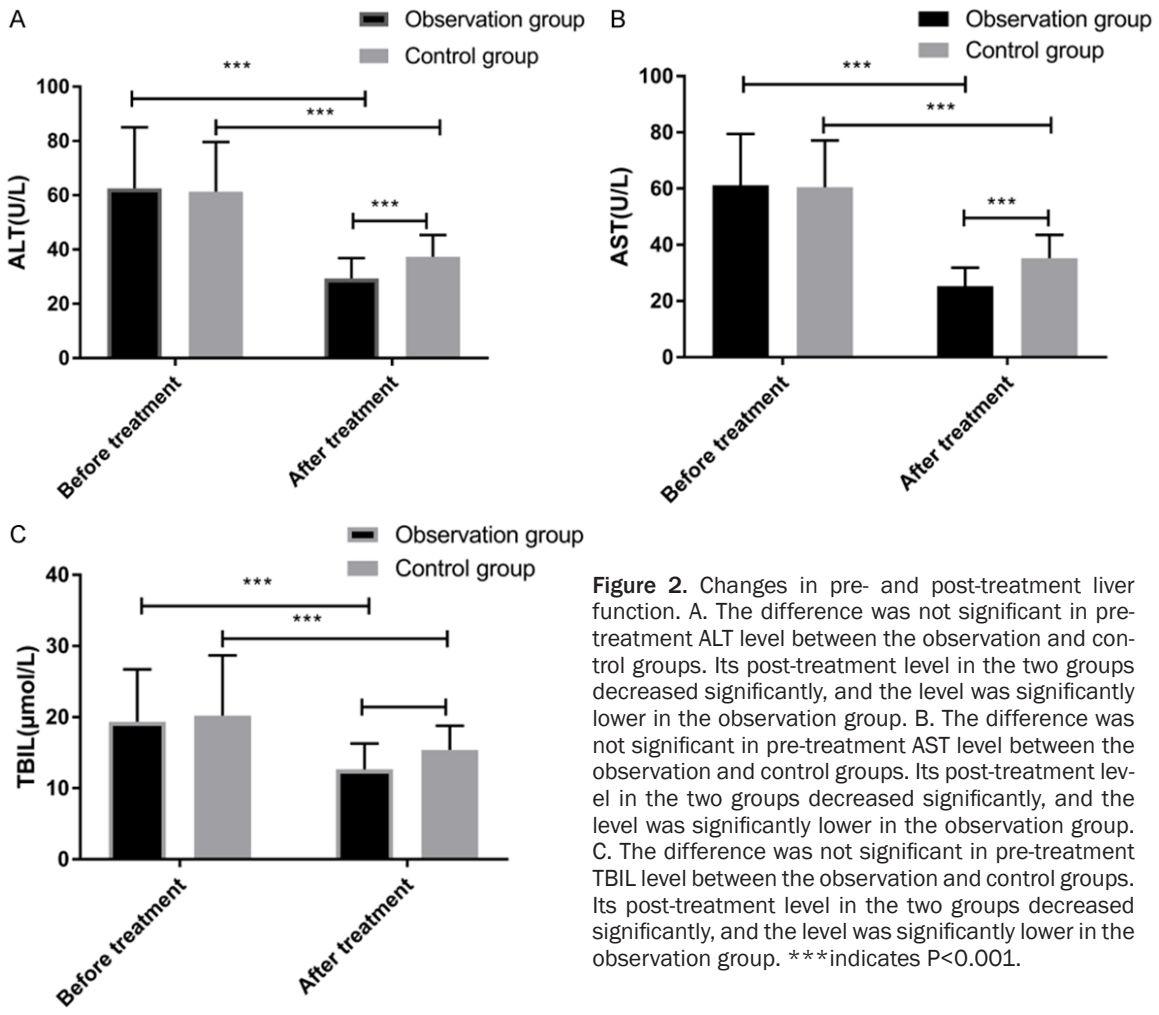

Figure 2. Changes in pre- and post-treatment liver function. A. The difference was not significant in pre-treatment ALT level between the observation and control groups. Its post-treatment level in the two groups decreased significantly, and the level was significantly lower in the observation group. B. The difference was not significant in pre-treatment AST level between the observation and control groups. Its post-treatment level in the two groups decreased significantly, and the level was significantly lower in the observation group. C. The difference was not significant in pre-treatment TBIL level between the observation and control groups. Its post-treatment level in the two groups decreased significantly, and the level was significantly lower in the observation group. ***indicates P<0.001.

