Research Paper

Clinical Efficacy of Tapazole Integrated with Anti-Heart Failure Drugs in the Remedy of Hyperthyroidism Merged with Heart Failure

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To observe the clinical efficacy and safety of tapazole integrated with anti-heart failure drugs in the remedy of hyperthyroidism merged with heart failure. Subjects (39-78) y suffering from hyperthyroidism and heart failure were enrolled, a total of 120 patients were divided into two subgroups according to different intervention methods, each of 60. Control subgroup was given anti-heart failure drugs, while the observation subgroup was given tapazole combined with anti-heart failure drugs. The clinical efficacy, thyroid functioning, cardiac functioning, immune functioning and adverse reactions of the two subgroups were compared. In terms of the total effective rate, *vs.* the observation subgroup (91.67 %) was notably higher than control subgroup (76.67 %). The concentrations of serum free triiodothyronine 3, free thyroxine 4 and n-terminal pro-brain natriuretic peptide in the observation subgroup were lower while thyroid stimulating hormone, left ventricular ejection fraction, stroke volume and ratio of mitral valve blood flow were higher. The increase of cluster of differentiation 3^+, cluster of differentiation 4^+ and cluster of differentiation 4^+/cluster of differentiation 8^+ ratio in the observation subgroup was greater and cluster of differentiation 8^+ declined more notably. The remedy of hyperthyroidism and heart failure with tapazole combined with anti-heart failure drugs is more effective. It is safe and can improve the thyroid and heart functioning, thereby enhancing the body immunity.

Key words: Hyperthyroidism, heart failure, tabazole, anti-heart failure therapy, cardiac function, immunity function

Hyperthyroidism is an endocrine disease mainly caused by abnormal thyroid hormone secretion. Its main clinical manifestations are hyper metabolism and increased excitability of nervous and digestive[1,2]. According to the epidemiological investigation[3], hyperthyroidism can occur at any age, with a high incidence of 30 y to 60 y old, and the majority of female subjects, with an overall incidence of about 1 %. Related studies have shown that hyperthyroidism can cause cardiomyopathy[4,5], and in severe cases can develop into heart failure. In other words, heart failure is one of the more serious complications of hyperthyroidism, which can lead to death, which should be paid attention to.

Angiotensin Receptor Neprilysin Inhibitor (ARNI), Beta Blockers (BB) and Mineralocorticoid Receptor Antagonists (MRA) are the three basic drugs for clinical remedy of heart failure with declined ejection fraction[6]. In recent years, numerous randomized researches have authenticated that Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2I) can notably benefit subjects[7,8], and the latest heart failure guidelines regard it as the fourth core remedy drug. Therefore, at present, the above four kinds of drugs are mainly used to treat heart failure, but for subjects with hyperthyroidism, the efficacy is poor.

Tabazol is the main drug for clinical remedy of hyperthyroidism, but its disadvantages are slow efficacy, long remedy course and many side effects[9]. At present, the combination regimen is often used in the remedy of hyperthyroidism, but there are few studies on Tabazol integrated with anti-heart failure in the remedy of hyperthyroidism complicated with heart failure. In view of this, the author does the following research, and elaborate in detail. As shown in fig. 1 for specific implementation ideas.

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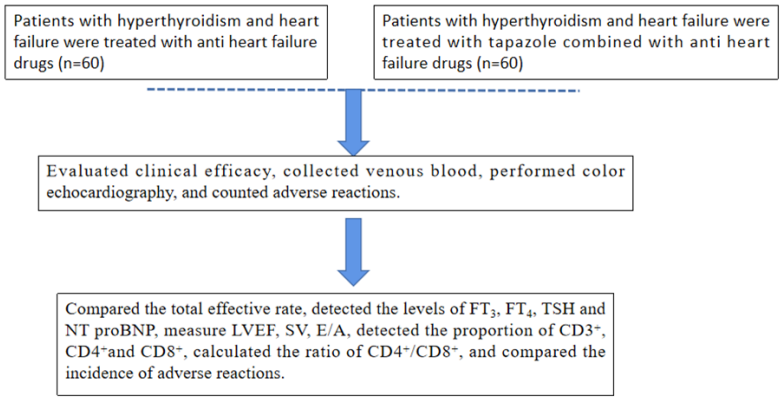

Fig. 1: Specific implementation ideas

MATERIALS AND METHODS

Design and procedures:

This was a double-arm cohort trial with repeated measurements from January 2020 to January 2022. In this retrospective analysis trial, the anti-heart failure drugs intervention group was compared with tapazole+anti heart failure drugs intervention group in order to expect a significant improvement in the clinical efficacy, thyroid function, cardiac function, immune function. The control subgroup was anti heart failure drugs subgroup, the observation subgroup was tapazole intervention on the grounds of the control subgroup.

