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Original Article

Clinical efficacy of *Yingliu* treatment for Graves disease

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Abstract: Objective: To observe the clinical efficacy and safety of the traditional Chinese medicine (TCM) mixture Yingliu combined with methimazole medication for the treatment of Graves disease (GD). Method: In a randomized, paralleled control study, 92 GD patients were randomized into a Yingliu mixture treatment and a control treatment group, both receiving methimazole. Both treatments lasted for 12 weeks and outcome parameter were thyroid function, thyroid autoantibodies, TCM symptome scores and safety indicators. Results: The clinical efficiency of the Yingliu mixture-methimazole combination was 92.5% vs. 82.5% ($P < 0.05$) of the solely methimazole medication group. After 12 weeks treatments the Yingliu mixture in combination with methimazole improved free triiodothyronine (FT3), free tetraiodothyronine (FT4), thyroid-stimulating hormone (TSH) receptor antibody (TRAb) and thyroglobulin antibody (TGAb) values significantly more than methimazole alone and TCM symptome scores were significant lower after 12 week treatment in the Yingliu mixture- methimazole group ($P < 0.05$). The thyroid enlargement (21 vs. 10, $P < 0.05$), fatigue (39 vs. 30, $P < 0.01$) and dry mouth symptoms (37 vs. 29, $P < 0.05$) were superior improved in the Yingliu than in the control medication group, respectively. There was no significant difference regarding safety evaluations between both treatment groups ($P = 0.499$). Conclusion: Yingliu mixture as combined medication with methimazole can significantly improve the outcome of a solely methimazole application for GD treatments.

Keywords: Graves disease, Yingliu mixture, methimazole, TCM

Introduction

With the improvements of diagnostic technologies in recent years, the detection of hyperthyroidism has increased and GD as the most common type accounts for about 85% of hyperthyroidism cases [1]. GD is a kind of autoimmune disorder of unknown etiology, which occurs in any age but is more common in women than in men [2]. Its prominent clinical appearances of hyperthyroidism were accompanied by diffuse goiter, exophthalmos and pretibial myxedema. However, most of the patients have only 1 or 2 of the above visible symptoms, but with noticeable enhanced metabolism and involvement of the nervous and cardiovascular systems. Hyperthyroidism, if not treated actively, will cause damage to multiple systems, such as cardiovascular (hyperthyroidism heart disease), nervous, blood, musculoskeletal, digestive and reproductive systems [3].

At present, Yingliu treatments for GD mainly include anti-thyroid drugs, radioactive iodine and surgery [4], which all have drawbacks, such as long Yingliu treatment period (an average of 18 to 24 months), high recurrence rates (50%) [5], drug-induced liver damage [6], lack of granulocytes, skin rashes and antithyroid drug (ATD)-induced antineutrophil cytoplasmic antibody (ANCA) associated vasculitis [7]. Other effects are hypothyroidism and cancer after radioactive iodine Yingliu treatments [8].

Clinical studies have shown that TCM for the Yingliu treatment of GD has certain beneficial effects like improving symptoms of hyperthyroidism, reducing side effects of western medicine, lowering recurrence rates and shortening the disease course [3].

According to many years of clinical observation in our department, we think TCM influences GD by eliminating phlegm, promoting blood flow and resolving masses as the basic therapeutic principle. The Yingliu mixture is a domestic preparation of our hospital derived from long-term clinical observations and mainly used for

goiter Yingliu treatments. In this study, we analyzed the efficiency of Yingliu mixture Yingliu treatment as combination with methimazole medication.

Patients and methods

Patients

The study has been approved by the ethical committee of the Longhua hospital shanghai University of TCM and written informed consent of all participating patients was provided. Ninety-two eligible GD patients who were hospitalized or in outpatient service of the endocrinological department of the Longhua Hospital affiliated to Shanghai University of TCM between April 2011 and March 2013 and met the inclusion criteria were included and randomly divided into Yingliu treatment and control treatment groups.

