Systematic Review and Meta-Analysis

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The effects of methimazole combined with propranolol on heart rate, bone metabolism, and thyroid hormone levels in patients with hyperthyroidism

A systematic review and a meta-analysis of case–control studies

Xingxing Xie, MM[a,*], Xiaodong Fan, MM[b], Ling Fan, MM[c], Xue Liu, MM[a], Yang Zheng, MD[d], Zhigang Yu, BS[a]

Abstract

Background: The combination of methimazole and propranolol is considered an effective treatment regimen for hyperthyroidism in clinical practice; however, detrimental effects on the heart rate, bone metabolism and thyroid hormone levels have been reported. Therefore, the present study aimed to systematically review the efficacy and safety differences in patients with hyperthyroidism and the effects of treatment on heart rate, bone metabolism, cortisol, and adrenocorticotropic hormone levels using case–control studies.

Methods: Clinical case–control trials of methimazole combined with propranolol for the treatment of hyperthyroidism were selected from Chinese and English databases, and data were collected from the establishment of the database until August 2024. Two independent researchers evaluated the quality of the literature using the Newcastle–Ottawa Scale (NOS). Meta-analysis of each effect index was performed using RevMan software (version 5.3), and the quality of the results was evaluated using the GRADE profiler system letter description method.

Results: Sixteen clinical case–control trials were included in this study. Of these, 2 trials exhibited NOS scores of 7, 6 trials exhibited NOS scores of 6, and 8 trials exhibited NOS scores of 5. These accounted for 12.5% of the high-quality literatures, and included 772 patients treated with methimazole combined with propranolol (observation group) and 771 patients treated with methimazole alone (control group). The results of the meta-analysis demonstrated that methimazole combined with propranolol improved the cure rate, the total effective rate, and heart rate, compared with the control group ($P < .05$). In addition, calcification, bone glutamate protein, free triiodothyronine, free tetraiodothyronine, thyroid-stimulating hormone, cortisol, and adrenocorticotropic hormone were significantly different between the 2 groups ($P < .05$). There were no significant differences in leukemia, headache, dizziness, skin pruritus, bone pain, arthralgia, or in improving parathyroid hormone or reducing gastrointestinal reactions between the 2 groups.

Conclusion: The present study demonstrated that methimazole combined with propranolol may significantly improve the heart rate, bone metabolism and associated hormone levels in patients with hyperthyroidism, without significantly increasing the risk of adverse reactions. However, due to the impact of primary literature type, quality or research methods high-quality, multicenter, rigorously designed clinical trials are required for further verification.

Abbreviations: ACTH = adrenocorticotropic hormone, BGP = bone glutamate protein, CI = confidence interval, COR = cortisol, FEM = fixed effects model, FT3 = free triiodothyronine, FT4 = free tetraiodothyronine, NOS = Newcastle-Ottawa Scale, OR = odds ratio, PTH = parathyroid hormone, REM = random-effect model, SMD = standard mean difference, TSH = thyroid stimulating hormone.

Keywords: bone metabolism, case–control study, hyperthyroidism, methimazole, thyroid hormone

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The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Pharmacy, Yaan People's Hospital, Yaan, China, [b] Department of Pharmacy, Xichong People's Hospital, Nanchong, China, [c] Clinical Trial Center for Drugs and Medical Devices, Yaan People's Hospital, Yaan, China. [d] Drug Clinical Trial Institute, Affiliated Hospital of Southwest Medical University, Luzhou, China.

** Correspondence: Xingxing Xie, Department of Pharmacy, Yaan People's Hospital, Yaan 625000, China (e-mail: xiexingxing07@163.com).*

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1. Introduction

Hyperthyroidism is a common endocrine disease caused by excessive secretion of thyroid hormone, which leads to the increased excitability of nervous, circulatory, and digestive systems and hypermetabolism in the body. Hypermetabolism is often manifested as palpitations, sweating, increased appetite, increased defecation, and weight loss.[1] Results of a previous study revealed that the incidence of hyperthyroidism is 2.48 times higher in females than in males and increases with age,[2] particularly in premenopausal and postmenopausal women.[3,4] Imbalances in thyroid function may also lead to increased risks of cardiovascular diseases such as ventricular fibrillation and thrombosis,[5] and these may be accompanied by abnormal changes in bone metabolism, and changes in blood glucose, lipid, and hormone levels,[6] In addition, hyperthyroidism may be associated with an increased risk of cancer.[7] At present, antithyroid drugs are one of the main therapeutic options for the treatment of hyperthyroidism, Notably methimazole is widely favored in clinical practice due to the unique inhibitory effect on thyroid peroxidase activity, and the inhibition of free triiodothyronine (FT3) and thyroxine synthesis.[8] However, previous studies have reported serious adverse reactions caused by methimazole alone in the treatment of hyperthyroidism, resulting in disputes over whether methimazole is still suitable for clinical use alone, or in combination with other therapeutic regimens. A cliometric statistical analysis was carried out based on uncommon adverse events, such as homeostatic liver injury induced by methimazole and insulin-induced autoimmune syndrome. Results of previous studies demonstrated that the incidence of adverse events was decreased compared with methimazole alone[9] or the incidence did not increase significantly.[10] At present, methimazole combined with propranolol is commonly used in the treatment hyperthyroidism in clinical practice. Moreover, there are numerous observational studies on the efficacy and safety of treatment, glucose and lipid metabolism, bone metabolism, and hormone levels in patients with hyperthyroidism. However, evidence-based studies using meta-analysis methods to determine the differences and quality of previous studies are limited. The present study aimed to systematically evaluate the efficacy and safety of methimazole combined with propranolol in patients with hyperthyroidism, as well as the effects on heart rate, bone metabolism, and hormone levels in patients, providing a novel theoretical basis for use in clinical practice.

2. Methods

This systematic review was registered in PROSPERO (registration no. CRD42023473709).

