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# Efficacy and safety of methimazole ointment for patients with hyperthyroidism

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ABSTRACT

Oral methimazole has been widely used to treat hyperthyroidism, but its usage is restricted by its adverse systemic effects. The aim of this study was to investigate the efficacy and safety of methimazole ointment for the treatment of hyperthyroidism. One hundred forty-four subjects with hyperthyroidism were initially enrolled. These patients were initially divided into two groups and given the following treatments for 12 weeks: patients in group A received 5% methimazole ointment applied to the skin around the thyroid and an oral placebo; and patients in group B received methimazole tablets and placebo ointment. One hundred thirty-one subjects were included in the final analysis. Therapeutic efficacy was assessed via the levels of free triiodothyronine and thyroxine in the serum and by biweekly monitoring of the symptoms of thyrotoxicosis. Adverse effects were recorded. Fifty-nine (89.40%) patients in group A and 57 (87.69%) patients in group B were euthyroid and experienced alleviation of thyrotoxicosis symptoms (complete control; $p > 0.05$). The median times required to achieve complete control for the patients in the two groups were 6.5 weeks and 6.4 weeks for groups A and B, respectively ($p > 0.05$). Systemic adverse effects (e.g., rash, liver dysfunction, leucopenia, etc.) were significantly less common in group A (1.5%) than in group B (12.3%; $p < 0.05$). This study showed that methimazole ointment has a clinical efficacy similar to that of oral tablets, but methimazole ointment caused fewer systemic adverse effects in patients with hyperthyroidism.



## 1. Introduction

Hyperthyroidism, a subcategory of thyrotoxicosis, is caused by excessive production of thyroxine (T4) and triiodothyronine (T3) and affects approximately 2% of women and 0.2% of men worldwide (Kahaly et al., 2011). Among the causes of hyperthyroidism, Graves' disease (diffuse toxic goiter) is the most common and accounts for as many as 50–80% of cases of hyperthyroidism in different regions of the world (Weetman, 2000; Brent, 2008). Other cases of hyperthyroidism are mainly caused by toxic nodular goiter or adenoma (Singer et al., 1995).

Antithyroid medications inhibit the formation and coupling of iodotyrosines in thyroglobulin, which is necessary for thyroid hormone synthesis. In China, anti-thyroid drugs (ATDs) are used as the first-line therapy for hyperthyroidism.

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Although oral methimazole has been widely used as an ATD for a long time, its usage is usually restricted by its systemic adverse effects (Karras et al., 2010). Rivkees et al. (2010) reported that methimazole is associated with a low but real risk of side effects, such as pruritus and hives, in children. Ziora et al. (2006) also reported that methimazole induced epidermal necrolysis in a 12-year-old girl. In the adult population, oral methimazole cholestatis has been reported to be associated with liver injury (Woeber, 2002; Yang et al., 2012).

Methimazole ointment is a new transdermal absorption preparation in which the active components infiltrate the thyroid and cure hyperthyroidism. It has been shown that methimazole ointment is an effective and safe alternative to conventional oral formulations in cats (Sartor et al., 2004; Lecuyer et al., 2006; Hill et al., 2011). In this study, we compared the efficacy and safety of methimazole ointment with orally administered methimazole in the treatment of hyperthyroidism and explored a new therapeutic method for the treatment of hyperthyroidism.

