

# Short-Term Efficacy and Safety of Haizao Yuhu Decoction Plus Methimazole versus Methimazole Monotherapy for Graves' Disease: A Prospective Study Using Propensity Score-Matching

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**Objective:** To investigate the efficacy and safety of the early addition of Haizao Yuhu Decoction (HYD) with methimazole (MMI) versus the monotherapy of MMI in treating Graves' disease (GD).

**Methods:** This was a prospective observational study. A total of 198 patients with GD were assigned to either the HYD combined with MMI group or the MMI monotherapy group according to clinical judgment and patient preference. To minimize confounding bias, propensity score matching (PSM) was performed to balance baseline characteristics between the two groups. Primary (thyroid function, MMI dose) and secondary outcomes (general conditions, thyrotrophin receptor antibody [TRAb], thyroid size, peak systolic velocity of the superior thyroid artery [STA-PSV], the Thyroid-related Patient-Reported Outcome 39 [ThyPRO39] scores, traditional Chinese medicine [TCM] syndrome scores, and safety) were measured at 0 ( $V_1$ ), 4 ( $V_2$ ), 8 ( $V_3$ ) and 12 weeks of treatment ( $V_4$ ).

**Results:** Each group consisted of 54 GD patients after a 1:1 PSM. A greater decline in free thyroxine (FT4) (16.67 [7.64, 24.43] pmol/L vs 9.82 [3.49, 19.02] pmol/L,  $P = 0.018$ ) and free triiodothyronine (FT3) (5.32 [3.10, 10.33] pmol/L vs 3.46 [1.16, 7.63] pmol/L,  $P = 0.043$ ) was observed at  $V_2$  in the combination group than in the MMI group. The cumulative dose of MMI during the 12-week treatment was significantly lower in the combination group than in the MMI group (814.20 [600.00, 1050.00] mg vs 1007.10 [782.10, 1125.00] mg,  $P = 0.004$ ). The combination group showed more pronounced reductions in the STA-PSV, TCM syndrome scores, and ThyPRO scores ( $P = 0.032$ , 0.010, and 0.044, respectively). The cumulative incidence of adverse events in the combination group was significantly lower than that in the MMI group (5.56% [3/54] vs 18.52% [10/54],  $P = 0.038$ ).

**Conclusion:** The combination of HYD and MMI serves as an effective and safe treatment of GD, accelerating thyroid function recovery, reducing thyroid hormone levels and ATD dosage, alleviating hyperthyroid symptoms, and lowering the risk of adverse events.

**Keywords:** Haizao Yuhu decoction, Graves' disease, methimazole, thyroid function, antithyroid drugs

## Introduction

Graves' disease (GD) is an autoimmune thyroid disorder triggered by genetic and environmental factors and serving as the primary inducer of hyperthyroidism. The prevalence of hyperthyroidism is approximately 0.78%, with GD



accounting for 0.53%. With an annual incidence of 15–30 cases per 100,000 individuals, GD exhibits a predominance by females or the population at 30–60 years of age.<sup>1</sup> At present, anti-thyroid drugs (ATDs), radioactive iodine therapy, and thyroidectomy are the mainstream approaches to treat GD. Both radioactive iodine therapy and surgery, however, are often followed with permanent hypothyroidism.<sup>2</sup> Meanwhile, the former may exacerbate thyroid eye disease,<sup>3</sup> and the latter carries a higher risk of inducing postoperative complications (eg, recurrent laryngeal nerve injury).<sup>4</sup> ATDs, most commonly methimazole (MMI), are the first-line treatment of GD.<sup>5</sup> The initial dose of MMI is generally set according to the patient's thyroid function. Nevertheless, its long-term use may result in adverse events like hepatic injury<sup>6</sup> and agranulocytosis,<sup>7</sup> the incidences of which are often dose-dependent.<sup>8</sup> It is therefore necessary to explore treatment options that are still effective and safe, but less dependent on ATDs.

In traditional Chinese medicine (TCM), hyperthyroidism and GD are categorized as “Ying-Bing” (goiter/tumor-associated diseases). Haizao (*Sargassum*) wine, initially noted in the documents from the Jin Dynasty, shows the potential in treating “Ying-Bing”. *Sargassum* and *Laminaria* have reaped remarkable therapeutic effects in treating GD. In our preliminary studies, both *Sargassum* and *Laminaria* have been validated to be rich in iodine.<sup>9</sup>

In 1948, the Wolff-Chaikoff effect was proposed, suggesting that the synthesis of thyroid hormones in the thyroid gland is inhibited in response to a serum iodine level exceeding a threshold.<sup>10</sup> This autoregulatory phenomenon provides a theoretical basis for iodine therapy in GD. Given that the reduction in thyroid hormone synthesis is temporary, an escape phenomenon eventually occurs, leading to the recurrence or even deterioration of hyperthyroidism.<sup>11</sup> Haizao Yuhu Decoction (HYD) is a classic herbal formula recorded in the *Waikie Zhengzong* to treat “Ying-Bing”.<sup>12</sup> As an iodine-rich prescription, HYD has long been used to alleviate the symptoms of hyperthyroidism. In the present study, we aim to assess the efficacy and safety of HYD combined with MMI in treating GD versus the monotherapy of MMI.

## Materials and Methods

### Study Design

This was a single-center, prospective, observational, propensity score matching (PSM) study. Patients with GD who were treated at Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine between September 2022 and September 2023 were enrolled in this study. Based on treatment selection determined by shared decision-making between clinicians and patients, participants were divided into 2 groups: the MMI group (MMI monotherapy) and the combination group (MMI plus HYD). GD-related indicators were examined at 0 ( $V_1$ ), 4 ( $V_2$ ), 8 ( $V_3$ ) and 12 weeks of treatment ( $V_4$ ). The study was conducted in accordance with the principles outlined in the *Helsinki Declaration for Humans* (Ethics Approval No. 2022-LWKYZ-076).