2.1. Inclusion and exclusion criteria

The inclusion criteria for this study on literature were as follows: (1) study design: previously published observational case-control studies, including prospective and retrospective studies, were selected from Chinese and English databases. (2) Subjects: patients diagnosed with hyperthyroidism according to the diagnostic criteria for hyperthyroidism in The Chinese Guidelines for the Diagnosis and Treatment of Thyroid Diseases[11] or Internal Medicine[12] were included in the present study. (3) Interventions: the observation group was treated with methimazole combined with propranolol, while the control group was treated with methimazole alone. (4) Outcome indicators: the main efficacy indicators were cure rate (number of cured cases/total cases × 100%) and total effective rate [(number of cured cases + number of significant cases + number of effective cases)/total cases × 100%]. The secondary efficacy indices were heart rate, bone metabolism (calcitonin, bone glutamate protein), FT3, free tetraiodothyronine (FT4), thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), cortisol (COR), and adrenocorticotropic hormone (ACTH). The safety index was defined as incidence of adverse reactions associated with drug therapy, such as gastrointestinal reactions, leukoplakia, headache, dizziness, skin pruritus, bone pain, and arthralgia.

Exclusion criteria were as follows: (1) review and clinical review; (2) unable to provide valid data; (3) statistical methods are not uniform or inappropriate; (4) case report/case analysis; (5) inclusion index units are not uniform.

2.2. Search strategy

Clinical case–control trials associated with methimazole combined with propranolol in the treatment of hyperthyroidism were selected from PubMed (pubmed.ncbi.nlm.nih.gov/), EBSCO (embase.com), OVID (ovidsp.ovid.com/), China National Knowledge Infrastructure (cnki.net/), Wanfang Medical network (wanfangdata.com.cn/), Web of Science (webofscience.com), and relevant clinical trial registries, such as China Clinical Trial Registry (chictr.org.cn/), International Clinical Trial Registration Platform (trialsearch.who.int/), Hong Kong Clinical Trials Registry (ccrb.cuhk.edu.hk/web/), and North American Clinical Trial Data Center (clinicaltrials.gov/) were collected from the establishment of the database to August 2024 according to the PRISMA guidelines.[13] The following terms were searched: hyperthyroidism AND methimazole combined with propranolol AND methimazole AND "randomized controlled trials (RCTs) odds ratios (OR) case–control studies OR prospective cohort study OR retrospective case study." Terms were searched in both Chinese and English, using the same combination of heterogeneous words, the combination of subject words and free words, and the default database extended search.

2.3. Literature screening and data extraction

Two independent researchers (XX and XD) reviewed the literature according to the inclusion and exclusion criteria, screened the included studies, and extracted the data. In the case of potential discrepancies, a third independent researcher (LF) analyzed the data. The quality-priority principle was used to include multiple articles with the same data.

2.4. Literature quality evaluation

Literature quality evaluation was performed using the Newcastle–Ottawa Scale (NOS),[14] which included: (1) selectivity (the representation of the exposed cohort, the representation of the nonexposed cohort, the determination of the exposure factors, and whether there were outcome events in the study subjects prior to the start of the study); (2) comparability (whether confounding factors were controlled); and (3) outcome (evaluation of outcome events, adequacy of follow-up and completeness of follow-up). The maximum total score is 9 points, and a total score of ≥7 points is considered high-quality.

2.5. Quality grade recommendation

The GRADE profiler system letter description method[15,16] was used to evaluate the quality of the results. Grade A (Make sure that the estimated effect is close to the true effect) is a strong recommendation, Grade B (The degree of confidence in the estimated effect value is medium, and the estimated value may be close to the true value) is a medium recommendation, Grade C (There is limited confidence in the estimated effect size, and the estimated value may differ from the true value) is a cautious recommendation, and Grade D (There is little confidence in the estimated effect size, which is likely to be completely different from the true value) is not recommended.

2.6. Statistical analysis

Meta-analysis of the included studies was performed using RevMan 5.3 software recommended by the Cochrane Collaboration Network. The statistical data were calculated using OR, risk ratios, and 95% confidence intervals (CI). Standard mean difference (SMD) and 95% CI were used as the statistical effect sizes. The Q-test was used to evaluate the heterogeneity of the literature. $I^2 \leq 50\%$ or $P \geq .05$ were considered homogenous, and all studies were combined for the meta-analysis using fixed effects model (FEM) with the Mantel–Haenszel (M–H) method. In contrast, the random effects model (REM) was used for meta-analysis. Publication bias of for each effect size was assessed using a funnel plot.

3. Results

3.1. Literature search results

According to the search strategy, 86 articles were obtained in the preliminary search, 33 were excluded by reprocessing, 53 were excluded after a brief evaluation of the title and abstract, and 37 were excluded due to inconsistent literature types, intervention measures, data indicators or statistical methods following the evaluation of the full text. After further evaluation of the remaining articles, 16 Chinese literatures[17–32] and 0 foreign studies were included in the meta-analysis (Fig. 1).

3.2. Literature features

According to the inclusion and exclusion criteria, a total of 16 case–control trials[17–32] were selected. Studies including complete basic data and baseline characteristics of patients, such as age, sex, intervention measures, course of treatment, and course of disease, were comparable between studies, with no statistical significance (Table 1).

3.3. Quality characteristics

In total, 16 case–control studies were scored, and 2 articles[24,30] exhibited NOS scores of 7, 6 articles[18,22,23,26,29,32] exhibited NOS scores of 6, 8 articles[17,19–21,25,27,28,31] exhibited NOS scores of 5, and high-quality articles accounted for 12.5% of all articles (Table 2).

3.4. Evaluation of efficacy

3.4.1. Cure rate. Cure rate was evaluated using 4 clinical case–control studies,[20,21,26,31] with a total of 408 patients. Results of the heterogeneity test demonstrated that homogeneity was met ($I^2 = 0.0\%$, $P = .86$), and results of the FEM analysis revealed that the difference between the 2 groups was statistically significant (OR = 2.57, 95% CI = [1.67, 3.95]). These results suggest that treatment of hyperthyroidism with methimazole combined with propranolol may significantly improve the cure rate. In addition, the GRADE quality recommendation was Grade C (Fig. 2).

