Control of Graves' Hyperthyroidism with Very Long-Term Methimazole Treatment: A Clinical Trial

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Research article

Keywords: Graves' disease, methimazole, hyperthyroidism

Posted Date: July 27th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-41877/v1

Version of Record: A version of this preprint was published on January 14th, 2021. See the published version at https://doi.org/10.1186/s12902-020-00670-w.

Abstract

Background: Long-term antithyroid drugs therapy has become one of the options for treatment of Graves' hyperthyroidism. The aim of this study was to compare thyroid status in those who discontinued methimazole (MMI) treatment after 12.8 years with those who continued MMI as long as 24 years.

Methods: Fifty nine patients with Graves' disease on long-term MMI for 14.2±2.9 years were recruited; 32 patients (54%) decided to discontinue MMI and 27 (46%) preferred additional years of MMI treatment. All patients were followed for a mean of 6 additional years.

Results: Of 27 patients who continued MMI, 16 and 11 subjects completed median of 20 and 24 years of MMI treatment, respectively. Suppressed serum thyrotropin (TSH) was not observed in any patient after seventh years of treatment. Serum free thyroxine, triiodothyronine, TSH and TSH receptor antibody concentrations remained normal up to the length of the study. Mean daily dose of MMI to maintain TSH in the reference range decreased gradually and reached to 2.8±1.7 mg by 24 years of MMI treatment. No adverse reaction related to MMI occured during additional years of therapy. In 32 patients who discontinued MMI, hyperthyroidism relapsed in 6 patients (19%), one left follow-up and 25 (78%) remained euthyroid during the study.

Conclusions: Long-term low dose MMI treatment may be a lifelong effective and safe therapeutic modality in patients with Graves' hyperthyroidism for prevention of relapse.

Trial registration: IRCT201009224794N, 2010-10-25. Retrospectively registered.

www. IRCT.IR/Trial/5143.

Introduction

Antithyroid thionamide drugs (ATDs) have become the treatment of choice for Graves' disease (GD) in the United States, and majority of patients in other countries worldwide [1–3]. The major drawback of ATD therapy is its 20–70% recurrence rate of hyperthyroidism following discontinuation of the traditional 12–18 month treatment [4]. Serum thyrotropin (TSH) receptor antibody (TRAb) concentration, one major predictor of GD relapse, may fluctuate or remain positive in many patients with GD following ATD withdrawal and median time to remission may last as long as 6.8 years [5]. Hence, a few studies from different regions of the world have adopted the long-term continuous ATD therapy [6–10]; based on findings of a meta-analysis, remission rate increases by 16% for each additional year of ATD therapy after 24 months of ATD treatment [11]. These findings indicate that failure to attain normal TRAb concentrations after conventional 12–18 months of ATD treatment does not rule out the possibility of remission over a long-term ATD therapy [12]; therefore, long-term treatment of Graves' hyperthyroidism has become an option in international societies recommendations [4, 13]. A recent randomized clinical trial reported that 5-year continuous methimazole (MMI) therapy is accompanied with 84% remission up to 4 years after drug

withdrawal [14]. However, the optimal duration of ATD therapy is still debatable. Likewise, details of clinical and biochemical changes in those with ATD treatment > 10–15 years are scarce. In the present study, we aimed to compare thyroid status in patients who discontinued MMI treatment after 12.8 years with those who continued MMI therapy for as long as 24 years.

Methods

The study protocol was approved by the ethics committee of the Research Institute for Endocrine Sciences and all patients gave written informed consent.

This study is an extension of long-term methimazole (LT-MMI) treatment of patients with GD [7]. From March 1987, all patients with recurrent GD who had ongoing long-term methimazole (LT-MMI) therapy, as part of a clinical trial entitled "*Towards Outstanding Hyperthyroid care Induced by anthithyroid Drugs*" (TOHID study), registered in the Iranian Registry of Clinical Trials (www. IRCT.IR/Trial/5143) were recruited. The aim of previous study was to compare the effectiveness of long-term continuous MMI therapy with radioiodine (RAI) treatment in patients with GD; 239 patients with recurrence of hyperthyroidism after a conventional 12–18 months of ATD treatment were divided into MMI and RAI groups. The diagnosis of Graves' hyperthydoidism was based on clinical findings of hyperthyroidism with or without Graves' orbitopathy, serum TSH < 0.4 mU/L, free thyroxine (fT4) > 23 pmol/L and/or serum triiodothyronine (T3) > 200 ng/dL, elevated TRAb levels > 1.75 IU/L and diffuse goiter without nodularity on technetium scintigraphy. Patients were prescribed 20–30 mg MMI for the first month and titration method was used to maintain serum fT4 between 10–23 pmol/L and serum TSH between 0.4-5.0 mU/L. Patients were visited monthly for the first 3 months of therapy and every six months thereafter. During each visit, complete history and a review of symptoms were documented and physical examination, in particular related to thyroid size and its function was performed. All possible adverse effects due to ATD therapy were ascertained. Cell blood count, serum levels of fT4, T3, TSH, alanine aminotransferase and aspartate aminotransferase were measured at baseline. At each visit, the dose of methimazole was adjusted to maintain serum fT4 and T3 concentration in the middle range of normal values and TSH in the reference range.