Diagnostic criteria of GD

TCM diagnosis criteria: Primary symptoms: swelling in the front of the neck, fatigue, and dry mouth and thirsty. Secondary symptoms: patient cannot stand heat and hydrosis, chest tightness, too much phlegm, heart palpitations, upset and irritability, insomnia and much dream, polyphagia and weight loss, dry eye and blurred vision, facial ecchymosis. Tongue picture: dark tongue with petechia or red tongue with teeth marks, thin and greasy fur or less fur or thin, white and dry fur. Pulse condition: slippery, thin or tart pulse. Patients, who met three primary symptoms and two secondary symptoms or above, combined with indicated tongue and pulse conditions, which was verified by two experienced medical doctors, were suspected with GD.

Further diagnoses included (1) symptoms of hyperthyroidism; (2) diffuse enlargement of the thyroid gland (confirmed by ultrasound or palpation); (3) decrease of TSH levels, increase of thyroid hormone levels; (4) exophthalmos; (5) pretibial mucous edema; (6) positive for TRAb or thyroid stimulating hormone receptor antibody (TSAb). Goitre was confirmed by palpation and thyroid enlargement was classified as I degree when not visible but palpable; II degree when visible and palpable, but within the sternocleidomastoid area; III degrees when extended beyond the outer edge of the sternocleidomastoid [9].

Inclusion and exclusion criteria

In inclusion criteria included diagnosed GD, age between 18 to 70 years old and informed consent. Exclusion criteria were GD without goitre, pregnancy or breast feeding; patients with the leukemia, aplastic anemia, leukopenia (white blood cell count lower than 3.0×10^9/l), granulocytopenia syndrome (neutrophilvalue less than 1.5×10^9/l) and cardiovascular, liver, kidney or other primary diseases and mental illness. Other exclusion criteria were hyperthyroidism crisis, significantly enlarged thyroid resulting in compression of adjacent organs, all kinds of thyroiditis but without hyperthyroidism; allergic constitution with allergic to a variety of drugs, having taken anti-thyroid drugs in the recent three months, level of alanine amino transferase (ALT) before Yingliu treatment 2 times higher than upper normal limit.

Reasons for preterm trial termination

The clinical trial should be stopped according to the doctor's judgment of aggravation of illness or other symptoms that can confound the observation of GD. Serious adverse reactions or drug allergy. The drugs lack efficacy or liver damage (ALT more or equal than 2 times the normal limit, white blood cells lower than 2.5×10^9/l, neutrophils less than $1.\times10^9$/l, after the drug use. No adverse drug events occurred, but the Yingliu treatment was discontinued for other reasons (for example, some other disease occurred and the Yingliu treatment had to be interrupted). The patients were the opinion that the drug is ineffective and gave up participating in the trial.

Methods

Experimental drug, dosage and course of Yingliu treatment: Both groups received 5 mg-25 mg/d methimazole (thyrozol) (based on the levels of T3, T4, TSH and the blood index) for 12 weeks. The Yingliu mixture was prepared by the TCM laboratory of the Longhua Hospital (approval number Shanghai Z05170226).The decoction has been prepared with oysters, radix astragali, radix ophiopogonis, smilax, radix scrophulariae, rhizoma anemarrhenae, prunella vulgaris, forsythia, alisma plantago-aquatica, white mustard seed, semen impatientis, thunberg fritillary bulb and 25 ml were administered 3 times a day.

Table 1. TCM symptome scoring (see details of goitre classification in the section of diagnostic criteria)