3.4.2. Total effective rate. Total response rate was evaluated using 13 clinical case–control studies[17–24,26–28,31,32] with a total of 1199 patients. Results of the heterogeneity test demonstrated that homogeneity was achieved ($I^2 = 0.0\%$, $P = 1.00$), and results of the FEM analysis revealed that the difference between the 2 groups was statistically significant (OR = 5.67; 95% CI = [3.72, 8.65]). These results suggest that treatment of hyperthyroidism with methimazole combined with propranolol may significantly improve the total effective rate. In addition, the GRADE quality recommendation was Grade B (Fig. 3).

3.4.3. Heart rate. Heart rate changes were evaluated in 3 clinical case–control studies[17,25,32] with a total of 267 patients. Results of the heterogeneity test demonstrated that homogeneity was not met ($I^2 = 97.1\%$, $P < .00001$), and results of the REM analysis revealed that the difference between the 2 groups was statistically significant (SMD = -2.16, 95% CI = [-4.00, -0.32]). These results suggest that treatment of hyperthyroidism with methimazole combined with propranolol may significantly improve the heart rate of patients with hyperthyroidism. In addition, the GRADE quality recommendation was Grade C (Fig. 4).

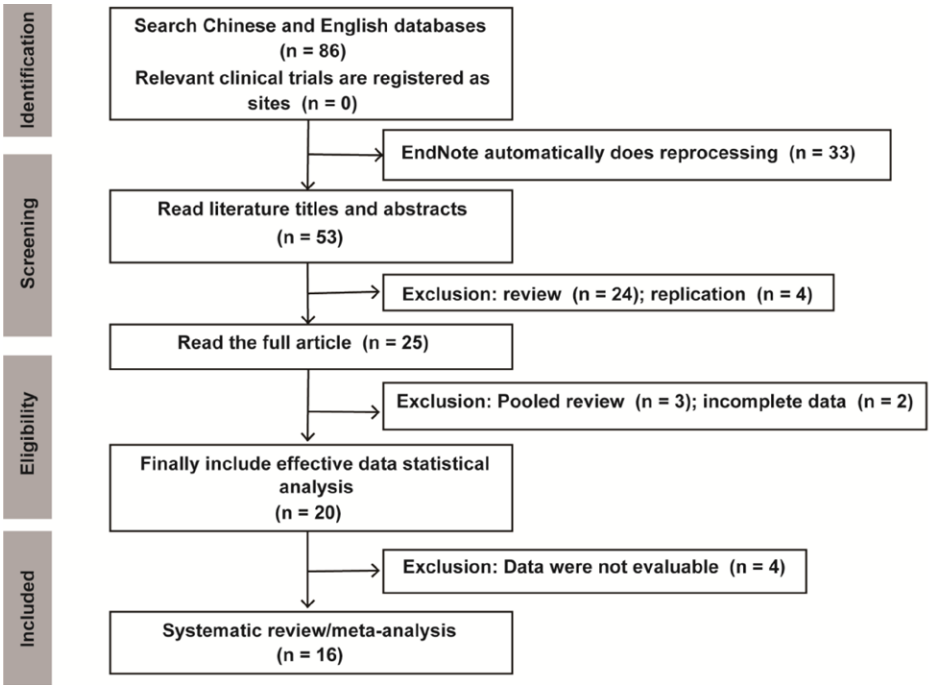

Figure 1. Flow chart of literature screening.

Table 1

Baseline characteristics of patients included in the present study.

Study	Group	Number of cases	Grouping method	Male/ female (n)	Intervention measure	Course of treatment (month)	BMI (kg/m^2)	Mean age (year)	Mean course of disease (month)	Follow-up visit time	City and Country	Ending index
Yun XL[17] 2018	Control Observation	39 39	Random mode is not mentioned	41/37	The control group was treated with 10 mg/ time, 3 times/day. After 10 days of treatment, the dose was changed to 10 mg/ time, once/day. Observation group was combined with propranolol 10 mg/ time, 3 times/day on the basis of control group.	3	/	36.18 ± 5.49 37.87 ± 6.91	/	/	Zhengzhou China	b.c.d.e.k
Yu Y[18] 2021	Control Observation	46 46	Random number table method	50/42	The control group was given methimazole 20 mg/ time, 3 times/day, orally. After the symptoms improved, the dose and frequency were appropriately reduced to 10 mg/ time, once/day. Observation group was orally administered in combination with propranolol, 10 mg/ time, once/day on the basis of control group.	3	25.56 ± 3.22 23.26 ± 3.19	38.6 ± 5.8 39.2 ± 6.5	/	/	Suizhou China	b.g.i.j
Tang ZH[19] 2021	Control Observation	44 44	Random number table method	55/33	The control group was given methimazole tablets at an initial dose of 0.4 mg/kg per day, taken orally in divided doses, and the maintenance dose was approximately halved according to the condition. Observation group was orally combined with propranolol 0.5–1.0 mg/kg daily on the basis of control group, divided into several times.	3	/	7. 09 ± 1. 52 7. 18 ± 1. 44	2. 62 ± 0.49 2. 49 ± 0.41	/	Shaoxing China	b.c.d.e.i.j.l
Fang YM[20] 2017	Control observation	29 29	Random mode is not mentioned	11/47	The control group was given methimazole orally 10mg/ time, 3 times/day, and gradually reduced 5 ~ 10 mg/ time after thyroid hormone level returned to normal. Observation group was combined with propranolol on the basis of control group Er tablet is taken orally 10 mg/ time, 3 times/day.	2	/	32.7 ± 5.3 33.2 ± 6.1	7.48 ± 2.13 8.12 ± 2.71	/	Dongguan China	a.b.c.d.e
Li J[21] 2018	Control observation	60 60	Envelope randomization	78/42	The control group was given methimazole tablets at the initial dose of 20 mg per time, once a day, and 10 mg per time, once a day after symptom improvement. Observation group was combined with propranolol tablet 10mg each time, 3 times a day on the basis of control group.	3	21.38 ± 3.92 21.16 ± 3.66	48.82 ± 6.98 49.35 ± 7.76	7.42 ± 3.89 7.15 ± 4.31	/	Beijing China	a.b.f.g.h.l
Li YL[22] 2020	Control Observation	35 35	Random mode is not mentioned	42/28	The control group was given methimazole tablets at the initial dose of 30 mg/d, which could be adjusted to 15~40 mg/d, with a maximum of 60 mg/d, according to the patient's tolerance and disease improvement. Observation group was combined with propranolol tablet 10 mg each time, 3 times a day on the basis of control group.	3	/	44.9 ± 1.0 45.2 ± 1.0	8.5 ± 1.0 8.6 ± 1.1	/	Huizhou China	b.c.d.g.h.l
Hong LQ[23] 2022	Control Observation	55 55	Random mode is not mentioned	39/71	The control group was given methimazole 10 mg orally 3 times a day. Observation group was orally combined with propranolol 5 mg 3 times/day on the basis of control group.	2	/	35.12 ± 4.27 35.24 ± 4.11	8.28 ± 1.31 8.35 ± 1.23	/	Yangjiang China	b.c.d.e.f.g.h
Pan W[24] 2018	Control Observation	43 43	Admission sequence	30/56	Control group was treated with 10mg/ time, 3 times/day. After thyroid hormone level returned to normal, the dosage was reduced to 5~10 mg/ time. Observation group was combined with propranolol orally 10mg/ time, 3 times/day on the basis of control group.	2	21.45 ± 0.13 21.23 ± 0.24	48.53 ± 6.14 49.15 ± 6.73	8.17 ± 0.25 8.42 ± 0.17	/	Qingdao China	b.c.d.e.f.g.h.l