### Participants

Participants aged 18–75 years, who were diagnosed as GD according to the *2022 Chinese Guidelines for the Diagnosis and Treatment of Hyperthyroidism and Thyrotoxicosis due to Other Causes*, were considered eligible.<sup>1</sup> Written informed consent was provided by all GD patients. Excluded were pregnant or lactating women, and individuals with thyroid storm, allergies to the components of HYD, primary diseases in the cardiovascular and cerebrovascular system/liver/kidney/hematopoietic system, medications affecting the thyroid function, and mental disorders that distort the comprehension on an informed consent. Trial termination could be triggered by severe adverse events, aggravation or other intractable complications, emergence of other serious diseases or conceptions during the trial period, and patients' poor compliance. Patients could voluntarily withdraw from the clinical trial at any time point.

A total of 241 GD patients were initially enrolled. After excluding 43 ineligible ones due to pregnancy, breastfeeding, severe liver dysfunction, leukopenia, or refusal to participate in this trial, 198 patients were finally included and divided into the combination group ( $n = 116$ ) and MMI group ( $n = 82$ ).

### Sample Size

The sample size was calculated with treatment effect as the outcome indicator, allowing a two-tailed test, an  $\alpha$  value of 0.05, a  $\beta$  value of 0.2, and a power of 80%. Based on the previous literature,<sup>13</sup> we assumed a treatment effect of 70.2%

(P1) in the MMI group, and 90.47% (P2) in the combination group. According to the calculation by PASS software, 57 patients were estimated to be required in each group. Considering a 10% dropout rate and an additional 40% sample loss after propensity score matching, the total target sample size was 211 patients. Therefore, we plan to enroll 106 patients in each group.

## Compositions in HYD

A HYD formulation is comprised of 11 Chinese herbs as follows: 12 g of *Sargassum* (Haizao), 18 g of *Laminaria* (Kunbu), 10 g of *Radix Glycyrrhizae* (Sheng Gancao), 9 g of *Pinelliae Rhizoma Praeparatum* (Fa Banxia), 9 g of *Fritillariae Thunbergii Bulbus* (Zhe Beimu), 9 g of *Forsythiae Fructus* (Lianqiao), 9 g of *Chuanxiong Rhizoma* (Chuanxiong), 9 g of *Angelicae Pubescentis Radix* (Duhuo), 9 g of *Citri Reticulatae Pericarpium Viride* (Qingpi), 9 g of *Citri Reticulatae Pericarpium* (Chenpi), and 9 g of *Angelicae Sinensis Radix* (Danggui). All Chinese herbs were provided by the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, and evaluated as qualified herbal slices based on the 2020 *Chinese Pharmacopoeia*. MMI (thyrozol®; specification: 10 mg) was obtained from Merck KGaA, Germany.

## Interventions

The MMI group was managed with MMI monotherapy, and the initial dose was determined according to baseline thyroid function. MMI tablets (10 mg per tablet) were administered as whole, half, or quarter tablets according to routine clinical practice. The total treatment duration was 3 months.

The combination group received HYD combined with MMI. HYD was administered twice daily for 1 to 3 months and discontinued after free thyroxine (FT4) normalization. The dosage of MMI was adjusted according to thyroid function, and the administration of MMI tablets was consistent with that in the MMI group.

Four medical visits were arranged at V<sub>1</sub> (baseline), V<sub>2</sub> (4 weeks ± 2 days), V<sub>3</sub> (8 weeks ± 5 days), and V<sub>4</sub> (12 weeks ± 5 days). Baseline characteristics of GD patients, including gender, age and disease duration, were recorded at V<sub>1</sub>. Serum thyroid hormone level, average daily MMI dose, thyrotropin receptor antibody (TRAb) level, heart rate, body weight, complete blood count, liver function, and renal function were recorded at each visit. Furthermore, the quality of life was assessed at V<sub>1</sub> and V<sub>4</sub> by grading the Thyroid-related Patient-Reported Outcome 39 (ThyPRO39) and scoring TCM syndrome. In addition, the thyroid volume and the peak systolic velocity of the superior thyroid artery (STA-PSV) on thyroid ultrasound were examined at V<sub>1</sub> and V<sub>4</sub>.

## Outcome Assessment

Primary outcomes included changes in the thyroid function and the average daily MMI dose during the treatment. Secondary outcomes consisted of general conditions (changes in the heart rate and body weight), serum TRAb level at each visit, thyroid size and STA-PSV on thyroid ultrasound, quality of life (ThyPRO39 and TCM syndrome scores before and after treatment) and safety (incidence of adverse events).

## Measurement of Thyroid Function and TRAb

Serum concentrations of TRAb, free triiodothyronine (FT3), FT4, and thyroid-stimulating hormone (TSH) were determined using a Roche cobas e411 electrochemiluminescence analyzer with corresponding commercial kits. Samples were fully incubated with biotinylated thyroid hormones (FT3, FT4), specific antibodies against TRAb and TSH, as well as tris(2,2'-bipyridyl)ruthenium-labeled thyroid hormones (FT3, FT4), TRAb derivatives and TSH derivatives to form pre-reaction complexes. Subsequently, streptavidin-coated magnetic microparticles were added and incubated. The pre-reaction complexes were immobilized on the magnetic microparticles via the specific interaction between biotin and streptavidin, forming antigen-antibody-magnetic particle complexes. The complexes were transferred into the measuring cell, and tripropylamine solution was added. A voltage was applied to induce an electrochemiluminescence (ECL) reaction, and the luminescence intensity was measured by a photomultiplier tube.

## Safety Assessment

The safety of two treatments was assessed based on laboratory testing of complete blood count, liver function and renal function, as well as self-reported discomforts. The incidence of adverse events was finally recorded.