Primary symptoms	0	2	4	6
Goitre	none	I degree	II degree	III degree
Fatigue	none	Not stand the labor force	Can insist physical labor	Reluctantly bear daily activities
Dry mouth and thirsty	none	Dry mouth but without thirsty	Like to drink	Drink frequently and much
Secondary symptoms	**0**	**1**	**2**	**3**
Unable to stand the heat	none	Feel hot after a little activity	Feel hot even in resting condition	Feel hot and sweatiness in resting condition
Hidrosis	none	Easy to sweatiness	Sweatiness after activity	Sweating continually
Chest tightness	none	Occasional chest tightness	Frequent chest tightness, which relieve in a short time	Always have chest tightness, which cannot relieve in a short time
Much phlegm	none	much phlegm occasionally	Always have much phlegm	Have much phlegm continually
Heart palpitations	none	Become marked after physical activity	Have heart palpitations once after physical activity	Have heart palpitations even in resting condition
Upset and irritability	none	Emotional instability, impatience	Tempered and irritability, which can be controlled by treatment	Tempered and irritability, which cannot be controlled by treatment
Insomnia and much dream	none	Have much dream and several awakening	Have much nightmares and easy to awakening	Hard to fall asleep
Polyphagia	none	meal size was increased by less than 1/2 after suffering the disease	Meal size was increased by 1/2 to 1 times	Meal size was increased by more than 1 times
Thin	none	Body weight was decreased by less than 20% after suffering the disease	Decreased by 20%-30%	Decreased by more than 30%
Dry eye and blurred vision	none	occasionally	Always have dry eye, blurred vision and diplopia	Continually have dry eye, blurred vision and diplopia
Facial ecchymosis	none	occasionally	multiple	Darkness and ecchymosis in whole face

Observation index and methods: The blood serum levels of FT3, FT4, TSH, TRAb, thyroid peroxidase antibodies (TPOAb) and TGAb were analyzed prior as well as 6 and 12 weeks after Yingliu treatment using electrochemiluminescence (E 170 module immunology analyzer, Roche, Germany). Hepatorenal functions were measured with the automatic biochemical analyzer, Roche DB-001 instrument (Roche Co., Shanghai, China). Routine blood and blood cell analysis was performed with a Beckman Coulter LH750 hematology analyzer (Beckman Coulter Inc. Fullerton, CA, USA). Blood routine and liver function was detected before Yingliu treatment, at 2, 6 and 12 weeks after Yingliu treatment start, and the kidney function was examined before and after the Yingliu treatment.

Efficacy evaluations: The TCM symptome score included primary and secondary symptoms (**Table 1**) and was evaluated before and 6 as well as 12 weeks after start of medication. According to the observation of symptoms, the primary symptom scored 0, 2, 4, 6 points and the secondary symptom scored 0, 1, 2, 3 points.

Thyroid palpation: Examinations were performed by specialized medical personnel during the follow-ups. The subjects were in sitting and the physician stood in front. Palpating started upward from the suprasternal notch with the thumb. When checking the thyroid gland lateral lobe, one thumb was used to press on the thyroid cartilage side to move the trachea contralateral. The index and middle fingers of the other hand were used to push forward the lateral lobes of the thyroid in the contralateral sternocleidomastoid trailing edge. Then the thyroid could be palpated with the thumb in the front edge of the sternocleidomastoid when the subjects were asked to swallow.

Evaluation of curative efficacy: The symptome score was calculated using the following formula: Symptome score = (score before treatment-score after treatment)/score before treatment ×100%. Curative efficiency was defined as (1) Cured, when clinical symptoms and signs disappear or nearly disappeared and the symptome scores were reduced by 95% or higher. (2) Marked efficacy was defined as clinical symptoms and signs in traditional Chinese medicine were improved markedly and symptome scores were reduced by 70% or higher. (3) Efficient was defined as clinical symptoms and signs were improved and symptome scores were reduced by 30% or higher, whereas when symptoms were not improved, or even worse and the symptome scores were reduced by less than 30% (4), the outcome was defined as invalid.

Safety evaluation levels: Level 1: secure, without any adverse reaction. Level 2: relative safe; drugs could be given continually without any treatment in case adverse reactions occurred. Level 3: there were security issues and moderate adverse reactions, but drugs could be given continually after treatment. Level 4: test was discontinued because of adverse reactions.

Statistical analysis: SPSS Statistics for Windows (Version 17.0. Chicago: SPSS Inc.) were used for statistical analyses. Measurement data in normal distribution were expressed using mean ± standard deviation and the median (interquartile range) was used for those in abnormal distribution. T-test, nonparametric test, or variance analysis were used for measurement data. Chi-square test was used for count data. Rank sum test was used for ranked data. $P < 0.05$ was considered to be statistically significant.