(Continued)

Table 1

(Continued)

Study	Group	Number of cases	Grouping method	Male/ female (n)	Intervention measure	Course of treatment (month)	BMI (kg/m^2)	Mean age (year)	Mean course of disease (month)	Follow-up visit time	City and Country	Ending index
Wang P[25] 2019	Control Observation	44 44	Random number table method	58/30	The control group was given 10mg oral methiol tablets, 3 times/d, and the dose was adjusted to 10 mg/d according to the specific examination conditions after 1 month of continuous treatment. Observation group was orally combined with propranolol tablet 10 mg/time, 3 times/day on the basis of control group.	3	/	38.01 ± 3.45 37.64 ± 3.26	8.57 ± 2.01 9.00 ± 1.85	/	Chengdu China	b.c.d.e.i.j.k.l
Hu SB[26] 2022	Control Observation	40 40	Random number table method	46/34	The control group was given methimazole 10 mg orally 3 times a day. Observation group was orally combined with propranolol 5 mg 3 times/day on the basis of control group.	2	/	39.83 ± 4.51 39.42 ± 4.34	0.86 ± 0.22 0.82 ± 0.24 (year)	/	Xiantao China	a.b.c.d.e.l
Fan SM[27] 2021	Control Observation	50 50	Random mode is not mentioned	51/49	The control group was given 10~30 mg methimazole tablets 3 times a day for 3~ 8 weeks, and the dose was reduced to 3~10 mg once or twice a day when the thyroid hormone level returned to normal. Observation group was orally combined with propranolol tablets on the basis of control group, 10 mg each time, 3 times/day.	2	/	33.60 ± 6.52 34.12 ± 6.85	4.86 ± 0.85 4.28 ± 0.76	/	Guangzhou China	b.c.d.e.f.g.h.l
Xie ZQ[28] 2022	Control Observation	33 33	Random number table method	37/29	The control group was given methimazole tablets 3 times/day, 10 mg/ day; after thyroid hormone level was normal, the dose was reduced to 10mg/day, once/day. Observation group was orally combined with propranolol 10mg 3 times/day on the basis of control group.	6	/	47.46 ± 4.33 47.52 ± 4.61	3.26 ± 1.11 3.47 ± 1.09 (year)	/	Guangzhou China	b.c.e.l
Guo J[29] 2021	Control Observation	75 75	Random number table method	68/82	The control group was given methimazole tablets 10mg/d, 3 times/d, and then gradually reduced to 10 mg/d. Observation group was orally combined with propranolol tablet 10 mg/time, 3 times/day on the basis of control group.	6	/	38.65 ± 2.58 38.63 ± 2.59	3.24 ± 0.52 3.27 ± 0.53 (year)	/	Yingkou China	c.d.e.i.j.l
Chen SL[30] 2019	Control Observation	53 53	Double- blind random grouping	62/44	Control group was given 10mg methimazole 3 times/day as appropriate. Observation group was combined with propranolol 5 mg oral dose 3 times/day on the basis of control group.	0.5	/	31.45 ± 5.34 32.15 ± 5.23	8.15 ± 1.05 8.07 ± 1.03	12 months	Xinyang China	c.d.l
Ma YY[31] 2020	Control Observation	75 75	Random number table method	72/78	In the control group, the oral dose of methimazole was 10mg/ time, 3 times/day before 10 d, and 10 mg/time, once/day after 10 d. Observation group was combined with propranolol 10 mg/ time, 3 times/day on the basis of control group.	3	/	47.92 ± 10.87 48.51 ± 9.62	5.84 ± 2.18 6.41 ± 3.82	6 months	Xiayi China	a.b.c.d.e.l
Ma J[32] 2023	Control Observation	50 51	Random number table method	35/66	The control group was given methimazole tablets 10 mg/ tablet, 3 times/day, and the dose was reduced once/day, 10 mg/ time after the symptoms were relieved. Observation group was orally combined with propranolol 10 mg~20 mg/time, 3 times/day on the basis of control group.	3	21.54 ± 0.27 21.58 ± 0.26	45.34 ± 4.21 45.78 ± 4.02	8.65 ± 1.43 8.49 ± 1.36	Not mentioned	Harbin China	b.c.d.e.g.h.i.j.k

a = cure rate; b = total effective rate; c = free triiodothyronine (FT3); d = free tetraiodothyronine (FT4); e = thyroid stimulating hormone (TSH); f = parathyroid hormone (PTH); g = calcitonin (CT); h = bone glutamate protein (BGP); i = cortisol (COR); j = adrenocorticotropic hormone (ACTH); k = heart rate; l = incidence of adverse drug reactions.

