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Original Article

Influence of propranolol plus methimazole on curative efficacy and thyroid function of patients with hyperthyroidism

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Abstract: Purpose: To analyze the influence of propranolol (Prop) plus methimazole (MMI) on curative efficacy and thyroid function (TF) of patients with hyperthyroidism (HT). Methods: In this retrospective study, 107 cases of HT presented between August 2019 and August 2021 were grouped according to different therapeutic regimens: a control group (the Con) with 53 cases treated with MMI, and a research group (the Res) with 54 cases treated with Prop + MMI. Inter-group comparisons were performed in terms of the following domains: heart rate (HR), efficacy, adverse reactions (ARs), TF parameters (free triiodothyronine, FT3; free thyroxine, FT4; thyroid stimulating hormone, TSH), hepatic function indicators (alanine aminotransferase, ALT; aspartate aminotransferase, AST), and quality of life (Short-Form 36 Item Health Survey, SF-36). Finally, multivariate analysis was performed by Logistic regression to determine the risk factors leading to the ineffectiveness of treatment. Results: The analysis showed an obviously higher total effective rate and an evidently lower AR rate in the Res compared with the Con group. Besides, the Res group had notably lower FT3, FT4, ALT and AST and statistically higher TSH after treatment compared with the baseline (before treatment) and the Con group. Higher SF-36 scores were also determined in the Res group. Finally, the results of Logistic regression analysis revealed that AST was an independent risk factor for ineffective treatment. Conclusions: Prop plus MMI is effective in the treatment of HT, which can effectively improve the HR, thyroid hormone levels, hepatic function, and quality of life of patients, with a lower incidence of ARs.

Keywords: Propranolol, methimazole, hyperthyroidism, therapeutic effect, thyroid function parameters

Introduction

Hyperthyroidism (HT) is a common endocrine disorder characterized by aberrantly elevated thyroid hormone levels in the body, often manifesting as palpitations, sweating, and increased food intake but weight loss [1-3]. According to relevant epidemiological data, HT affects 0.2-1.3% of people in the world's iodine-sufficient areas [4]. A brief increase in the incidence of HT was reported following the introduction of iodine-fortified salt in Denmark, suggesting a link between iodine and the pathogenesis of HT [5]. In previous studies, untreated HT was shown to be associated with a greatly increased risk of complications and even the possibility of miscarriage in pregnant women, so timely management of the disease is critical [6, 7]. This study, which uses combination therapy as a breakthrough, aims to find better treatment schemes for such patients.

Propranolol (Prop) is a β-adrenergic blocker that is extensively applied to treat vascular tumors and HT in clinical practice [8, 9]. After years of clinical application, Prop is considered as the drug of choice for HT [10]. However, in a clinical study on Prop, it is mentioned that Prop has a long duration of use, resulting in treatment complications in some patients [11]. This suggests the feasibility of a combination therapy approach to circumvent the limitations and risks of Prop monotherapy. Methimazole (MMI) is an antithyroid drug that is generally well tolerated as an inhibitor of thyroid peroxidase [12]. Its common adverse reactions (ARs), such as

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rashes, vomiting, indigestion, etc., usually can be tolerated. The study of Sun et al. on the clinical efficacy of MMI also indicated a higher safety profile of the adjuvant therapy with MMI [13, 14].

Currently, there are a number of combination therapies for HT, but there is limited research data on Prop + MMI. Consequently, this study mainly compared and analyzed the heart rate (HR), curative effects, ARs, TF parameters, hepatic function indicators and quality of life (QoL) of HT patients with Prop + MMI therapy, hoping to provide new evidence for clinical treatment of HT patients.

Data and methods

General data

This research, after obtaining approval from the Ethics Committee of Chongming hospital affiliated to Shanghai University of Health & Medicine Sciences, included 107 cases of HT treated between August 2019 and August 2021 and collected their clinical for retrospective analysis. Based on different medication regimens, 53 cases treated with MMI were set as the control group (the Con) and 54 cases given Prop + MMI were set as the research group (the Res). The mean age and average disease course of the Con were (31.4±5.77) years and (8.53±2.53) months, respectively. Patients in the Res aged (29.59±6.65) years on average, with a mean disease course of (8.35±2.88) months. The general data of the two groups were similar and clinically comparable (P>0.05). All participants provided informed consent before enrollment.