Sample size estimation: The number of cases in the Yingliu and control treatment groups was required to be equal in this trial and the sample size was estimated based on the equation:

$N = 2\times[(\alpha+\beta)\sigma/\delta]^2$ (δ refers to the required differentiation degree, σ was the overall standard deviation, α and β were respectively the corresponding u values of α and β, which could be derived by checking the t boundary value table).

It was presumed that it would be of clinical interest when an average decrease of TRAb became 3.5 mIU/ML higher in the Yingliu treatment than that in control treatment group. Based on relevant literature, standard deviation of TRAb in GD patients was 5.3 mIU/ML, and therefore $\delta = 3.5$ mIU/ML, $\sigma = 5.3$ mIU/ML, $\alpha = 0.05$, $\beta = 0.10$, $1-\beta = 0.90$; after checking a t boundary value table (unilateral), $t0.05 = 1.645$, $t0.1 = 1.282$, n was calculated as $2\times[(1.645+1.282)\times5.3/3.5]^2 = 39$. At least 39 cases were needed in each group. As the rate of follow-up losses was estimated to be not more than 15%, the sample size was eventually determined to be 92 after the adjustment by 78/(1-0.15).

Table 2. Baseline data of the two groups

	YM (40 cases)	Control treatment (40 cases)
Gender		
Male	8	11
Female	32	29
Age (year)	36.50 (17.00)	38.00 (24.50)
Course of disease (month)	11.00 (16.25)	12.50 (18.50)
Primary cases (number)	18	18
Recurrent cases (number)	22	22
FT3 (pmol/l)	18.22 (14.87)	14.25 (14.88)
FT4p (mol/l)	46.75 (34.95)	39.34 (27.24)
TSHm (IU/L)	0.004 (0.00)	0.004 (0.00)
TGAb (IU/ML)	89.90 (370.92)	89.62 (355.11)
TPOAb (IU/ML)	54.80 (229.20)	27.80 (250.15)
TRAbm (IU/ML)	12.89 (17.10)	12.17 (7.43)
Symptome score ($\overline{X}$ ±sd)	18.45±2.50	18.55±2.05

Results

General information of the patients

92 GD patients were involved in this study, but 12 (13.04%) of them were lost for the final follow up (6 cases in the YM group and 6 cases in the C group). 40 patients in the YM group (8 males and 32 females, aged between 22 and 65 years with a course of disease ranging from 0.5 to 26 months) and 40 patients in control treatment group (11 males and 29 females, aged between 21 and 64 years, with the course of disease ranging from 0.5 to 24 months) finally finished the trial. Most of the patients were females, which was in accordance with the literature [10]. There were 36 cases of primary GD (18 cases in the YM and 18 cases in control treatment group) and 44 cases of recurrent GD (22 cases in YM and 22 cases in control treatment group). There were no significant differences in gender ratio, age and initial thyroid specific blood serum levels as well as pre Yingliu treatment symptome scores between the two groups (P = 0.431, P = 0.977, P = 0.483) (**Table 2**).

Evaluation of therapeutic efficacy

After 6 weeks of Yingliu treatment, FT3, FT4 in two groups were obviously decreased (P < 0.05) and TSH was increased (P < 0.05), suggesting that the thyroid function effectively improved in both groups, but there were no significant differences of FT3, FT4, TSH concentrations between Yingliu treatment and control treatment group. In addition, TGAb, TPOAb, TRAb thyroid autoantibody levels were significantly lower after Yingliu treatment in both groups (P < 0.05), but without differences between Yingliu and control treatment (**Table 3**). After 12 weeks, FT3, FT4 and TSH in both groups were all improved effectively (P < 0.001). However, there were significant differences of FT3, FT4 (P = 0.038, P = 0.041) between the Yingliu treatment and control treatment groups, suggesting that a better therapeutic efficacy for FT3 and FT4 improvements could be achieved with the Yingliu treatment. Also TGAb, TPOAb, TRAb levels were significantly lower than before treatments in both groups (P < 0.001), and there were significant differences of TGAb, TRAb (P = 0.026, P = 0.019) between the Yingliu and the control treatment group (**Table 3**).