BMI = body mass index.

Table 2

Literature quality evaluation.

Study	Selectivity				Comparability	Ending			Total points
	Representation of the exposed cohort	Representation of the nonexposed cohort	Identification of exposure factors	Whether any outcome events occurred before the study began	Whether confounding factors are controlled	Evaluation of outcome events	Adequacy of follow-up	Integrity of follow-up	
Yun XL[17] 2018	1	1	1	0	1	1	0	0	5
Yu Y[18] 2021	1	1	1	1	1	1	0	0	6
Tang ZH[19] 2021	1	1	1	1	1	0	0	0	5
Fang YM[20] 2017	1	1	1	0	1	1	0	0	5
Li J[21] 2018	1	1	1	0	1	1	0	0	5
Li YL[22] 2020	1	1	1	0	2	1	0	0	6
Hong LQ[23] 2022	1	1	1	1	1	1	0	0	6
Pan W[24] 2018	1	1	1	0	1	1	1	1	7
Wang P[25] 2019	1	1	1	0	1	1	0	0	5
Hu SB[26] 2022	1	1	1	0	2	1	0	0	6
Fan SM[27] 2021	1	1	1	0	1	1	0	0	5
Xie ZQ[28] 2022	1	1	1	0	1	1	0	0	5
Guo J[29] 2021	1	1	1	1	1	1	0	0	6
Chen SL[30] 2019	1	1	1	1	1	2	0	0	7
Ma YY[31] 2020	1	1	1	0	1	1	0	0	5
Ma J[32] 2023	1	1	1	0	2	1	0	0	6

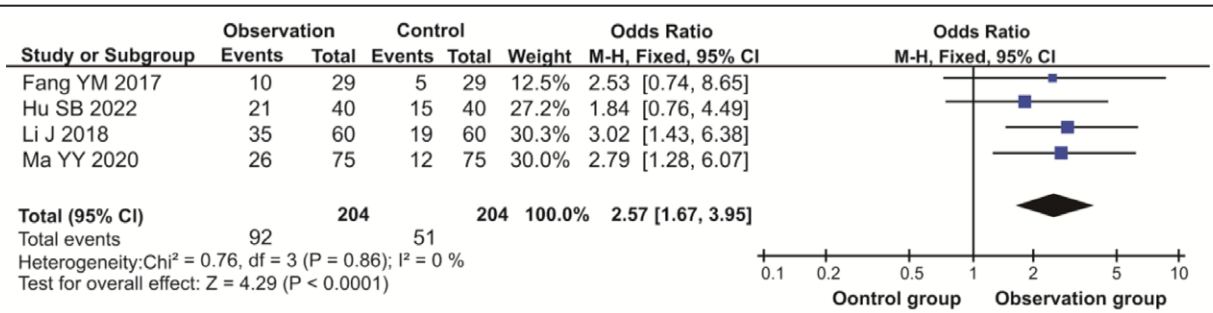

Figure 2. Forest plot comparing cure rates between 2 groups in the meta-analysis.

3.4.4. Calcimining (CT) levels. CT levels were evaluated in 5 clinical case–control studies,[21,22,24,27,31] with a total of 477 patients. Results of the heterogeneity test demonstrated that homogeneity was not met (I^2 = 89.3%, P < .00001), and results of the REM analysis revealed that the difference between the 2 groups was statistically significant (SMD = -1.28, 95% CI = [-1.90, -0.66]). These results suggest that treatment of hyperthyroidism with methimazole combined with propranolol may significantly improve CT levels in patients with hyperthyroidism. In addition, the GRADE quality recommendation was Grade B (Fig. 5).

3.4.5. Bone glutamate protein (BGP) level. BGP levels were evaluated in 6 clinical case–control studies[21–24,27,31] with a total of 587 patients. Results of the heterogeneity test demonstrated that homogeneity was not met (I^2 = 88.1%, P < .00001), and results of the REM analysis revealed that the difference between the 2 groups was statistically significant (SMD = -1.63, 95% CI = [-2.18, -1.08]). These results suggest that treatment of hyperthyroidism with methimazole combined with propranolol may significantly improve BGP levels in patients with hyperthyroidism. In addition, the GRADE quality recommendation was Grade B (Fig. 6).