Clinical data:

The eligibility and exclusion criteria of patients were evaluated according to the inclusion situation. After screening, the participants were assigned according to the intervention method.

Inclusion criteria: The clinical diagnostic criteria for hyperthyroidism was conformed[10]; conformed to the diagnostic criteria for heart failure[11], and was of reduced ejection fraction type; cardiac function class II-IV; good compliance and the clinical data were complete.

Exclusion criteria: Subjects merged with severe heart, liver and kidney dysfunction; subjects merged with severe infection or blood system disease; subjects with malignant tumors and subjects with serious mental illness and those who do not tolerate the remedy drugs.

Criteria for shedding or elimination: Those who did not complete the remedy as directed by the doctor; those who were seriously ill and needed to take active measures to save them; those who withdrew voluntarily and those who were unreachable. All the subjects did not fall off. The ethics committee of the hospital approved this study.

Procedure:

Methods of drug use: Both subgroups were instructed to quit smoking and drinking, ate low sodium diet, ate less and had more meals, exercised moderately, worked and rested reasonably, and maintained a happy mood.

Control subgroup: The subjects were treated with anti-heart failure drugs. The drug regimen was ARNI (such as sacubitril valsartan sodium tablets)+BB (such as metoprolol succinate, bisoprolol, metoprolol tartrate)+MRA (such as spironolactone)+SGLT2I (such as dapagliflozin).

Observation subgroup: The subjects were given tapazole (GYZZ H11020440, Beijing Yanjing Pharmaceutical Co., Ltd., 5 mg/tablet) orally with warm water on the basis of the control subgroup, 1-2 tablets/time, 3 times/d. Both subgroups were treated continuously for 3 mo.

Measures:

Thyroid function index: 5 ml of the subjects' venous blood from the morning before and after remedy was taken. After separation, the supernatant was taken, sub packaged and froze. The automatic biochemical analyzer was used to detect the concentrations of Free Triiodothyronine (FT3), Free Thyroid Hormone (FT4) and Thyroid Stimulating Hormone (TSH).

Cardiac function index: Before and after remedy, the Left Ventricular Ejection Fraction (LVEF), Stroke Volume (SV) per minute and ratio of mitral valve blood flow (E/A) were measured by color echocardiography, and the average value was taken for three consecutive measurements. At the same

time, the supernatant after sub package was taken, and the content of N-Terminal pro Brain Natriuretic Peptide (NT-proBNP) in serum was detected by enzyme-linked immunosorbent assay.

Immunity function: Before and after remedy, 5 ml of subjects' peripheral blood was collected, and the changes of T lymphocyte subsets (including Cluster of Differentiation (CD) 3^+, $CD4^+$, $CD8^+$) were detected by flow cytometry, and the $CD4^+/CD8^+$ ratio was calculated.

Adverse reactions: The adverse reactions of the two subgroups were counted.

Efficacy evaluation[12]:

The subject's clinical symptoms and signs disappeared, the serum indicators TSH, FT3 and FT4 returned to normal, and the improvement concentration of cardiac function was ≥2 or returned to normal, which was marked as notablely effective.

The subject's clinical symptoms and signs were notablely improved, the serum indicators TSH, FT3, FT4 were close to the normal range, and the improvement concentration of cardiac function was ≥1, which was marked as effective.

The subject's clinical symptoms, signs, serum indicators and cardiac function had no notable change or aggravation, which was marked as invalid. Total efficiency rate=(Notably effective+effective)/ total patients×100 %.

Statistical data:

Data was analyzed by Statistical Package for the Social Sciences (SPSS) 22.0 software. The measurement data were in accordance with normal distribution and uniform variance, expressed in (x±s). The paired sample t-test was applied for intra subgroup difference, and the independent sample t test was applied for inter subgroup difference; the counting data were expressed as n (%), and tested with Chi-Square (χ^2) values. The difference was statistically notable with $p<0.05$.