Comparison of TCM symptom scores

Repeated measured data were analyzed using variance analysis and the results suggested that there were differences of TCM symptom scores at different time points in both groups which was significant lower in the Yingliu treatment group at week 12 compared to the control treatment group (**Table 4**).

After 12 weeks of treatments, the goitre, fatigue and dry mouth and thirst was significantly better improved in the Yingliu than the control treatment group (21 cases vs. 10 cases (P = 0.012), 39 cases vs. 30 cases (P = 0.003) and 37 cases vs. 29 cases (P = 0.019), respectively) (**Table 5**). In addition, there were 0 cases of clinical recovery, 14 cases of marked efficacy, 23 cases of effectiveness and 3 cases of invalid outcomes in the Yingliu treatment group with a total effectiveness rate of 92.5%. In the control treatment group were 0 cases of clinical recovery, 6 cases of marked efficacy, 27 cases of effectiveness and 7 cases of invalid outcomes, with a total effectiveness rate of 82.5%. The effectiveness rate was significantly better

Table 3. Comparison of observed index of pre-treatment and post-treatment at 6 and 12 weeks between two groups (M (QR)

		Yingliu Treatment (40)	Control Treatment (40)
FT3 (pmol/l)	pre-treatment	18.22 (14.87)	14.25 (14.88)
	6 weeks after treatment	8.92 (8.53)*	5.60 (6.42)*
	Difference after 6 weeks of treatment	9.3 (6.35)	8.65 (8.46)
	12 weeks after treatment	5.44 (3.52)*	5.61 (5.19)*
	Difference after 12 weeks of treatment	12.78 (11.35)▲	8.64 (9.69)
FT4 (pmol/l)	pre-treatment	46.75 (34.95)	39.34 (27.24)
	6 weeks after treatment	25.76 (20.10)*	19.30 (14.00)*
	Difference after 6 weeks of treatment	20.99 (14.85)	20.04 (13.24)
	12 weeks after treatment	15.85 (11.64)*	16.93 (10.50)*
	Difference after 12 weeks of treatment	30.90 (23.31)▲	22.41 (16.74)
TSH (mIU/L)	pre-treatment	0.004 (0.00)	0.004 (0.00)
	6 weeks after treatment	0.004 (0.003)*	0.004 (0.080)*
	Difference after 6 weeks of treatment	0.00 (0.003)	0.00 (0.080)
	12 weeks after treatment	0.010 (2.26)*	0.005 (0.59)*
	Difference after 12 weeks of treatment	-0.006 (2.26)	-0.001 (0.59)
TGAb (IU/ML)	pre-treatment	89.90 (370.92)	89.62 (355.11)
	6 weeks after treatment	77.35 (335.90)*	83.00 (338.20)*
	Difference after 6 weeks of treatment	12.55 (35.02)	6.62 (16.91)
	12 weeks after treatment	65.75 (295.71)*	71.35 (334.23)*
	Difference after 12 weeks of treatment	24.15 (75.21)▲	18.27 (20.88)
TPOAb (IU/ML)	pre-treatment	54.80 (229.20)	27.80 (250.15)
	6 weeks after treatment	58.50 (193.30)*	24.40 (225.60)*
	Difference after 6 weeks of treatment	-3.70 (35.9)	3.40 (24.55)
	12 weeks after treatment	40.40 (168.83)*	24.60 (202.58)*
	Difference after 12 weeks of treatment	14.40 (60.37)	3.20 (47.57)
TRAb (mIU/ML)	pre-treatment	12.89 (17.10)	12.17 (27.43)
	6 weeks after treatment	8.46 (12.55)*	12.68 (24.91)**
	Difference after 6 weeks of treatment	4.43 (4.55)	0.51 (2.52)
	12 weeks after treatment	6.17 (9.11)*	9.04 (19.57)*
	Difference after 12 weeks of treatment	6.72 (7.99)▲	3.13 (7.86)

Compared with pre-treatment, $^{**}P < 0.01$, $^{*}P < 0.05$; compared with control group, $^{▲}P < 0.05$.

in the Yingliu than in the control treatment group ($P = 0.025$, **Table 5**).