## Statistical Analysis

To reduce potential confounding, a 1:1 propensity score matching analysis was conducted. The propensity score will be estimated using binary logistic regression analysis, with treatment assignment (HYD combined with MMI vs MMI alone) as the dependent variable and the following covariates: age, gender, disease duration, heart rate, TRAb, FT3, and FT4, using the nearest neighbor method with a caliper of 0.05. All statistical analyses were operated on SPSS 25.0. Measurement data within a normal distribution were expressed as mean  $\pm$  standard deviation, and compared by the *t*-test; otherwise, they were expressed as median (interquartile range [IQR]) and processed by the nonparametric rank-sum test. Enumeration data and rank data were compared via Chi-square test and rank sum test, respectively.  $P < 0.05$  was considered to indicate a significant difference.

## Results

### Baseline Characteristics

Baseline characteristics, including age, gender, disease duration, body weight, thyroid function, TRAb, thyroid volume and STA-PSV, were comparable between groups ( $P > 0.05$ ). However, a significantly higher heart rate was seen in the combination group than the MMI group ( $P = 0.005$ ). After a 1:1 PSM, 54 GD patients were included in each group, with all baseline characteristics comparable ( $P > 0.05$ ) (Table 1).

The combination group consisted of 12 (22.22%) males and 42 (77.78%) females, with a male-to-female ratio of 1:3.5, a median age of 35 (range 19–70) years, and a median disease duration of 24 months. In the MMI group, there were 11 (20.37%) males and 43 (79.63%) females, with a male-to-female ratio of 1:3.91, a median age of 36.49 (range 18–60) years, and a median disease duration of 24 months. Generally, a predominance by females, a peak incidence in the middle age, and a relatively short disease duration were observed in each group, complying with the epidemiological characteristics of GD. In addition, pre-treatment thyroid function in both groups, characterized by significantly elevated FT3, FT4, and TRAb and reduced TSH levels, was consistent with the serological features of GD.

**Table 1** Comparison of Baseline Characteristics Between the Two Groups Before and After PSM

Characteristics	Pre-PSM		P	Post-PSM		P
	Combination Group (n = 116)	MMI Group (n = 82)		Combination Group (n = 54)	MMI Group (n = 54)	
Age (years)	35 (29.00, 49.00)	36.14 $\pm$ 11.40	0.166	35 (31.00, 48.500)	36.49 $\pm$ 11.33	0.815
Sex (male/female)	30/86	17/65	0.254	12/42	11/43	0.500
Duration of disease (months)	15.5 (4, 60)	24 (5.75, 51)	0.563	24 (5.25, 60)	24 (11.5, 60)	0.885
Body weight (kg)	61.38 $\pm$ 12.14	60.35 $\pm$ 9.07	0.687	60.08 $\pm$ 11.12	59.51 $\pm$ 8.19	0.794
Heart rate (bpm)	94.70 $\pm$ 14.80	88.71 $\pm$ 13.83	0.005	90.30 $\pm$ 13.30	89.96 $\pm$ 12.43	0.893
TRAb (IU/L)	7.67 (3.34, 13.78)	7.27 (3.03, 12.76)	0.112	7.49 (3.27, 13.18)	6.04 (3.81, 15.52)	0.914
FT3 (pmol/L)	12.01 (8.58, 16.83)	10.11 (7.03, 13.22)	0.077	10.90 (7.45, 15.50)	9.19 (6.92, 14.42)	0.203
FT4 (pmol/L)	35.39 (27.65, 47.23)	33.64 (26.58, 39.55)	0.208	31.94 (25.59, 44.35)	30.05 (24.28, 37.93)	0.441
TSH ( $\mu$ IU/mL)	0.005 (0.005, 0.013)	0.005 (0.005, 0.019)	0.565	0.005 (0.005, 0.010)	0.005 (0.005, 0.007)	0.839

**Abbreviations:** PSM, propensity score matching; TRAb, thyrotropin receptor antibody; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; MMI, methimazole.