Criteria for patient inclusion and exclusion

The eligible patients all met HT-related diagnostic criteria [15], with varying degrees of goiter, exophthalmos, hyperphagia, weight loss and other clinical symptoms, as well as normal communication and cognitive function.

In contrast, pregnant or lactating women, and those with severe heart, lung, liver and kidney dysfunction and other diseases, malignant tumors or infectious diseases, allergies to the drugs used in this study, or HT crisis or storm were excluded.

Medication regimens

The Con: oral MMI (PB4232, Beijing Puffe Biotech Co., Ltd., China) was given 10 mg each time, three times a day, for 30 days continuously. The dose was then reduced to 10 mg once daily. On this basis, the Res was additionally given oral Prop (YT08074, Beijing Yita Biotech Co., Ltd., China), 10 mg/time, three times a day. Patients in each group were treated continuously for 3 months.

Criteria for efficacy judgment

Overall response rate (ORR) = (cured + markedly effective + effective) cases/total cases.

Cured: the patient's symptoms such as goiter, exophthalmos, sweating and palpitations disappear completely after treatment, with normal thyroid function (TF) parameters and HR.

Markedly effective: the clinical symptoms described above are obviously improved, and the TF parameters and HR basically return to normal.

Effective: the above clinical symptoms are gradually improved, with improvements in TF parameters and HR.

Ineffective: the above clinical symptoms do not improve, and the condition worsens.

Analysis measures

We mainly analyzed patients' HR, curative efficacy, ARs, TF parameters, hepatic function indicators and QoL. Among them, HR was tested with an electronic blood pressure monitor. The efficacy evaluation criteria and calculation method of ORR can be found in *Criteria for Efficacy Judgment*. The ARs recorded mainly included skin rashes, abnormal liver function, leukopenia, and hypothyroidism, and the incidence rate was calculated. As for TF parameters, we mainly measured free triiodothyronine (FT3), free thyroxine (FT4) and thyrotropin (TSH) using a chemiluminescence detector. Enzyme-linked immunosorbent assays (ELISAs) were performed to quantify hepatic function indicators alanine aminotransferase (ALT) and aspartate aminotransferase (AST), strictly following the human ALT kit (YK-06610, Beijing Yita Biotech Co., Ltd., China) and AST ELISA kit (YK-04544, Beijing Yita Biotech Co., Ltd., China)

Table 1. Patients' general data [n (%), mean ± SD]

Factors	n	Control group (n=53)	Research group (n=54)	χ^2/t	P
Sex				0.822	0.365
Male	43	19 (35.85)	24 (44.44)		
Female	64	34 (64.15)	30 (55.56)		
Mean age (years old)	107	31.40±5.77	29.59±6.65	1.503	0.136
Course of disease (months)	107	8.53±2.53	8.35±2.88	0.343	0.732
Weight (kg)	107	48.87±8.42	50.93±11.17	1.076	0.285
Disease types				0.990	0.320
Graves' disease	73	35 (66.04)	38 (70.37)		
Toxic nodular goiter	34	18 (33.96)	16 (29.63)		
Degree of goiter				0.325	0.850
I	67	32 (60.38)	35 (64.81)		
II	20	11 (20.75)	9 (16.67)		
III	20	10 (18.87)	10 (18.52)		
Family disease history				0.466	0.495
No	86	44 (83.02)	42 (77.78)		
Yes	21	9 (16.98)	12 (22.22)		
Residence				0.084	0.773
Urban areas	53	27 (50.94)	26 (48.15)		
Rural areas	54	26 (49.06)	28 (51.85)		