Safety evaluation

There were 16 cases of leucopenia (less than 4.0×10^9/l (5 cases in the Yingliu and 11 cases in control treatment group), and 6 cases of ALT level increase (5 cases in Yingliu treatment group and 1 case in control treatment group), but there was no significant difference between the groups ($P = 0.094$, $P = 0.203$, **Table 5**).

According to the safety evaluating criteria, there were 31 level 1cases, 2 level 2 cases, 7 level 3 cases and no level 4 case in the Yingliu treatment group. In the control treatment group 28 level 1 cases, 4 level 2 cases, 8 level 3 cases and no level 4 case occurred. After non-parametric test, no significant differences of safety evaluation was found between two groups ($Z = -0.675$, $P = 0.675$, **Table 5**).

Discussion

The remission rate for GD by antithyroid drugs (ATD) (MMI, PTU commonly used) has been reported to range from 32% to 45.7% [11-13]. The Yingliu mixture is a homemade preparation by our hospital derived from long-term clinical experience and could improve the thyroid

Table 4. Comparison of TCM symptome scores at different time points ($\overline{X} \pm s$)

group	Yingliu treatment	Control treatment
Pre-treatment	18.45±2.50	18.55±2.05
2 weeks	16.88±2.28	17.10±2.12
4 weeks	14.93±2.40	15.68±2.07
6 weeks	12.58±2.38	14.13±2.23
8 weeks	10.73±2.41	12.35±2.36
10 weeks	9.15±2.47	11.15±2.92
12 weeks	7.78±2.70▲	9.85±3.14

Note: Compared with control treatment group, ▲F = 6.417, $P < 0.05$.

enlargement (21 vs. 10, $P < 0.05$), fatigue (39 vs. 30, $P < 0.01$) and dry moth symptoms (37 vs. 29, $P < 0.05$) to better scores than the control medication. The clinical efficiency of the Yingliu mixture-methimazole combination was 92.5% vs. 82.5% ($P < 0.05$) of solely methimazole medication (**Table 5**). In addition, after 12 weeks treatments the Yingliu mixture in combination with methimazole improved FT3, FT4, TGAb and TRAb values significantly more than methimazole alone (**Table 3**) and TCM symptome scores were significant lower after 12 week treatment in the Yingliu mixture-methimazole group ($P < 0.05$). From the 12 Yingliu mixture ingredients, Radix astragali, Rhizoma anemarrhenae and Prunella vulgaris have been used for Yingliu treatments of hyperthyroidism as single applications already. Radix astragali, which has an effect on non-specific, humoral and cellular immunity, was applied in combination with prednisone to hyperthyroidism patient with leukopenia. In the Yingliu treatment group CD4 cells were obviously decreased and CD8 cells increased. The improved CD4/CD8 ratio promoted the recovery of thyroid functions and shortened the course of the treatment [14]. Rhizoma anemarrhenae, which eliminates internal excessive heat and has antipyretic effects, reduced the oxygen consumption caused by thyroxine via inhibiting the Na+-K+-ATPase activities of hyperthyroidism rats [15]. Prunella vulgaris has effects of clearing body heat and resolving hard masses. A previous study revealed that in hyperthyroidism patients treated with prunella liquid plus methidathion the thyroid size was obviously more reduced than in the control treatment group treated with methidathion alone [16]. Radix ophiopogonis can remove dysphoric heat. A study showed that it promotes immunity and has antithrombotic effects. The chemical components of the herb evidently increased the thymus and spleen weights as well as activated the phagocytosis of the reticuloendothelial system in mice [17]. Smilax is dispelling cold and improving body dampness, detoxifying and removing tumescences via blood-activating and stasis-dissolving properties [18]. Radix scrophulariae is decreasing excessive internal heat, detoxifying and removing urine and blood circulation stagnations and was also shown to have antipyretic and immunity enhancement effects [19, 20]. Forsythia can reduce internal excessive heat and has anti-inflammatory and anti-endotoxin effects [21]. Thunberg fritillary bulb is clearing body heat and dispersing blood stasis due to anti-inflammatory, blood-activating and stasis-dissolving properties [22]. Alisma plantago-aquatica is a mild diureticum and used to treat difficulty in micturition, edema, diarrhea, as well as clearing heat. The effect of white mustard seed, which is also a radical quencher [23], is softening hard masses. Semen impatient is improving blood stasis as well as softening and resolving hard masses. A pharmacological study showed that semen impatientis decoction reduced whole blood viscosity, plasma viscosity, erythrocyte sedimentation rate, fibrinogen and hematocrit [24]. Oysters are included into TCM preparations for softening and resolving hard masses and used for treating subcutaneous nodules, tuberculous lymph nodes and abdominal mass. They also have been shown to enhance immunity [25]. Taken together, Yinliu herbs have mainly beneficial effects on excessive body heat, followed by softening and resolving hard masses, improving immunity and stasis dissolving. There were 16 cases of leucopenia (5 cases in the Yingliu treatment group and 11 cases in the control treatment group) and increase of ALT in 6 cases (5 cases in the Yingliu treatment group and 1 case in the control treatment group). Although the leukopenia case number of in the Yingliu treatment group was less than in the control treatment group the difference was not significant, suggesting that the Yingliu mixture did not reduce the adverse effects of methimazole. This is not consistent with a previous report that the YiQi and YangYin method could effectively improve GD related leukopenia and further research is needed to confirm it.