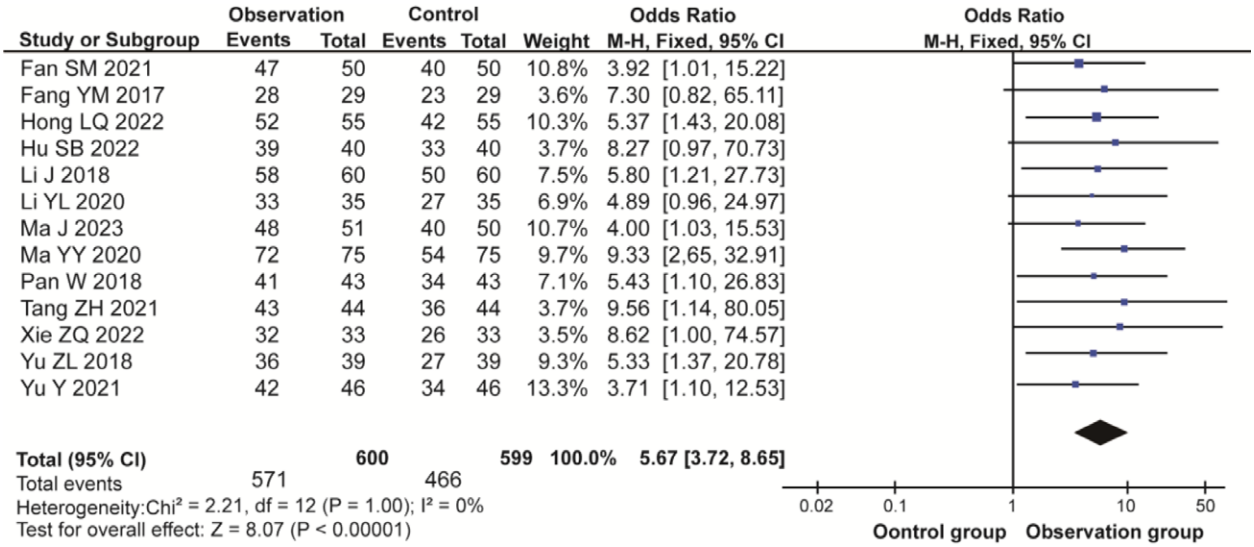

Figure 3. Forest plot comparing total effective rates between the 2 groups in the meta-analysis.

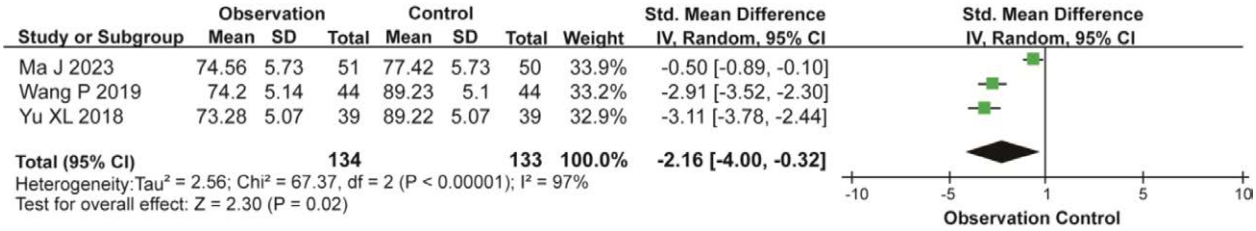

Figure 4. Forest plot comparing heart rate changes between the 2 groups in the meta-analysis.

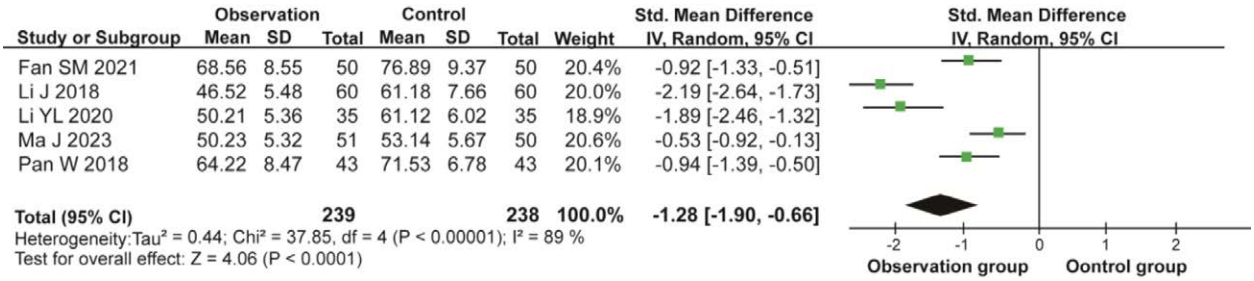

Figure 5. Forest plot comparing the levels of CT between the 2 groups in the meta-analysis. CT = calcitonin.

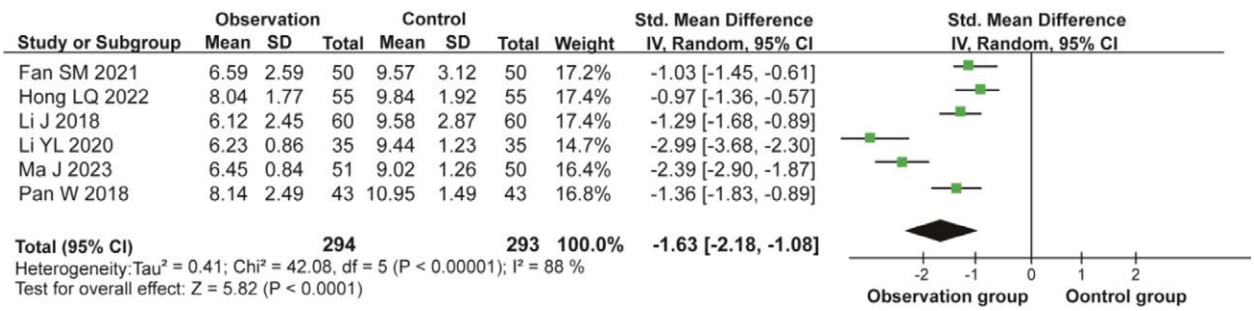

Figure 6. Forest plot comparing the levels of BGP between the 2 groups in the meta-analysis. BGP = bone glutamate protein.

3.4.6. Thyroid and other hormone levels. A combined meta-analysis was conducted to determine the FT3, FT4, TSH, PTH, COR, and ACTH levels in the 2 groups. The results of the present study demonstrated that FT3, FT4, TSH, and COR levels significantly improved in the control group. Notably, the differences between the 2 groups were statistically significant. In addition, the GRADE quality recommendations for FT3 and FT4 was Grade B (medium), and the GRADE quality

Table 3

Results of the meta-analysis were combined to determine changes in hormone levels in the 2 groups.