## An Early Addition of HYD Assists MMI in Decreasing Thyroid Hormone Levels in GD Patients

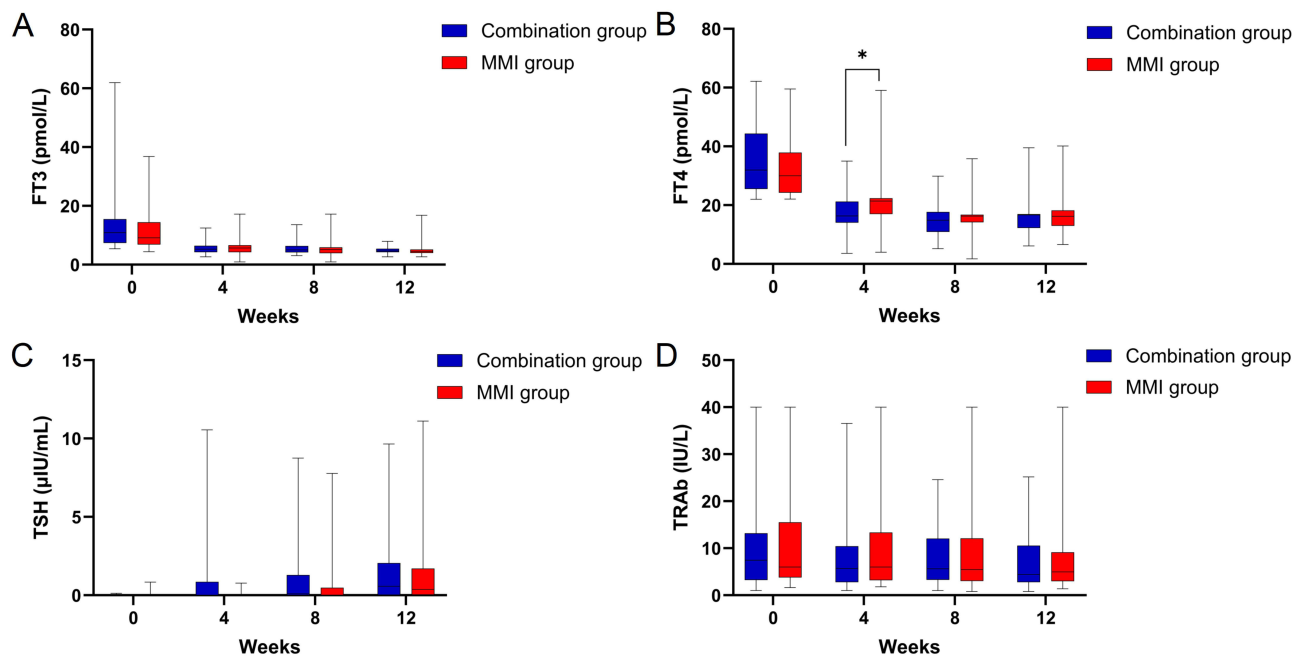
Post-treatment FT3, FT4, and TRAb levels significantly decreased, while TSH levels significantly increased in both groups (Table 2 and Figure 1). Notably, the magnitude of reduction in FT3 and FT4 at V2 was significantly greater in the combination group than in the MMI group (5.32 [3.10, 10.33] pmol/L vs 3.46 [1.16, 7.63] pmol/L,  $P = 0.043$ ; 16.67 [7.64, 24.43] pmol/L vs 9.82 [3.49, 19.02] pmol/L,  $P = 0.018$ ) (Table 3), indicating a higher recovery rate of thyroid function by the combination of HYD and MMI (75.93% [41/54] vs 62.96% [34/54]), although the difference was not statistically significant ( $P = 0.144$ ). Also, the increase in TSH at V2 was significantly greater in the combination group than in the MMI group (0.003 [0.000, 0.814]  $\mu$ IU/mL vs 0.000 [0.000, 0.009]  $\mu$ IU/mL,  $P = 0.037$ ) (Table 3). TRAb levels in the combination group significantly decreased to 5.72 (2.83, 10.45) IU/L ( $P < 0.001$ ), 5.65 (3.31, 12.08) IU/L ( $P < 0.001$ ), and 4.46 (2.81, 10.55) IU/L ( $P < 0.001$ ) at V<sub>2</sub>, V<sub>3</sub>, and V<sub>4</sub>, respectively. In the MMI group, TRAb levels significantly decreased to 6.01 (3.24, 13.36) IU/L ( $P < 0.001$ ), 5.47 (3.08, 12.09) IU/L ( $P < 0.001$ ), and 4.99 (3.02, 9.14) IU/L ( $P < 0.001$ ) at the corresponding time points, respectively. During the treatment, although no statistical difference

**Table 2** Comparison of Treatment Outcomes Before and After Treatment Between the Two Groups

Parameters	Time Points	Combination Group (n = 54)	MMI Group (n = 54)	P
<b>TRAb (IU/L)</b>	V <sub>1</sub>	7.49 (3.27, 13.18)	6.04 (3.81, 15.52)	0.914
	V <sub>2</sub>	5.72 (2.83, 10.45)**	6.01 (3.24, 13.36)**	0.344
	V <sub>3</sub>	5.65 (3.31, 12.08)**	5.47 (3.08, 12.09)**	0.993
	V <sub>4</sub>	4.46 (2.81, 10.55)**	4.99 (3.02, 9.14)**	0.593
<b>FT3 (pmol/L)</b>	V <sub>1</sub>	10.90 (7.45, 15.50)	9.19 (6.92, 14.42)	0.203
	V <sub>2</sub>	5.30 (4.33, 6.41)**	5.69 (4.30, 6.67)**	0.627
	V <sub>3</sub>	5.03 (4.24, 6.39)**	5.17 (3.94, 5.90)**	0.815
	V <sub>4</sub>	4.72 (4.32, 5.41)**	4.49 (4.03, 5.16)**	0.065
<b>FT4 (pmol/L)</b>	V <sub>1</sub>	31.94 (25.59, 44.35)	30.05 (24.28, 37.93)	0.441
	V <sub>2</sub>	16.39 (14.12, 21.21)**	21.42 (17.00, 22.38)**	<b>0.002</b>
	V <sub>3</sub>	14.92 (10.98, 17.67)**	16.33 (14.21, 16.75)**	0.453
	V <sub>4</sub>	16.70 (12.30, 16.98)**	16.67 (13.41, 18.80)**	0.236
<b>TSH (<math>\mu</math>IU/mL)</b>	V <sub>1</sub>	0.006 (0.005, 0.010)	0.005 (0.005, 0.011)	0.839
	V <sub>2</sub>	0.009 (0.005, 0.855)**	0.005 (0.005, 0.028)*	0.080
	V <sub>3</sub>	0.124 (0.005, 1.508)**	0.022 (0.005, 0.486)**	0.238
	V <sub>4</sub>	0.690 (0.013, 2.708)**	0.385 (0.033, 1.713)**	0.497
<b>Body weight (kg)</b>	V <sub>1</sub>	60.08 $\pm$ 11.12	59.51 $\pm$ 8.19	0.794
	V <sub>2</sub>	60.65 $\pm$ 11.34*	59.55 $\pm$ 6.94	0.677
	V <sub>3</sub>	60.39 $\pm$ 10.66**	59.84 $\pm$ 7.36*	0.854
	V <sub>4</sub>	62.61 $\pm$ 13.10**	60.19 $\pm$ 8.26**	0.532
<b>Heart rate (bpm)</b>	V <sub>1</sub>	90.30 $\pm$ 13.30	89.96 $\pm$ 12.43	0.893
	V <sub>2</sub>	86.70 $\pm$ 12.39*	88.03 $\pm$ 10.88**	0.623
	V <sub>3</sub>	84.33 $\pm$ 10.81*	84.26 $\pm$ 13.49**	0.986
	V <sub>4</sub>	82.94 $\pm$ 11.91*	86.42 $\pm$ 9.75**	0.413
<b>Thyroid volume (mL)</b>	Pre-treatment	32.01 $\pm$ 10.06	31.04 $\pm$ 9.16	0.853
	Post-treatment	30.22 $\pm$ 12.83	29.44 $\pm$ 10.71	0.936
<b>STA-PSV</b>	Pre-treatment	0.56 $\pm$ 0.16	0.65 $\pm$ 0.25	0.366
	Post-treatment	0.27 $\pm$ 0.14	0.57 $\pm$ 0.12	<b>0.032</b>
<b>ThyPRO score</b>	Pre-treatment	20.02 $\pm$ 5.90	20.04 $\pm$ 6.48	0.986
	Post-treatment	14.06 $\pm$ 4.40	16.10 $\pm$ 5.69	<b>0.044</b>
<b>TCM syndrome score</b>	Pre-treatment	7.94 $\pm$ 3.23	7.84 $\pm$ 2.94	0.862
	Post-treatment	5.47 $\pm$ 2.22	6.69 $\pm$ 2.48	<b>0.010</b>