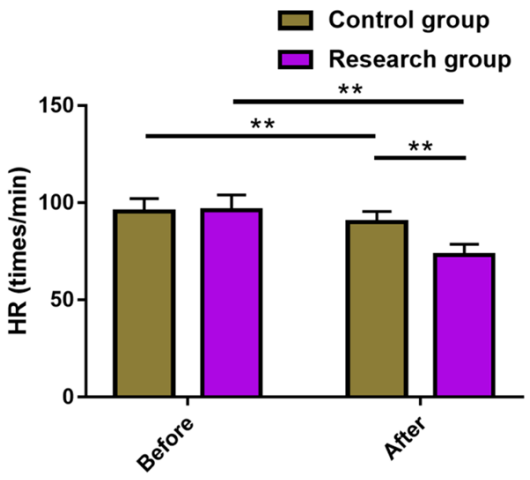

Figure 1. Influence of propranolol (Prop) plus methimazole (MMI) on heart rate (HR) of patients with hyperthyroidism. **P<0.01.

instructions. The QoL was mainly evaluated by the Short-Form 36 Item Health Survey (SF-36), which covered eight dimensions including physical (PF) and social functioning (SF), role-physical (RP) and emotional (RE), bodily pain (BP), general health (GH), vitality (VT), and mental health (MH). The score ranges from 0 to 100 for all sub-scales and is proportional to the QoL.

Statistical processing

This study used SPSS18.0 software package for statistical analysis. The number of cases/percentage (n/%) was used to indicate count data (sex, disease type, goiter degree, etc.); measurement data (age, course of disease, weight, etc.) were represented by (mean ± SD). Among them, χ^2 test was performed to analyze count data, and independent sample t test was adopted for inter-group comparisons of measurement data. Risk factors affecting treatment ineffectiveness were analyzed by Logistic regression. P<0.05 was regarded as statistically significant.

Results

Patients' general information

As aforementioned, the two cohorts of patients were clinically comparable, with no notable difference in sex, age (mean), disease course, weight, disease type, goiter degree, family disease history, residence and other general data (all P>0.05, **Table 1**).

Influence of Prop + MMI on HR of HT patients

We measured HR in both patient cohorts (**Figure 1**). Data showed no significant difference in pre-treatment HR between the two groups (P>0.05); HR decreased remarkably after treatment (P<0.05), with lower post-treatment levels in the Res than in the Con (P<0.05).

Influence of Prop + MMI on curative efficacy of HT patients

We evaluated the curative efficacy of both cohorts of patients (**Table 2**). The ORR was found to be 87.04% in the Res and 71.70% in the Con, indicating statistically higher efficacy of the combination therapy used in the Res (P<0.05).

Table 2. Influence of Prop plus MMI on the curative effect of HT patients [n (%)]

Groups	n	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Control group	53	17 (32.08)	16 (30.19)	20 (37.74)	15 (28.30)	38 (71.70)
Research group	54	24 (44.44)	23 (42.59)	10 (18.52)	7 (12.96)	47 (87.04)
χ^2 value	-	-	-	-	-	3.853
P value	-	-	-	-	-	0.0497

Note: MMI, Methimazole; HT, Hyperthyroidism.

Table 3. Influence of Prop plus MMI on adverse reactions in HT patients [n (%)]

Categories	Control group (n=53)	Research group (n=54)	χ^2 value	*P* value
Rashes	3 (5.66)	2 (3.70)	-	-
Abnormal liver function	1 (1.89)	1 (1.85)	-	-
Leukopenia	3 (5.66)	2 (3.70)	-	-
Hypothyroidism	2 (3.77)	0 (0.00)	-	-
Total incidence	9 (16.98)	5 (9.26)	1.402	0.236

Note: MMI, Methimazole; HT, Hyperthyroidism.