## 2. Subjects and methods

### 2.1. Subjects

This trial was approved by the Ethics Committees of Fudan University, and all patients provided written informed consent before the trial. Three medical centers (the Department of Endocrinology, Huashan Hospital, Fudan University; the Department of Endocrinology, Changzheng Hospital, Second Military Medical University; and Jinan Central Hospital, Jinan, Shandong) participated in this randomized, double-blind, double-analog, parallel controlled trial. The enrolled patients were free of FT3 and FT4 serum levels above the upper limits of the normal range due to untreated Graves' disease or toxic nodular goiter or relapsed disease after discontinued oral ATD (methimazole or propylthiouracil) or thyroidectomy. Patients who had previously been treated with an oral ATD were only enrolled if they had undergone a two-week wash-out period. Thyrotropin receptor antibody (TRAb), 99 mI scintigraphy, and I-131 uptake were used for the differential diagnoses of thyrotoxicosis due to thyroiditis when necessary. The exclusion criteria included thyrotoxicosis due to painless thyroiditis, subacute thyroiditis and other destructive forms of thyroiditis, previous isotope treatment for Graves' disease, pregnancy, lactation, and treatment with β-blockers, sedatives, thyroxine pills, or glucocorticoids. Treatment was stopped for any patient who experienced serious adverse effects of treatment, such as liver dysfunction or leukopenia (leukocyte numbers lower than 3000 $mm^{-3}$).

### 2.2. Methodology

Subjects with hyperthyroidism ($n = 144$, 18–65 years old) were enrolled in a 12-week trial. Subjects were randomly divided into group A ($n = 72$) or group B ($n = 72$). The group A subjects were given a placebo tablet and 5% methimazole ointment at a dosage of 0.2 g/d (equivalent to a 10-mg methimazole tablet) applied to the skin around the thyroid three times daily. Subjects in group B received 10-mg methimazole tablets three times daily and a placebo ointment. Once symptoms of thyrotoxicosis were relieved, as indicated by normal FT3 and FT4 levels, the administration frequencies for patients in both groups were changed to twice daily, and, subsequently, to a single daily dose based on the alleviation of pathogenic conditions.

During the trial period, all subjects were evaluated biweekly for symptoms of thyrotoxicosis (e.g., palpitations, heat intolerance, body weight reduction, trembling of hands, etc.), serum levels of FT3, FT4, and TSH (thyroid stimulating hormone/thyrotropin), and blood and liver function. Complete control was indicated by the relief of the symptoms of thyrotoxicosis and the normalization of FT3 and FT4 levels (euthyroidism); partial control was indicated by improvement in thyrotoxicosis symptoms and decreased FT3 and FT4 levels that remained above the normal range; and inefficacy was indicated by a lack of improvement in either thyrotoxicosis symptoms or FT3 and FT4 levels. Adverse events included systemic adverse effects such as drug rash, liver dysfunction, leukopenia, gastrointestinal reaction, arthritis, calvities, etc., and local adverse effects included dermal lesions and paresthesia at the drug application area. Serum FT3 and FT4 and TSH levels were measured using time-resolved fluoroimmunoassay. The normal reference ranges were as follows: FT3, 3.8–6.8 pmol/L; FT4, 8.7–17.3 pmol/L; and TSH, 0.3–4.5 mIU/L.

### 2.3. Drugs

Methimazole ointment (5%; 0.5 g/10 g, batch number: 990220) was obtained from Qilu Pharmaceutical Factory (Shandong, China). Methimazole tablets (5 mg, batch number: 980402) were provided by the Dezhou Pharmaceutical Factory (Shandong, China). The oral and topical placebos were provided by Qilu Pharmaceutical Factory (Shandong, China).

### 2.4. Statistical analyses

Continuous data are presented as the means ± the standard deviations and numerical data are presented as quantities or percentages. Student's *t*-tests and $\chi^2$ tests were applied to continuous data (a natural logarithm transformation was performed on non-normally distributed data before *t*-tests) and numerical data, respectively. $P < 0.05$ was considered to be statistically significant.

## 3. Results

### 3.1. Characteristics of subjects

One hundred forty-four subjects were originally enrolled in this trial, of which 131 (91.0%) completed the trial. Thirteen patients withdrew from the trial for personal reasons that did not included inefficacy or adverse events; one subject in the control group withdrew because of surgery for hyperthyroidism; 6 subjects from group A and 6 subjects from group B withdrew due to mild skin rashes, and the other patients were lost during the follow-up. The numbers of subjects lost during the follow-up were not significantly different between the two