There were some drawbacks in this study. The sample size was relative small and changes of

Table 5. Comparison of primary symptome improvement, clinical efficacy and adverse reaction events between the two groups

		Yingliu Treatment (40)	Control Treatment (40)
Goiter	Total efficacy score	21▲	10
Fatigue	Total efficacy score	39▲▲	30
Dry mouth and thirsty	Total efficacy score	37▲	29
Clinical efficacy	Cured	0	0
	Marked efficient	14	6
	Efficient	23	27
	Invalid	3	7
	Total effective rate (%)	92.50▲	82.50
Adverse reaction event	Leukopenia	5	11
	ALT elevation	5	1
	Abnormal renal function	0	0
	Rush	0	0
Safety evaluation	Level 1	31	28
	Level 2	2	4
	Level 3	7	8
	Level 4	0	0

Compared with control group, ▲: $P < 0.05$, ▲▲: $P < 0.01$.

TSH levels may not have been manifested due to the limited observation time.

In conclusion, Yingliu mixture as combination with methimazole could improve effectively the thyroid gland function, decrease the level of thyroid gland autoantibodies and improve the symptoms and signs of GD compared to a solely methimazole medication.

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Disclosure of conflict of interest

None.

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References

[1] Galofre JC and Davies TF. Autoimmune thyroid disease in pregnancy: a review. J Womens Health (Larchmt) 2009; 18: 1847-1856.

[2] Vanderpump MPJ and Tunbridge WMG. The epidemiology of autoimmune thyroid disease. Humana Press 1999; 15: 141-162.

[3] Gao XW and Li JL. Thyroid disease. People's Medical Publishing House 2000; 93-95.

[4] Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, Bruno-Bossio G, Nardi M, Bartolomei MP, Lepri A, Rossi G, Martino E and Pinchera A. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998; 338: 73-78.

[5] Benker G, Reinwein D, Kahaly G, Tegler L, Alexander WD, Fassbinder J and Hirche H. Is there a methimazole dose effect on remission rate in Graves' disease? Results from a long-term prospective study. The European Multicentre Trial Group of the Treatment of Hyperthyroidism with Antithyroid Drugs. Clin Endocrinol (Oxf) 1998; 49: 451-457.

[6] Fu SX. The current treatment of hyperthyroidism hepatic dysfunction. Hebei medical joural 2009; 31: 2.