Effect index	Research number (references)	Q test		Statistical model	SMD	95% CI	*P*-value	GRADE
		I^2	*P*-value					
FT3	14[17,19,20,22–32]	88	<.05	REM	-1.24	-1.59 to -0.89	<.05	B
FT4	13[17,19,20,22–27,29–32]	84	<.05	REN	-1.23	-1.53 to -0.93	<.05	B
TSH	4[17,24,25,27]	91	<.05	REM	1.14	0.37 to 1.91	<.05	C
COR	5[18,19,25,29,31]	82	<.05	REM	0.88	0.45 to 1.31	<.05	C
ACTH	5[18,19,25,29,32]	90	<.05	REM	-1.68	-2.34 to -1.03	<.05	C
PTH	4[21,23,24,27]	97	<.05	REM	0.63	-0.54 to 1.80	>.05	C

FT3 = free triiodothyronine, FT4 = tetraiodothyronine, REM = random-effect model, SMD = standard mean difference, TSH = thyroid stimulating hormone.

Table 4

Results of the meta-analysis were combined to determine the incidence of adverse drug reactions in the 2 groups.

ADR symptom	Incidence rate/%		Research number (Refs.)	Q test		Statistical model	RR	95% CI	*P*-value	GRADE
	Observation group	Control group		I^2	*P*-value					
Gastrointestinal reaction	4.35	7.45	3[28,30,31]	0	.45	FEM	0.58	0.24 to 1.45	>.05	C
Rash	3.11	4.15	6[19,25,26,28–30]	0	.94	FEM	0.76	0.34 to 1.72	>.05	B
Leukopenia	3.87	2.21	4[19,24,25,27]	0	.70	FEM	1.67	0.53 to 5.27	>.05	C
Headache and dizziness	2.89	5.06	8[21,22,24,25,27–29,31]	8	.37	FEM	0.61	0.32 to 1.17	>.05	B
Pruritus	3.07	2.19	5[21,22,24,26,27]	0	.99	FEM	1.44	0.45 to 4.35	>.05	C
Osteoarthralgia	2.56	1.42	7[19,21,22,24,25,27,29]	0	.82	FEM	1.57	0.62 to 4.01	>.05	B

ADR = adverse drug reaction, RR = risk ratios.

recommendations for TSH, COR and ACTH was Grade C (caution). There was no significant difference in the improvement of PTH levels between the 2 groups, and the GRADE quality recommendation was Grade C (Table 3).

3.4.7. Safety evaluation. Potential adverse drug reactions, with an incidence of 2% were evaluated following treatment with methimazole combined with propranolol or methimazole alone. The results of the present study demonstrated that 7 adverse symptoms met the statistical requirements, including gastrointestinal reaction, rash, leukoplakia, headache, dizziness, skin pruritus, bone pain, and arthralgia. A combined meta-analysis of the incidence of the aforementioned symptoms revealed no statistically significant differences between the 2 groups. Notably, the GRADE quality recommendation for rash, headache, dizziness and bone and arthralgia was Grade B (medium), and the GRADE quality recommendation for the remaining symptoms was Grade C (Table 4).

3.5. Publication offset evaluation

The total effective rate, FT3 levels, FT4 levels headache and dizziness were selected as evaluation indicators. Funnel plots were created for the articles that included the 4 aforementioned indicators. The results of the present study demonstrated that the scatter points of the 4 evaluation indicators were asymmetrically unbalanced along the center line, and the scatter points were scattered in the stratification. However, the 4 evaluation indicators included in the present study may be at a risk of publication bias (Fig. 7).

3.6. Sensitivity analysis

Sensitivity correction was carried out using the REM results of the REM and further statistical analysis was performed once research items with large weight ratio differences were removed, including heart rate, TSH, ACTH, and PTH. The results of the present study demonstrated that there were no statistically significant differences in the effect indicators following verification. Notably, the aforementioned evaluation indices were stable (Table 5). However, these results may be limited by literature type, selection bias, and a small sample size.

4. Discussion

Hyperthyroidism is a collective term for diseases mainly characterized by systemic hypermetabolism caused by a loss in the feedback control mechanism of normal thyroid secretion.[33] There are numerous causes of hyperthyroidism, including autoimmune thyroid disease thyrotoxicosis caused by thyroid lesions, Graves' disease multimodular toxic goiter, and autonomic hyperfunctional thyroid adenoids.[34] However, clinical manifestations are not limited to the thyroid. Symptoms may also include hypermetabolism, thyroid eye syndrome, skin lesions, and most patients with hypermetabolic syndrome and Graves' disease.[35] Due to the systemic effects of the thyroid hormones, imbalance in secretion and regulation often leads to systemic abnormal changes in the body.[36] Notably, heart disease is one of the most common complications, affecting 8.6% to 17.5% of hospitalized patients with hyperthyroidism.[37] Additional complications such as abnormal blood sugar, blood pressure, blood lipids, and bone metabolism are also more common.[38] Thus, current treatment options aim to control hyperthyroidism while also improving or treating cardiovascular complications. Currently, the most common clinical treatment regimen for hyperthyroidism is antithyroid drugs combined with β-blockers. Notably, methimazole combined with propranolol is the most common treatment option in clinical practice; however, the efficacy of treatment and physical improvement in of patients remains controversial.

The present study aimed to investigate the effects of combination therapy on bone metabolism and levels of COR, ACTH, FT3, and FT4 in patients with hyperthyroidism, using previous prospective and retrospective case–control studies. The levels of T3, rT3, and T4 are increased in patients with hyperthyroidism, and T3 is often higher than T4. Notably, lower TSH levels are often observed when using more sensitive radiological