**Notes:** Time points: V<sub>1</sub> (baseline), V<sub>2</sub> (4 weeks  $\pm$  2 days), V<sub>3</sub> (8 weeks  $\pm$  5 days), and V<sub>4</sub> (12 weeks  $\pm$  5 days). Compared to V<sub>1</sub>, \* $P < 0.05$ , \*\* $P < 0.01$ . Bold values indicate  $P < 0.05$  compared with the MMI group.

**Abbreviations:** TRAb, thyrotropin receptor antibody; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; MMI, methimazole.



**Figure 1** Serum FT3, FT4, TSH, and TRAb levels in both groups at 0, 4, 8, and 12 weeks. **(A)** Serum FT3 levels (pmol/L); **(B)** Serum FT4 levels (pmol/L); **(C)** Serum TSH levels (µIU/mL); **(D)** Serum TRAb levels (IU/L). Compared to MMI group, \**P* < 0.05.

**Abbreviations:** FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TRAb, thyrotropin receptor antibody; MMI, methimazole.

was seen in the changes of TRAb levels between the two groups, the overall situation of patients with hyperthyroidism in both groups improved gradually.

### An Early Addition of HYD Decreases the Average Daily and Cumulative Doses of MMI Required for GD

Following the treatment, the average daily MMI dose was gradually reduced in all GD patients. A significantly lower average daily dose of MMI at V<sub>2</sub> was seen in the combination group than the MMI group (10.00 [7.14, 15.00] mg/day vs 12.50 [10.00, 15.00] mg/day, *P* = 0.027), and this reduction remained more obvious until the end of the treatment period (Table 4 and Figure 2). In addition, the cumulative dose of MMI during the 12-week treatment was significantly lower in the combination group than the MMI group (814.20 [600.00, 1050.00] mg vs 1007.10 [782.10, 1125.00] mg, *P* = 0.004). Collectively, an additional use of HYD reduced the average daily and cumulative doses of MMI required for treating GD.

**Table 3** Comparison of Changes in FT3, FT4, and TSH Between the Two Groups

Parameters	Time Point	Combination Group (n = 54)	MMI Group (n = 54)	<i>P</i>
ΔFT3 (pmol/L)	V <sub>2</sub>	5.32 (3.10, 10.33)	3.46 (1.16, 7.63)	<b>0.043</b>
	V <sub>3</sub>	5.30 (1.90, 10.89)	4.08 (2.06, 7.34)	0.323
	V <sub>4</sub>	5.80 (2.66, 11.34)	4.34 (2.43, 8.80)	0.167
ΔFT4 (pmol/L)	V <sub>2</sub>	16.67 (7.64, 24.43)	9.82 (3.49, 19.02)	<b>0.018</b>
	V <sub>3</sub>	17.26 (8.65, 27.85)	12.86 (9.09, 21.70)	0.306
	V <sub>4</sub>	16.36 (9.61, 28.04)	15.20 (7.67, 20.68)	0.318
ΔTSH (µIU/mL)	V <sub>2</sub>	0.003 (0.000, 0.814)	0.000 (0.000, 0.009)	<b>0.037</b>
	V <sub>3</sub>	0.100 (0.000, 1.490)	0.008 (0.000, 0.413)	0.145
	V <sub>4</sub>	0.678 (0.008, 2.703)	0.350 (0.013, 1.708)	0.466

**Notes:** Time points: V<sub>2</sub> (4 weeks ± 2 days), V<sub>3</sub> (8 weeks ± 5 days), and V<sub>4</sub> (12 weeks ± 5 days). Bold values indicate *P* < 0.05 compared with the MMI group.

**Abbreviations:** ΔFT3, reduction of free triiodothyronine compared with the baseline; ΔFT4, reduction of free thyroxine compared with the baseline; ΔTSH, increase in thyroid-stimulating hormone compared with the baseline; MMI, methimazole.