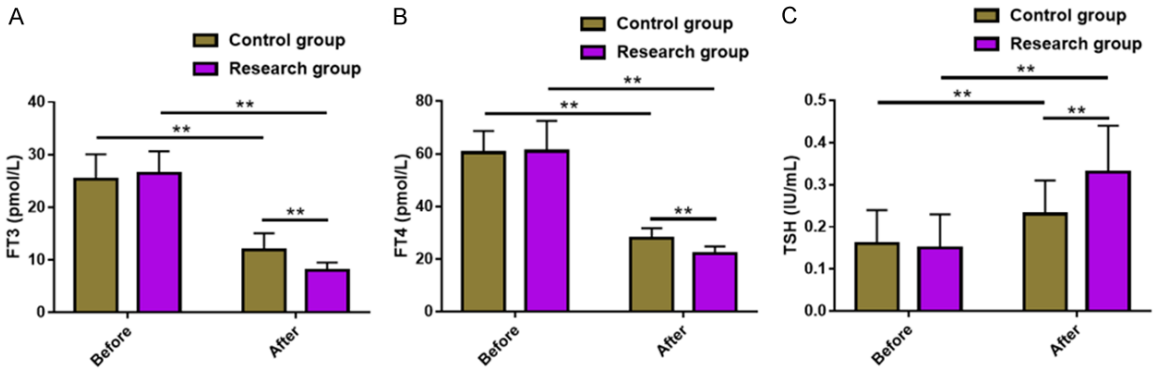

Figure 2. Influence of propranolol (Prop) plus methimazole (MMI) on thyroid function parameters of HT patients. A. The research group had statistically reduced FT3 that was lower compared with the control group after treatment. B. The research group had statistically reduced FT4 that was lower compared with the control group after treatment. C. The research group had statistically increased TSH that was higher compared with the control group after treatment. Note: ***P*<0.01. FT3, Free Triiodothyronine; FT4, Free Thyroxine; TSH, Thyroid Stimulating Hormone.

Influence of Prop + MMI on ARs of HT patients

We observed and recorded the occurrence of ARs to better understand the safety profile of the two interventions (**Table 3**); the AR rate in the Res was 9.26%, which was not significantly lower than that of 16.98% in the Con (*P*>0.05).

Influence of Prop + MMI on TF parameters of HT patients

We compared the levels of FT3, FT4 and TSH of two cohorts to observe the effects of two treatment methods on TF (**Figure 2**). The three TF parameters differed insignificantly between groups before treatment (all *P*>0.05). After treatment, significant increases in FT3 and FT4 and a notable reduction in TSH were observed in both groups (all *P*<0.05). In addition, the Res showed lower FT3 and FT4 and higher TSH than the Con after treatment (all *P*<0.05).

Influence of Prop + MMI on hepatic function indicators of HT patients

We also compared the levels of ALT and AST between two groups to verify the influences of the two interventions on their hepatic function (**Figure 3**). The data also showed no evident difference in pre-treatment ALT and AST between

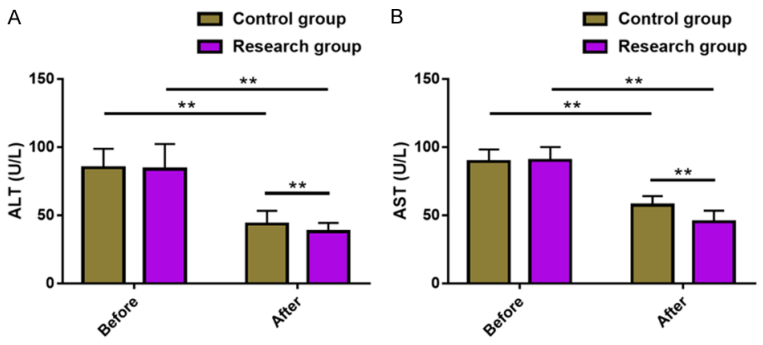

Figure 3. Influence of propranolol (Prop) plus methimazole (MMI) on hepatic function indicators of HT patients. A. The research group showed statistically reduced ALT that was lower compared with the control group after treatment. B. The research group showed statistically reduced AST that was lower compared with the control group after treatment. Note: **P<0.01. ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

Table 4. Analysis of risk factors affecting treatment ineffectiveness in patients

Factors	B	SE	Wald	P	OR (95% CI)
HR	-0.029	0.050	0.336	0.562	0.971 (0.881-1.071)
FT3	-0.059	0.101	0.343	0.558	0.943 (0.774-1.148)
FT4	0.054	0.076	0.501	0.479	1.055 (0.909-1.225)
TSH	-2.560	3.030	0.714	0.398	0.077 (0.000-29.339)
ALT	-0.031	0.031	1.004	0.316	0.970 (0.913-1.030)
AST	0.097	0.038	6.513	0.011	1.102 (1.023-1.187)
Treatment method	0.251	1.215	0.043	0.837	1.285 (0.119-13.897)

Note: HR, Heart Rate; FT3, Free Triiodothyronine; FT4, Free Thyroxine; TSH, Thyroid Stimulating Hormone; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

groups (all P>0.05). While obvious decreases in these two indexes were observed after treatment (P<0.05), with more marked reductions in the Res (P<0.05).