[7] Bonaci-Nikolic B, Nikolic MM, Andrejevic S, Zoric S and Bukilica M. Antineutrophil cytoplasmic antibody (ANCA)-associated autoimmune diseases induced by antithyroid drugs: comparison with idiopathic ANCA vasculitides. Arthritis Res Ther 2005; 7: R1072-1081.

[8] Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, Mandel SJ and Stagnaro-Green A. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2007; 92: S1-47.

[9] WHO/UNICEF/ICCIDD Joint Consultation. Indicators for assessing iodine deficiency disorders and their control through salt iodization. WHO/NUT/94.6. Geneva: WHO; 1994.

[10] Wong GW and Cheng PS. Increasing incidence of childhood Graves' disease in Hong Kong: a follow-up study. Clin Endocrinol (Oxf) 2001; 54: 547-550.
[11] Ishtiaq O, Waseem S, Haque MN, Islam N and Jabbar A. Remission of Grave's disease after oral anti-thyroid drug treatment. J Coll Physicians Surg Pak 2009; 19: 690-693.
[12] Lumholtz IB, Poulsen DL, Siersbaek-Nielsen K, Friis T, Rogowski P, Kirkegaard C and Hansen JM. Outcome of long-term antithyroid treatment of graves' disease in relation to iodine intake. Acta Endocrinol (Copenh) 1977; 84: 538-541.
[13] Peixoto MC, Coeli CM and Vaisman M. [Evaluation of the medical treatment of Graves' disease (GD)]. Arq Bras Endocrinol Metabol 2005; 49: 410-419.
[14] Wang D, Fang XM and Liu Y. The changes of T cell subsets after the treatment of astragalus injection in hyperthyroidism (Graves disease). West China Medical Journal 2001; 16: 465-466.
[15] Kun LT, Gao H and Jiang YL. Influences of Anemarrhenae Rhizoma and One Processed with Salt-Water on Na +-K +-ATP Enzyme in Erythrocyte Membrane in Rats with Hyperthyroidism and Yin Deficiency. Chinese Journal of Experimental Traditional Medical Formulae 2011; 17: 184-186.
[16] Yang K, Guo KQ and Wu HY. Clinical effect of prunrllae oral solution in treating hyperthyrea. China Journal of Chinese Materia Medica 2007; 32: 1706-1708.
[17] Tang J, Huang Q and Xu ZY. Study on the immune activity of polysaccharides in Ophiopogon japonicus. Journal of Basic Medicine in Traditional Chinese Medicine in China 1998; 4: 44-46.
[18] Lv YN, Cheng DS and Xu CH. Study on the pharmacological effects of Smilax China L on promoting blood circulation. Chin J Hosp Pharm 2002; 22: 538-540.
[19] Zhang JC and Zhu JM. Advance of research on chemical constituents and pharmacological activities of Scrophularia Ningpoensis. Handong Pharmaceutical Industry 2003; 22: 25-27.
[20] Garg HS and Bhandari SPS. Antihepatotoxic and Immunositumlant Porperties of Iirdoid Glycosides of Scorphulaira Koelzii. Phytother Res 1994; 8: 224.
[21] Hu JY, Lei L and Yu Y. The study on antiinflammatory and antipyretic effect of Forsythia suspensa. Pharmacology and Clinics of Chinese Materia Medica 2007; 23: 51-52.
[22] Zhang MF, Shen YQ and Zhu ZP. Study of the property in Chinese herbs with spicy warm/thermal (Sinwin) in spleen and stomach (III): anti-inflammatory effect. Pharmacol Clin Chin Mater Med 1998; 14: 12-16.
[23] Li WY and Li Q. Protective effects of Sinapine on DNA damage caused with radiation and reactive oxygen species. Plant Physiology 1997; 23: 319-323.
[24] Zhao Q. Effects of Semen Impatientis decoction on blood rheology in rabbits with the syndrome of experimental blood stasis. Shanxi College of Traditional Chinese Medicine 2006; 29: 47-48.
[25] Li M, Du GW and Liu S. Experimental study of antivirus effect of glycosaminoglycan from oyster against herpes simplex virus type 1. Chin J Mar Drugs 2008; 2: 50.