trol group (14.46±3.50, 32.27±4.78), while the TSH level was significantly higher than that in the control group. See **Figure 1** and **Table 4**.

Better post-treatment liver function in the observation group

The differences were not significant in pre-treatment levels of ALT, AST, and TBIL between the observation group and the control group. Their post-treatment levels in the two groups reduced remarkably. The post-treatment levels in the observation group were significantly lower than those in the control group. See **Figure 2** and **Table 5**.

Univariate analysis of risk factors inducing hyperthyroidism

According to the comparison of clinical data, the differences were statistically significant between the hyperthyroidism and normal groups in hyperthyroidism family history, FT_3, FT_4, TSH, ALT, AST, and TBIL. See **Table 6**.

Multivariate analysis of risk factors inducing hyperthyroidism

Indices with differences in the univariate analysis were included into assignment (assignment table is shown in **Table 7**), and then forward: LR was chosen for multivariate Logistics regression analysis. Hyperthyroidism family history (OR: 6.435, 95% CI: 1.342-30.861), TSH (OR: 0.309, 95% CI: 0.117-0.819), FT_3 (OR: 1.072, 95% CI: 1.033-1.111), and FT_4 (OR: 6.784, 95% CI: 2.265-20.324) were independent risk factors inducing hyperthyroidism. See **Table 8**.

Discussion

At present, surgery, radioiodine, and drugs are commonly used to treat hyperthyroidism in clinical practice. The former two methods

Table 5. Liver function before and after treatment

		Observation group (n=71)	Control group (n=63)	t	P
ALT (U/L)	Before treatment	62.52±22.55	61.31±18.28	0.338	0.736
	After treatment	29.35±7.56*	37.37±7.98*	5.971	<0.001
AST (U/L)	Before treatment	61.17±18.25	60.46±16.67	0.234	0.815
	After treatment	25.27±6.64*	35.31±8.26*	7.791	<0.001
TBIL (μ(IL/L))	Before treatment	19.36±7.36	20.20±8.47	0.614	0.540
	After treatment	12.64±3.65*	15.37±3.42*	4.451	<0.001

Note: *indicates a statistically significant difference between before and after treatment.

Table 6. Univariate analysis

	Hyperthyroidism group (n=134)	Normal group (n=69)	X^2/t	P
Age	48.2±7.7	49.3±8.3	0.939	0.349
Gender			0.939	0.333
Male	74 (55.22)	43 (62.32)		
Female	60 (44.78)	26 (37.68)		
BMI	21.20±1.32	20.94±1.34	1.323	0.188
Place of residence			0.070	0.791
City	107 (79.85)	54 (78.26)		
Countryside	27 (20.15)	15 (21.74)		
History of smoking	28 (20.90)	9 (13.04)	1.884	0.170
History of alcoholism	23 (17.04)	7 (10.14)	1.729	0.189
Hyperthyroidism family history	21 (15.67)	3 (4.35)	5.602	0.018
History of thyroid hypofunction	7 (5.22)	2 (2.90)	0.581	0.446
History of traumatic infection	12 (8.96)	8 (11.59)	0.357	0.550
FT_3 (nmol/L)	18.04±4.37	7.48±0.93	19.820	<0.001
FT_4 (nmol/L)	36.43±6.56	8.36±1.26	35.171	<0.001
TSH (μIU/mL)	0.86±0.16	1.87±0.35	28.211	<0.001
ALT (U/L)	61.98±19.34	17.94±3.62	18.726	<0.001
AST (U/L)	60.83±17.36	17.34±3.25	20.601	<0.001
TBIL (μmol/L)	19.62±4.52	10.23±1.46	16.794	<0.001