Analysis of risk factors affecting treatment ineffectiveness in patients

According to the multivariate analysis by Logistic regression, HR, FT3, FT4, TSH, ALT, and treatment method were not significantly associated with treatment ineffectiveness, but AST was an independent risk factor for treatment ineffectiveness (P=0.011; **Table 4**).

Influence of Prop + MMI on QoL of HT patients

We measured the level of QoL in both groups after treatment by SF-36 to assess the impact of the two interventions on patients' life quality (**Figure 4**). The results revealed notably higher SF-36 scores in all sub-scales in the Res compared with the Con (all P<0.05).

Discussion

HT is a common global health issue and a risk factor for cardiovascular mortality [16]. The prevalence of goiter can be as high as 20.4% in iodine-deficient areas. According to past experience, HT can be prevented by adding iodine to salt, which also greatly reduces the incidence of HT [17, 18]. Nevertheless, it is important to pay attention to the adverse consequences of over- and under-treatment in the clinical treatment of HT [19]. Therefore, there is an urgent need for a treatment plan that takes both efficacy and safety into consideration during HT treatment. This study focuses on the combination therapy of Prop and MMI, hoping to contribute to the clinical treatment of HT.

The 107 HT patients enrolled in this study were assigned to the Con (MMI monotherapy) and the Res (Prop + MMI) groups according to the medication methods. First of all, we measured the HR of the patients. HT patients usually present significantly increased HR, but our results showed a significant reduction in the HR in both groups after treatment, with better improved HR in the Res using the combination therapy. In a study of HR variability in HT patients by Tankeu et al. [20], short-term use of Prop was found to reduce tachycardia, which is consistent with our results. In another study of Prop, significantly reduced exercise-induced tachycardia was observed in healthy volunteers after Prop infusion. This is because Prop, as a non-selective β-adrenergic receptor antagonist, can block β1 receptors primarily distributed in the myocardium, thereby reducing HR [21]. Then we compared the differences in efficacy. It was found that the ORR was notably higher in the Res than in the Con (87.04% vs.