**Table 4** Comparison of the Average Daily MMI Dose Between the Two Groups

Parameters	Time Point	Combination Group (n = 54)	MMI Group (n = 54)
Average daily MMI dose (mg/d)	V <sub>1</sub>	15.00 (10.00, 20.00)	12.50 (10.00, 20.00)
	V <sub>2</sub>	10.00 (7.14, 15.00)**,#	12.50 (10.00, 15.00)
	V <sub>3</sub>	10.00 (7.50, 10.00)**;###	12.50 (10.00, 12.50)*
	V <sub>4</sub>	7.14 (5.00, 8.13)**;###	9.29 (5.00, 10.00)**

**Notes:** Time points: V<sub>1</sub> (baseline), V<sub>2</sub> (4 weeks ± 2 days), V<sub>3</sub> (8 weeks ± 5 days), and V<sub>4</sub> (12 weeks ± 5 days). Compared to V<sub>1</sub>, \**P* < 0.05, \*\**P* < 0.01; Compared to MMI group, #*P* < 0.05, ###*P* < 0.01.

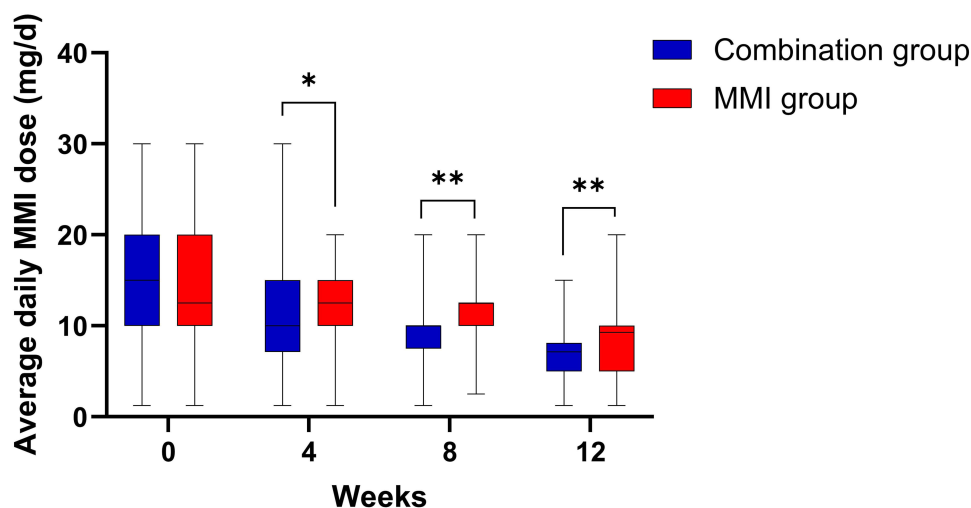
**Abbreviation:** MMI, methimazole.

## An Early Addition of HYD Assists MMI in Reducing STA-PSV, Lowering Heart Rate and Increasing Body Weight in GD Patients

Compared with baseline, the thyroid volume of GD patients significantly decreased after treatment in both groups, suggesting that HYD and MMI effectively prevented thyroid enlargement. However, the post-treatment thyroid volume was comparable between the two groups (*P* > 0.05) (Table 2). STA-PSV decreased significantly after the treatment, and this decrease was more prominent in the combination group than in the MMI group (*P* = 0.032) (Table 2 and Figure 3). The heart rate decreased and body weight increased significantly in both groups after the treatment (Table 2). Over 12 weeks of treatment, the heart rate in the combination group decreased significantly from 90.30 ± 13.30 beats per minute (bpm) to 82.94 ± 11.91 bpm, and the body weight increased from 60.08 ± 11.12 kg to 62.61 ± 13.10 kg. In the MMI group, the heart rate decreased significantly from 89.96 ± 12.43 bpm to 86.42 ± 9.75 bpm, and the body weight increased from 59.51 ± 8.19 kg to 60.19 ± 8.26 kg. However, no significant differences in post-treatment heart rate and body weight were observed between the two groups (*P* > 0.05).

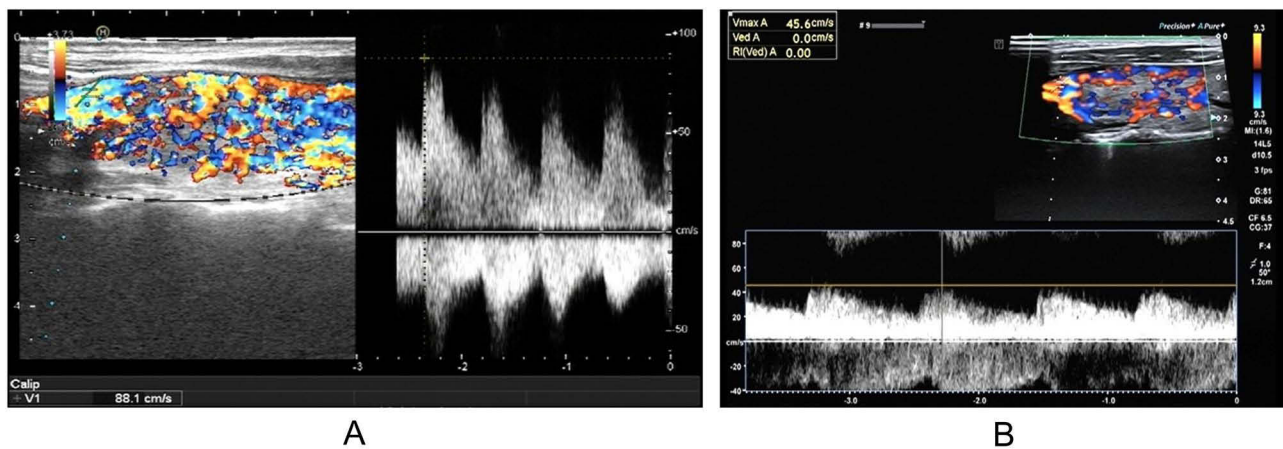
## An Early Addition of HYD Assists MMI in Improving the Quality of Life in GD Patients

After 12 weeks of treatment, both the TCM syndrome and ThyPRO scores decreased significantly in all GD patients (*P* < 0.05). Notably, the post-treatment scores were significantly lower in the combination group than in the MMI group (ThyPRO scores, 14.06 ± 4.40 vs 16.10 ± 5.69, *P* = 0.044; TCM syndrome scores, 5.47 ± 2.22 vs 6.69 ± 2.48, *P* = 0.01) (Table 2).