RESULTS AND DISCUSSION

The gender, age, Body Mass Index (BMI), hyperthyroidism degree and cardiac function grade in the control subgroup and observation subgroup was no notable difference ($p>0.05$), which was comparable as shown in Table 1. *vs.* the control subgroup (76.67 %), the total effective rate of the observation subgroup (91.67 %) was notablely higher ($p<0.05$) as confirmed in Table 2 and fig. 2.

Before remedy, there was no distinction in serum FT3, FT4 and TSH concentrations ($p>0.05$) between the two subgroups. But after remedy, the concentrations of serum FT3 and FT4 in the two sub groups declined ($p<0.05$), and the concentrations of TSH boosted ($p<0.05$); compared with the control subgroup, the changes of serum FT3, FT4 and TSH concentrations in the observation subgroup after remedy were greater ($p<0.05$) as shown in Table 3 and fig. 3.

Before remedy, there was no notable distinction in LVEF, SV, E/A and NT proBNP between the two subgroups ($p>0.05$); *vs.* before remedy, LVEF, SV, E/A in the two subgroups increased notablely after remedy ($p<0.05$), and NT-proBNP declined notablely ($p<0.05$); *vs.* the control subgroup, the changes of the above indicators in the observation subgroup after remedy were greater ($p<0.05$) as shown in Table 4 and fig. 4.

TABLE 1: GENERAL INFORMATION OF THE TWO SUBGROUPS

	Observation subgroup	Control subgroup	t/χ^2	p
Gender				
Male	18	15	0.376	0.539
Female	42	45		
Age (y)	60.28±7.59	58.77±7.80	1.074	0.284
Disease course (months)	24.16±5.50	25.02±5.43	0.861	0.390
BMI (kg/m^2)	22.47±2.15	22.85±2.09	0.981	0.328
Hyperthyroidism degree				
Mild	16	14	0.338	0.844
Moderate	38	41		
Severe	6	5		
Cardiac function grade				
II~III	41	43	0.158	0.690
IV	19	17		

TABLE 2: COMPARISON OF CLINICAL EFFICACY, n (%)

Subset	n	Notably effective	Effective	Invalid	Total efficiency rate
The observation subgroup	60	37 (61.67)	18 (30.00)	5 (8.33)	55 (91.67)
The control subgroup	60	20 (33.33)	26 (43.33)	14 (23.33)	46 (76.67)
χ^2					5.065
p					0.024