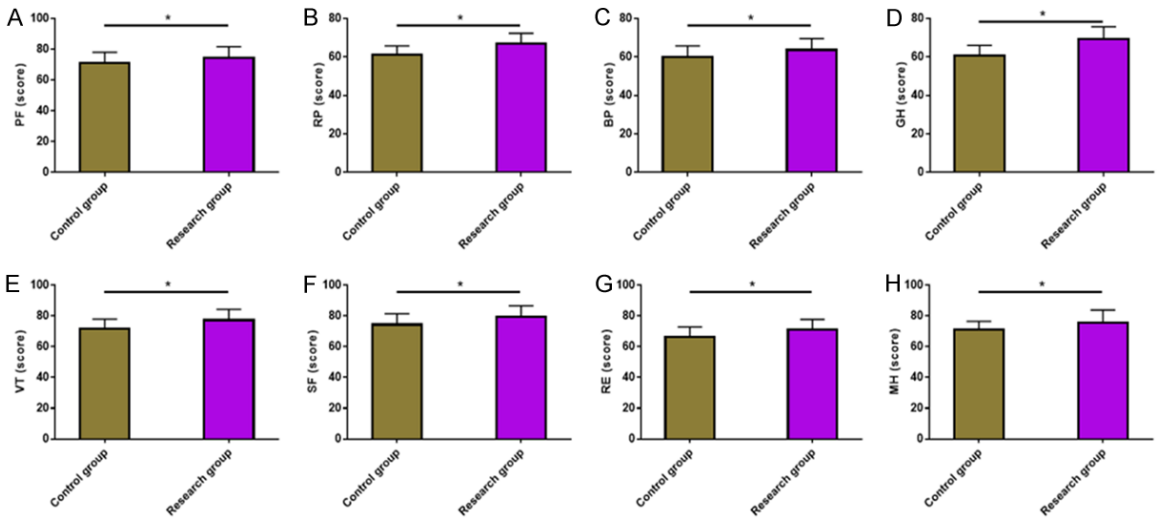

Figure 4. Effect of propranolol (Prop) plus methimazole (MMI) on quality of life of HT patients. A. The research group showed statistically higher physical functioning (PF) scores than the control group. B. The research group showed statistically higher role-physical (RP) scores than the control group. C. The research group showed statistically higher bodily pain (BP) scores than the control group. D. The research group showed statistically higher general health (GH) scores than the control group. E. The research group showed statistically higher vitality (VT) scores than the control group. F. The research group showed statistically higher social functioning (SF) scores than the control group. G. The research group showed statistically higher role-emotional (RE) scores than the control group. H. The research group showed statistically higher mental health (MH) scores than the control group. Note: *P<0.05.

71.70%), indicating the ability of the combined intervention to validly enhance clinical efficacy. As far as the treatment safety was concerned, a lower but not significantly different AR rate was determined in the Res compared with the Con (9.26% vs. 16.98%), suggesting that the safety of the combination therapy remained relatively stable. MMI is generally well tolerated. In addition, Lee et al. pointed out that Prop can provide safe and effective preparation for patients with thyrotoxicosis during the perioperative period [22, 23]. Due to the excellent performance of the two drugs in terms of safety when used alone, there is little room for improvement in the safety of their combined intervention in HT, which is consistent with our study results.

Further, we measured three TF indicators, namely, FT3, FT4 and TSH, in both cohorts, and found markedly lower FT3 and FT4 while statistically higher TSH in the Res compared with the Con. There is a positive correlation between the FT3/FT4 ratio and the total thyroid volume, and the significant decrease of FT3 and FT4 in our study suggests the relief of HT symptoms and the recovery of TF [24]. Besides, the quantification of serum TSH is a major measurement to determine whether HT treatment can be discontinued, and the decrease of TSH will increase the risk of death in HT patients [25]. The rise of post-treatment TSH in the Res in this study suggests that the combined treatment has a positive effect on the recovery of TF. As for hepatic function indicators, the Res showed evidently lower post-treatment ALT and AST than the Con, indicating that Prop + MMI had a better effect on hepatic function recovery than single drug treatment. In the report of Ding et al. [26] on Prop and liver cirrhosis, Prop prevented liver injury and fibrosis, and occupied a place in the first-line treatment of patients with chronic liver disease, which is consistent with our findings. Furthermore, through multivariate analysis, we learned that AST was a risk factor for treatment ineffectiveness in patients. AST levels in the Res using the combination therapy were more effectively controlled, which greatly reduced the risk of ineffective treatment. In the above results on efficacy, the Res with lower AST levels had a higher ORR, which can be mutually validated. Finally, we evaluated the influence of Prop + MMI on patients' QoL from eight aspects (PF, RP, etc.). The Res showed higher QoL scores in all dimensions than the Con, demonstrating that Prop + MMI therapy has more advantages in improving HT patients' QoL compared with MMI alone.

Although this study confirmed the effectiveness of Prop + MMI in improving ORR and QoL, reducing ARs, and enhancing TF and hepatic function in HT patients, there are still room for improvement. First, due to the fact that only 107 cases were included, we need to include more cases to improve the accuracy of the research results. Second, due to the absence of patient follow-up, a 6-12-month follow-up can be supplemented in future studies to observe disease recurrence in patients. In addition to addressing the above two deficiencies, the treatment plan will be constantly improved in future research to facilitate patient recovery.

Conclusion

To sum up, Prop plus MMI is effective and safe in treatment of HT patients, which provides an effective treatment plan for the rehabilitation of HT patients.

Disclosure of conflict of interest

None.

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