**Figure 2** Changes in the average daily MMI dose of both groups. Compared to MMI group, \**P* < 0.05, \*\**P* < 0.01.

**Abbreviation:** MMI, methimazole.



**Figure 3** Changes in STA-PSV on ultrasonography before and after treatment. (A) Pre-treatment of a 53-year-old woman in the combination group, (B) Post-treatment of a 53-year-old woman in the combination group.

**Abbreviation:** STA-PSV, peak systolic velocity of the superior thyroid artery.

### The Combination of HYD with MMI Shows a Higher Safety Profile in GD Patients

Severe adverse events were not reported in either group. In the MMI group, liver function impairment was reported in four GD patients, which was relieved by lowering the dose of MMI and hepatoprotective therapy. One patient experienced leukopenia, which resolved following leukocyte-increasing treatments. Skin rashes or self-reported pruritus were found in three GD patients, which were relieved by antihistamine administration. Two patients reported other self-perceived discomforts, both of whom were cured by symptomatic treatments. All adverse events reported in the combination group, including liver injury (n = 1), skin rash (n = 1), and gastrointestinal discomfort (n = 1), were relieved by symptomatic treatments. Overall, the incidence of adverse events was significantly lower in the combination group than in the MMI group (5.56% [3/54] vs 18.52% [10/54], *P* = 0.038) (Table 5).

### Discussion

ATDs are currently preferred as the first-line treatment of GD. However, their long-term use brings clinical challenges, like a slow return to normal thyroid function and a risk of adverse events, resulting in a poor patient compliance.<sup>14</sup> HYD, as a classic TCM formula, has long been prescribed to treat thyroid diseases. In this study, we systematically assessed the potential of HYD combined with MMI in accelerating the recovery of thyroid function, reducing the dose of MMI, and lowering the incidence of adverse events in GD patients. Our findings showed that in comparison to the MMI monotherapy, the combination of HYD with MMI decreased thyroid hormone levels faster, resulting in a higher proportion of GD patients achieving normalization of thyroid function in the early stage. Moreover, the combination treatment greatly decreased the average daily and cumulative doses of MMI, thereafter achieving a lower incidence of adverse events than the monotherapy. Overall, the addition of HYD to MMI helps to rapidly control hyperthyroidism, decreasing the risk of adverse events.

**Table 5** Comparison of Adverse Events During the Treatment Between the Two Groups

Adverse Events (n)	Combination Group (n = 54)	MMI Group (n = 54)	<i>P</i>
<b>Liver dysfunction</b>	1	4	0.169
<b>Abnormal WBC count</b>	0	1	0.315
<b>Rash</b>	1	3	0.308
<b>Other discomforts</b>	1	2	1.000
<b>Total</b>	3	10	<b>0.038</b>

**Note:** Bold values indicate *P* < 0.05 compared with the MMI group.

**Abbreviations:** MMI, methimazole; WBC, white blood cell.

We found that HYD not only assisted MMI in controlling hyperthyroidism in GD patients but also decreased the dose of MMI and the incidence of adverse events. MMI, as a thionamide antithyroid agent that inhibits the activity of thyroid peroxidase (TPO), suppresses the synthesis of thyroid hormones by blocking the iodination and coupling of tyrosine residues in thyroglobulin.<sup>15</sup> However, the use of high-dose MMI frequently induces adverse events, including elevated liver enzymes,<sup>16,17</sup> rash,<sup>18</sup> decreased white blood cell count,<sup>19</sup> and even agranulocytosis.<sup>20</sup> A proportion of GD patients, as a result, cannot tolerate the medication of MMI, due to the dose-dependent risk of adverse events. Previous studies demonstrated the superiority of iodine-rich TCM formulations combined with ATDs in rapidly controlling thyroid function, reducing the dose of MMI, and lowering the risk of adverse events, which is consistent with the toxicity-reducing and efficacy-enhancing effects of HYD in the present study.<sup>21,22</sup>

The high-content iodine in HYD may account for its alleviative effects on hyperthyroidism. Accumulating studies have shown the potential of iodine in treating GD and the underlying molecular mechanisms. Zhang et al<sup>23</sup> reported that high-dose iodine impairs thyroid hormone synthesis through inhibiting the activity of sodium-iodide symporter (NIS) and downregulating the mRNA and protein levels of TPO. Fujikawa et al<sup>24</sup> observed thyroid function indexes that are normal or in a range lower than the reference in 50.6% of GD patients at 4 weeks of potassium iodide (KI) therapy alone or in combination with MMI; moreover, a monotherapy of KI is effective enough to maintain normal thyroid function in 76.5% of GD patients at 2 years of follow-up. In comparison to the monotherapy of 30 mg/d MMI, 15 mg/d MMI combined with 38.2 mg/d KI accelerates the recovery of FT4 levels, indicating that the additional use of iodine preparations not only enhances the efficacy but also decreases the dose of ATDs.<sup>14</sup> Stemming from the TCM theory, iodine-rich TCM formulations have been widely applied to thyroid diseases. Cao et al<sup>25</sup> reported a larger proportion of regulatory T cells (Tregs) in the peripheral blood from GD patients treated with MMI combined with an iodine-rich TCM formulation that contains *Sargassum* and *Laminaria*, indicating the capacity of iodine-rich TCM in re-balancing the immune function and restoring the immune homeostasis. Our previous study has confirmed an iodine content as high as 64,641.60 µg/L in HYD.<sup>9</sup> In the present study, we proved the high efficacy and safety of HYD combined with MMI in treating GD, further emphasizing the potential of iodine-rich TCM formulations in treating hyperthyroidism, and providing a solid foundation for the clinical management of GD via integrated TCM and Western medicine. Notably, we limited the duration of HYD treatment within three months, which effectively prevented iodine escape; thereafter, a monotherapy of low-dose MMI was able to maintain the normal thyroid function.