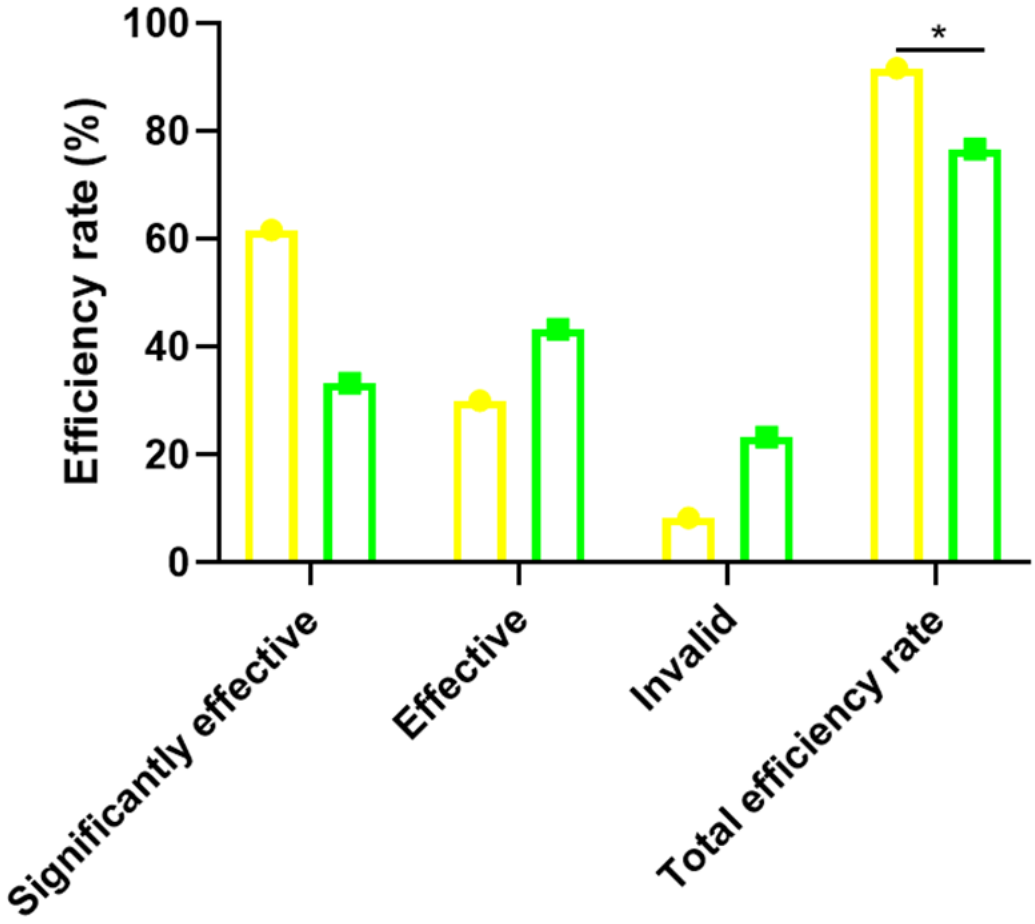

Fig. 2: Clinical efficacy between the two subgroups
Note: *p<0.05, ( ): Observation subgroup and ( ): Control subgroup

TABLE 3: COMPARISON OF THYROID FUNCTION INDICES (x̄±s)

Subgroups	n	FT3 (pg/ml)		FT4 (ng/dl)		TSH (mU/l)	
		Before remedy	After remedy	Before remedy	After remedy	Before remedy	After remedy
Observation subgroup	60	12.58±3.12	3.61±0.95*	7.16±1.23	1.20±0.65*	0.24±0.06	2.63±0.75*
Control subgroup	60	12.64±3.45	5.24±1.17*	7.07±1.38	2.36±0.74*	0.23±0.07	1.87±0.50*
t		0.1	8.378	0.377	9.123	0.84	6.531
p		0.621	<0.001	0.707	<0.001	0.403	<0.001

Note: *p<0.05, comparison of observation subgroup *vs.* control subgroup after remedy

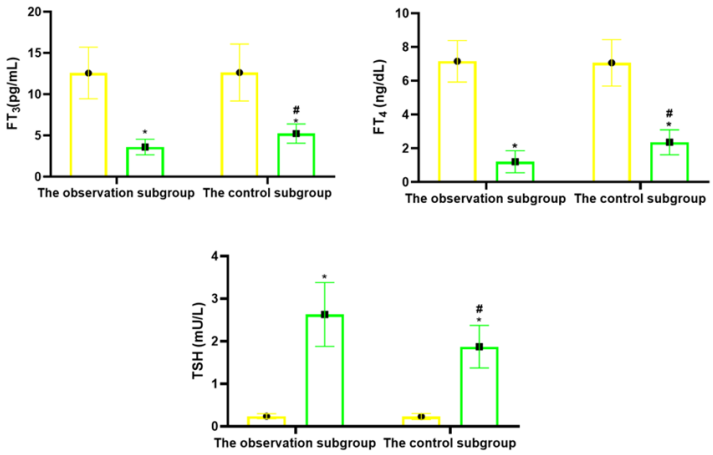

Fig. 3: Thyroid function indices between the two subgroups
Note: *p<0.05, compared to the control subgroup and #p<0.05, compared to the observation subgroup, (●): Before remedy and (■): After remedy

TABLE 4: COMPARISON OF CARDIAC FUNCTION INDICES (x̄±s)

Subgroup	n	LVEF (%)		SV (ml)		E/A		NT- proBNP (pg/ml)	
		Before remedy	After remedy	Before remedy	After remedy	Before remedy	After remedy	Before remedy	After remedy
Observation subgroup	60	38.45±4.26	49.74±5.20*	65.81±7.55	78.29±8.01*	0.88±0.21	1.25±0.30*	2549.50 ±576.22	946.37 ±162.55*
Control subgroup	60	37.81±4.50	43.16±4.79*	66.23±7.40	73.14±7.85*	0.85±0.23	1.07±0.28*	2487.35 ±600.41	1268.00 ±210.25*
t		0.800	7.209	0.308	3.557	0.746	3.398	0.578	9.374
p		0.425	<0.001	0.759	0.001	0.457	0.001	0.564	<0.001