Table 7. Assignment table

Factors	Assignment
FT_3	A continuous variable analyzed by initial data
FT_4	A continuous variable analyzed by initial data
TSH	A continuous variable analyzed by initial data
ALT	A continuous variable analyzed by initial data
AST	A continuous variable analyzed by initial data
TBIL	A continuous variable analyzed by initial data
Hyperthyroidism family history	Yes = 1; no =0
Hyperthyroidism	Yes = 1; no = 0

may change thyroid structure, but oral drugs do not lead to this situation, so oral drug treatment is widely used in patients with the disease [20].

However, the use of antithyroid drugs may cause hepatic damage [21]. In our study, levels of ALT, AST, and TBIL were detected to be higher than their normal ranges, indicating that the patients' hepatic function had been damaged before treatment. As the main target of hormones in vivo, the liver can be affected by many endocrine interfering substances, and the exposure of thyroid hormones leads to impaired glycogen storage capacity and abnormal lipid accumulation in liver cells [22]. Therefore, the failure to

Table 8. Multivariate analysis

Factors	B	S.E,	Wals	Sig.	Exp (B)	95% CI. for EXP (B)	
						Lower	Upper
Hyperthyroidism family history	1.862	0.800	5.418	0.020	6.435	1.342	30.861
TSH	-1.156	0.498	5.387	0.020	0.315	0.118	0.835
FT_3	0.069	0.019	13.858	0.000	1.072	1.033	1.111
FT_4	1.915	0.56	11.697	0.001	6.784	2.265	20.324

control over liver function will cause unsafe medication during treatment [23]. In our study, post-treatment levels of ALT, AST, and TBIL in the two groups reduced remarkably, which shows that the two therapeutic schemes can relieve hepatic injury and prevent the hepatotoxicity of drugs. The three post-treatment levels were lower in the observation group, which also reveals that bicyclol combined with berberine can better improve the patients' hepatic function. At the same time, we assessed and compared the therapeutic effects between the two groups, and found that the efficacy was remarkably better in the observation group. This suggests that the combination can better improve the therapeutic effect on the patients. Hyperthyroidism patients suffer from problems of immune function because of endocrine disorders [24], and berberine can relieve inflammation and regulate immune function [25], so it is suspected that berberine may improve the body and the efficacy through relieving inflammation and enhancing immunity. We detected the patients' thyroid hormones (FT_3, FT_4, and TSH). Pre-treatment FT_3 and FT_4 levels in the two groups were remarkably higher than their normal levels, while TSH level was significantly lower, which is similar to previous studies. The secretion of thyroid hormones is closely related to patients' central nervous system, so its abnormalities lead to their mental disorders [26]. Post-treatment FT_3 and FT_4 levels in the two groups were remarkably lower but post-treatment TSH level was remarkably higher than their pre-treatment levels; post-treatment FT_3 and FT_4 levels were remarkably lower but post-treatment TSH level was remarkably higher in the observation group. Finally, we included a group of healthy people and analyzed the risk factors for hyperthyroidism through Logistics regression. The results showed that hyperthyroidism family history, TSH, FT_3, and FT_4 were the risk factors.

However, there are still deficiencies in this study. First, hyperthyroidism patients were not subdivided, and there were differences among different types of the patients. Second, the drugs used in this study had fixed doses, so their optimal therapeutic doses were not explored. Finally, specific influencing mechanisms of berberine and bicyclol were not fully investigated, which is hoped to be further explored in subsequent studies.

In summary, bicyclol combined with berberine has good efficacy on hyperthyroidism patients. Hyperthyroidism family history, low TSH, high FT_3, and high FT_4 are risk factors for inducing the disease.

Disclosure of conflict of interest

None.

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