In addition to its iodine-rich ingredients that act on the Wolff-Chaikoff effect, multiple active components of HYD regulate thyroid function via various targets and signaling pathways. As identified in our previous integrative research of network pharmacology, molecular docking and non-targeted serum metabolomics, the top five ingredients of HYD are quercetin, β-sitosterol, naringenin, kaempferol, and wogonin. Additionally, the top 10 targets of active ingredients of HYD are deeply enriched in angiogenesis and inflammatory response.<sup>26</sup> β-sitosterol, naringenin and wogonin execute their anti-angiogenesis roles by regulating the VEGF signaling pathway.<sup>27–29</sup> In the present study, a more pronounced decrease in the STA-PSV was observed in the combination group than the MMI group. STA-PSV is a key imaging indicator of GD activity and treatment response.<sup>30</sup> Its change directly reflects blood perfusion and metabolic activity of thyroid tissues, and provides an objective assessment for therapeutic efficacy. Consistent with our previous findings that HYD inhibits angiogenesis by downregulating CD31, VEGF and DLL4, and upregulating Notch1,<sup>26</sup> HYD combined with MMI resulted in a greater decline of STA-PSV than the monotherapy of MMI. The reduction in thyroid blood perfusion further limited the supply of raw materials and created a metabolic microenvironment unfavorable for the synthesis and release of thyroid hormone, thus eventually controlling GD. In addition, the anti-inflammatory property of active ingredients of HYD should be underscored. Kaempferol, as a flavonoid selectively inhibiting TPO, shows a promising potential in treating hyperthyroidism.<sup>31</sup> Quercetin is a potent anti-inflammatory compound by reducing the expressions of cyclooxygenase and lipoxygenase, maintaining the stability of mast cells, inhibiting the release of pro-inflammatory factors (eg, TNF-α), and accelerating the production of anti-inflammatory factors.<sup>32</sup> Other key ingredients of HYD, like naringenin, β-sitosterol and wogonin, also exert diverse effects on anti-inflammation, antioxidation and immunoregulation.<sup>33–36</sup> Collectively, HYD benefits GD patients through various mechanisms, including the suppression on thyroid hormone synthesis, regulation on the immune function, inhibition on inflammatory responses, and blockage of local blood perfusion.

Here, the additional use of HYD produced a more pronounced improvement of the quality of life in GD patients than those treated with the monotherapy of MMI, manifesting as significantly lower TCM syndrome and ThyPRO scores. Patients with hyperthyroidism usually suffer from an overall low quality of life, especially those with poor living conditions, tense family relationships, anxiety and depression.<sup>37</sup> In TCM theory, “Ying-Bing” (thyroid diseases) is closely engaged in emotional disorders and the dysfunction of the five internal organs. The pathogenesis of GD can be explained by the following TCM mechanism: in the context of emotional discomforts, Qi is depressed into fire, further harming the spleen (attributed to earth in the Five-Elements) and stimulating the endogenous production of phlegm and damp. Consecutively, exuberant heat dries body fluid, stagnates Qi, and obstructs blood circulation, ultimately producing phlegm and stasis that block the liver meridian coursing anteriorly through the cervical region, and triggers the development of GD. *Sargassum* and *Laminaria*, as monarch drugs of HYD, are salty in taste and cold in nature. Being salty, both can soften the hardenings and decompose the nodes; being cold, both can clear heat and purging fire. Due to these properties, their combination directly eliminates the pathogenic triggers of GD, including the phlegm and blood stasis, and excessive heat. *Citri Reticulatae Pericarpium Viride* and *Citri Reticulatae Pericarpium*, as assistant drugs of HYD, can soothe the liver and articulate Qi, further easing GD-related emotional symptoms like impatience and irritability. In summary, HYD simultaneously relieves GD and enhances the overall constitution, and its combination with MMI offers a superior performance in improving the quality of life than the monotherapy of MMI, suggesting the advantage of holistic treatment on GD.

Limitations in this study should be noted. First of all, this was a single-center prospective study with a small sample size, which may introduce potential selection and confounding biases. Second, the lack of a HYD monotherapy group represents an important methodological limitation. This prevents us from determining its independent efficacy and clarifying whether the combined effect with MMI is synergistic or merely additive, thus bringing some uncertainty to the mechanistic interpretation of its adjuvant effect. Third, the follow-up period in this study was only 12 weeks. As Graves' disease is a chronic autoimmune disorder, long-term outcomes including sustained efficacy, recurrence, iodine escape, and long-term safety of the combined treatment cannot be fully addressed by the present short-term results. Further multicenter, large-sample, randomized controlled trials with a HYD monotherapy arm are warranted to verify the present findings, clarify the exact therapeutic effect of HYD, and evaluate its long-term efficacy and safety in the treatment of GD.

## Conclusion

Combination therapy with HYD plus MMI can rapidly reduce thyroid hormone levels and effectively control hyperthyroidism, with obvious benefits in reducing the MMI dose, improving quality of life, and lowering the risk of adverse events. Therefore, the combination of HYD and MMI appears to be an effective and safe therapeutic option for GD.

## Data Sharing Statement

The datasets generated and analyzed in the present study are available from the corresponding authors.

## Ethical Approval and Consent to Participate

The study was designed and conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Clinical Ethics Committee of the Affiliated Hospital of Nanjing University of Traditional Chinese Medicine for Integrative Medicine and Western Medicine (No. 2022-LWKYZ-076).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Fengyun Cheng and Wenbin Huang are co-first authors for this study. All authors have no competing interests or personal financial interests to disclose for this work.

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