Note: *p<0.05, comparison of observation subgroup *vs.* control subgroup after remedy

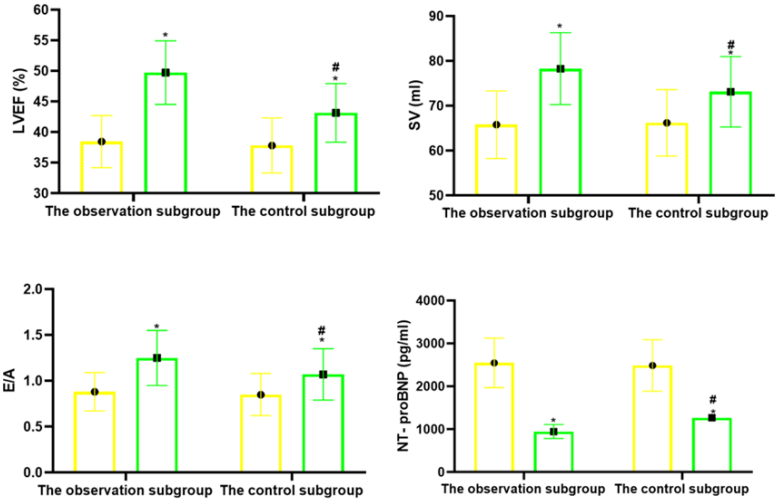

Fig. 4: Cardiac function indices between the two subgroups
Note: *p<0.05, compared to the control subgroup and #p<0.05, compared to the observation subgroup, (●): Before remedy and (■): After remedy

Before remedy, there was no notable distinction between the two subgroups in $CD3^+$, $CD4^+$, $CD8^+$ and the ratio of $CD4^+/CD8^+$ (p>0.05); *vs.* before remedy, the ratios of $CD3^+$, $CD4^+$and $CD4^+/CD8^+$ in the two subgroups increased notablely after remedy (p<0.05), while the ratio of $CD8^+$ declined (p<0.05); *vs.* the control subgroup, the changes of the above indicators in the observation subgroup after remedy were greater (p<0.05) as confirmed in Table 5.

TABLE 5: COMPARISON OF IMMUNE FUNCTION INDEXES ($\bar{x}\pm s$)

Subset	n	$CD3^+$ (%)		$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$	
		Before remedy	After remedy	Before remedy	After remedy	Before remedy	After remedy	Before remedy	After remedy
Observation subgroup	60	50.12±4.30	58.87±6.20	34.45±3.28	38.62±3.70	27.86±2.79	22.43±1.85	1.24±0.32	1.72±0.40
Control subgroup	60	50.07±4.18	54.76±5.57	34.01±3.14	36.52±3.46	27.60±2.55	25.13±1.54	1.23±0.35	1.45±0.38
t		0.065	3.82	0.751	3.211	0.533	5.689	0.163	3.791
p		0.949	<0.001	0.454	0.002	0.595	<0.001	0.871	<0.001

There were 2 patients having skin rash, 3 patients having damaged liver functioning, 1 patient with leukopenia in the observation subgroup, and the total adverse reaction was 10.00 % (6/60) *vs.* the control subgroup which had 2 patients having skin rash, 2 patients having damaged liver cell, and the total adverse reaction was 6.67 % (4/56). The distinction was not statistically notable (χ^2=0.436, p=0.509).

According to the location and etiology, hyperthyroidism can be divided into two categories; primary hyperthyroidism and central hyperthyroidism, in which primary hyperthyroidism can be divided into autoimmune hyperthyroidism (Graves's disease), thyroid autonomic hyper functional adenoma, multinodular toxic goiter and iodine hyperthyroidism[13]. Of all types of hyperthyroidism, 80 % are autoimmune hyperthyroidism. Clinical studies have found that Thyroid Stimulating Antibody (TSAB) is the main pathogenic factor of autoimmune diseases, which can induce hyperthyroidism by activating TSH receptor, causing thyroid gland to synthesize and secrete a large amount of thyroid hormone to induce hyperthyroidism[14,15]. Some studies have found that too much thyroid hormone will have some effects on the heart[16-18], causing cardiomyopathy, arrhythmia, heart failure, etc. With the increase of age, the prevalence of cardiovascular diseases caused by hyperthyroidism has increased year by year, and the number of hyperthyroidism deaths has also increased notably[19]. Heart failure has become a major global public health problem[20], but little attention has been paid to people such as hyperthyroidism merged with heart failure, so it is of great significance to explore the medication scheme of hyperthyroidism merged with heart failure.