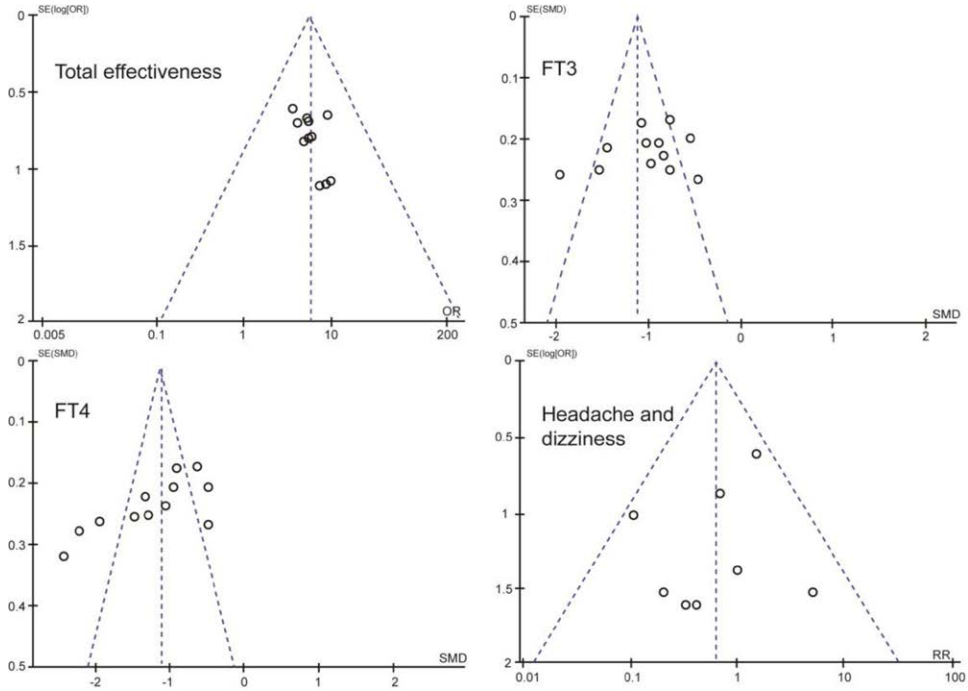

Figure 7. Publication bias of each effect size assessed using a funnel plot.

Table 5

Results of the sensitivity analysis.

	Before excluding			After eliminating			
Effect index	**SMD**	**95% CI**	***P*-value**	**SMD**	**95% CI**	***P*-value**	**Check result**
Heart rate	-2.16	-4.00 to –0.32	<.00001	-3.00	-3.45 to –2.55	<.00001	Stabilization
TSH	1.14	0.37 to 1.91	<.00001	1.37	0.41 to 2.33	<.00001	Stabilization
ACTH	-1.68	-2.34 to –1.03	<.00001	-1.81	-2.69 to –0.94	<.00001	Stabilization
PTH	0.63	-0.54 to 1.80	<.00001	0.38	-1.11 to 1.86	<.00001	Stabilization

ACTH = adrenocorticotropic hormone, PTH = parathyroid hormone, SMD = standard mean difference, TSH = thyroid stimulating hormone.

tests. Hyperthyroidism may lead to increased serum PTH levels owing to high metabolic syndrome, abnormal calcium metabolism, and osteoporosis.[39] Numerous previous studies have demonstrated that thyroid dysfunction is associated with the hypothalamo–pituitary–adrenal axis (HPA), and COR and ACTH are HPA-related indicators that are indicative of adrenal cortex function.[40–42] In total, 16 case–control studies involving 1543 patients were included in the present study, and 17 indices including cure rate, total response rate, safety, heart rate change, CT, BGP, PTH, and COR were systematically and comprehensively analyzed. The results of the present study revealed that the combined treatment with propranolol may significantly improve the cure rate and total response rate of patients compared with methimazole treatment alone. While the heart rate improved and the risk of adverse drug reaction was not significantly increased, the levels of serum FT3, FT4, ACTH, CT, and BGP were significantly decreased, and the levels of TSH and COR increased.

Although the present study revealed new findings, it confirmed that methimazole combined with propranolol has an important effect on heart rate, bone metabolism, and thyroid hormone levels in hyperthyroid patients. There are still some non-ignorable limitations: (1) all the studies included in this paper are retrospective case–control studies, the case data are relatively backward, and due to the different rigor of the clinical trial design of the implementer, the exposure traceability of the integrity of the intervention measures, outcome data, and follow-up quality in the included literature cannot be unified, resulting in a relatively small number of high NOS scores in the included literature. Therefore, multicenter, rigorously designed, randomized clinical trials are needed for validation. (2) The included analysis data may be interfered with by uncertain factors, such as missing literature, differences in researchers' subjective judgments, and language restrictions. The results of the meta-analysis may have certain volatility, and the results should be further validated in future studies. (3) There is a lack of in vivo and in vitro experimental studies to clarify the mechanism of action of methimazole combined with propranolol on bone metabolism and thyroid hormone levels, which warrants further research. (4) The diagnostic criteria of the patients in this study were relatively uniform, with mild symptoms and no other serious comorbidities, and all were Chinese. Further studies are needed to verify whether the results of this study are applicable to populations a dated to non-Chinese or other diagnostic criteria. (5) For unpublished negative results or literature with no results in literature traceability, we have not received enough supplements in the literature search, and the impact of this on the analysis results needs to be verified by larger samples of high-quality clinical trial data.

5. Conclusion

The combination of methimazole and propranolol in the treatment of hyperthyroidism can significantly improve the therapeutic effect of hyperthyroidism and improve the heart rate, bone metabolism, and related hormone levels of patients, and the risk of adverse reactions is not significantly increased. However, we also found that the design of many clinical trials is not sufficiently rigorous, the amount of effective analysis data that can be included in meta-analysis is still limited, and the real value of objective responses is still insufficient. Therefore, large samples, strict design and high-quality clinical research data are needed to supplement and verify the conclusions.

Author contributions

Data curation: Xiaodong Fan, Ling Fan.
Formal analysis: Ling Fan, Xue Liu.
Investigation: Xingxing Xie, Xiaodong Fan, Ling Fan, Xue Liu, Yang Zheng.
Methodology: Xingxing Xie, Zhigang Yu.
Resources: Xingxing Xie, Yang Zheng, Zhigang Yu.
Supervision: Yang Zheng, Zhigang Yu.
Writing – original draft: Xingxing Xie.
Writing – review & editing: Xingxing Xie, Zhigang Yu.

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