The results of this study showed that the total effective rate of the observation subgroup was notablely higher than that of the control subgroup, suggesting that tapazole integrated with anti-heart failure drugs can improve the therapeutic effect of hyperthyroidism merged with heart failure. Hyperthyroidism is mainly manifested by excessive thyroid hormone secretion, and the remedy principle is to regulate the thyroid hormone concentration[21]. Thiourea drugs (Including methimazole and propylthiouracil) are commonly used in clinical remedy of hyperthyroidism. Generally, imidazole is the first choice. Tabazol is the representative of imidazole drugs. The mechanism of action is to reduce the thyroid hormone concentration by reducing the activity of thyroid endoperoxide, preventing the further oxidation of iodide, and blocking the coupling of tyrosine to reduce thyroid hormone concentrations[22,23]. Heart failure refers to the dysfunction of cardiac systolic and diastolic functions, which leads to the reduction of ventricular pumping function, the aggravation of myocardial load and the reduction of cardiac output. ARNI+BB+MRA are the three cornerstones for clinical remedy of heart failure. Long term regular medication can reduce the heart load and improve the heart function of subjects[24]. SGLT2I daggligin is a new hypoglycemic drug, which can improve left ventricular diastolic function, delay myocardial fibrosis, and inhibit myocardial remodeling[25]. In recent years, studies have shown that daggligin can reduce the incidence of major cardiovascular events and the risk of hospitalization and death of subjects with heart failure[26], and it is recommended as a class of drugs in the new version of the heart failure guidelines. The combination of anti-heart failure drugs and tapazole can play a synergistic role in further improving the clinical symptoms of

subjects and improving the therapeutic effect. In this study, the indexes of thyroid function and heart function in the observation subgroup were notablely better than those in the control subgroup, which also showed that the combination of drugs could enhance the therapeutic effect. Related studies also show that BB can not only inhibit the activity of sympathetic adrenoceptor[27,28], reduce the release of catechol, improve the symptoms such as fidgety mood, muscle tremor and tachycardia, but also inhibit the transformation between peripheral T4 and T3, and reduce the myocardial damage caused by thyroid hormone. Another study shows that hyperthyroidism is a high-risk factor for atrial fibrillation[29,30]. On the one hand, tapazole can maintain TSH in a normal range and reduce the occurrence of atrial fibrillation; on the other hand, it can also reduce the damage of thyroid hormone to myocardial cells and improve the myocardial hypertrophy caused by T3.

Researches have shown that humoral immunity and cellular immunity are involved in the pathogenesis of hyperthyroidism[31,32], and the immune function of subjects is obviously abnormal. In this study, the ratio of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ in the observation subgroup was notablely higher than that in the control subgroup, while the concentration of $CD8^+$ in the observation subgroup was notably lower than that in the control subgroup, indicating that methimazole integrated with anti-heart failure drugs can enhance the immune function of subjects. At present, the relevant evidence shows that tapazole can play an indirect immunomodulatory effect through thyroid cells, and the expression of First apoptosis signal Ligand (FasL) in thyroid cells interfered by tapazole is increased, which proves that tapazole can inhibit T lymphocyte apoptosis through FasL pathway[33]. The common adverse reactions of tapazole are liver function damage, peripheral blood leucopenia, allergic rash, etc.,[34]. *vs.* the control subgroup, the incidence of adverse reactions in the observation subgroup did not increase notablely, indicating that the combination of tapazole and anti-heart failure drugs is safe and controllable, and will not increase the side effects of drugs.

To sum up, tapazole integrated with anti-heart failure drugs has a notable effect in the remedy of hyperthyroidism with heart failure, which can effectively reduce the serum thyroid hormone concentration of subjects, improve cardiac function, enhance cellular immune function, and will not increase the side effects of drugs.

Conflict of interests:

The authors declared no conflict of interests.

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