Procedures

For this study, all 59 patients who had been on LT-MMI treatment for 14.2 ± 2.9 years were recruited and informed about advantages and disadvantages of MMI withdrawal versus MMI continuation for additional years. They were given the choice of either discontinue MMI treatment or continue LT-MMI therapy; 32 patients (54%) decided to discontinue MMI and 27 (46%) preferred continuous LT-MMI treatment (Fig. 1). All patients were followed every three to six months for an additional six years..

Laboratory measurements

Between 2001 and 2005, serum fT4 and T3 were measured by radioimmunoassay kits from DiaMetra, Milan, Italy and serum TSH by immunoradiometric assay using kits from Izotop (Budapest, Hungary). Serum TRAb concentration was measured by enzme-linked immunoabsorbent assay (Bio Vendor Laboratory Medicine Inc., Czech Republic). Subsequently, all analyses were determined by electrochemiluminescence immunoassay (Roche Diagnostic GmbH, Mannheim, Germany). Interassay and intra-assay coefficients of variation of all tests were < 6.1% and < 9.1%, respectively.

Definitions

Thyroid function status was defined as follows: Euthyroidism, TSH 0.4-5.0 mU/L; hypothyroidism, TSH > 5.0 mU/L and fT4 < 9 pmol/L; subclinical hypothyroidism, TSH > 5.0 mU/L and fT4 9–23 pmol/L; hyperthyroidism, TSH < 0.4 mU/L and fT4 > 23 pmol/L and/or T3 > 200 ng/dL and subclinical hyperthyroidism, TSH < 0.4 mU/L and fT4 9–23 pmol/L and T3 80–200 ng/dL.

Outcomes

The primary outcome of the study was sustained euthyroidism during the additional six years of follow-up. Key secondary outcomes were the occurrence of both clinical and subclinical hyper- and hypothyroidism during the length of study. Assessment of safety of MMI therapy was performed by observation of adverse events during the treatment.

Statistical Analysis

Data are reported as mean ± SD for continuous and number (percentages) for categorical variables. Significant differences were assessed by Student's t, Mann-Whitney, Chi-square and Fisher exact tests. Time to relapse of hyperthyroidism after MMI withdrawal was compared using Kaplan-Meier curves and log-rank test was used to compare survival curves. Statistical analysis was performed by SPSS 20 (SPSS Inc., Chicago, IL) and $p < 0.05$ was considered significant.

Results

Baseline characteristics of two study groups are shown in Table 1. There were no significant differences in age, sex distribution, smoking status, goiter size and serum concentrations of fT4, T3, TSH and TRAb and daily MMI dosage at the time of this study entry between those who continued versus stopped MMI treatment. Nonetheless, patients who continued MMI therapy had received MMI for longer duration as compared to those who discontinued MMI (15.6 ± 1.9 vs. 12.8 ± 4.0 years, respectively).

Table 1
Baseline Characteristics of two study groups

Variables	Continued MMI (n = 27)	Discontinued MMI (n = 32)
Age, year	53.1 ± 19.8	49.7 ± 12.4
Female, n (%)	19 (70)	22 (69)
Goiter grade, n (%)		
0 or 1	9 (33)	10 (31)
2	18 (67)	22 (69)
Current smoking, n (%)	4 (15)	5 (16)
fT4, pmol/L	16.1 ± 2.4	15.8 ± 2.6
T3, ng/dL	125 ± 21	132 ± 26
TSH, mIU/L	3.0 ± 0.6	2.9 ± 1.2
TRAb, IU/L	1.3 ± 0.6	1.1 ± 0.7
MMI dose, mg/day	3.4 ± 1.1	3.8 ± 1.2
Duration of MMI therapy, years*	15.6 ± 1.9	12.8 ± 4.0

Abbreviations: MMI, methimazole; fT4, free thyroxine; T3, triiodothyronine; TSH, thyrotropin; TRAb, TSH receptor antibody.

*P-value < 0.001.

Continued MMI group. At the start of the current study, 27 patients including 19 females and 8 males of this group were 53.1 ± 19.8 years old and have already been on 15.6 ± 1.9 years of LT-MMI therapy. By the end of the study, 16 and 11 patients had completed median of 20 and 24 years of MMI treatment, respectively. Figure 2 shows serum concentrations of TSH and MMI dosages used to maintain euthyroidism during 24 years of continuous LT-MMI treatment. After 3 months of MMI treatment, serum TSH increased to normal range in 12 (44%) of patients. By 4 years after LT-MMI, only 4 (15%) had at least one suppressed TSH during the follow-up. Seven years after the start of LT-MMI, no suppressed TSH was observed and TSH remained in normal range in all patients up to 24 years following MMI treatment. Serum fT4 decreased from a mean of 39.1 ± 9.2 pmol/L at the baseline to 16.1 ± 25, 16.3 ± 2.4 and 16.2 ± 2.2 pmol/L at 15, 20 and 24 years after LT-MMI treatment; the decreasing trend of fT4 concentration from the first to the 24th year of treatment was significant ($p < 0.001$). Mean serum T3 concentration decreased from 401 ± 126 ng/dL to 125 ± 18, 123 ± 17 and 124 ± 17 ng/dL at 15, 20 and 24 years of treatment; the decreasing trend of T3 from the first to the 24th year of treatment was also significant ($p < 0.001$) (Table 2). Mean serum concentration of TRAb was 15 ± 8 IU/ml at baseline and decreased to 1.2,

1.1, 1.0 and 0.9 IU/ml after 2, 8, 16 and 24 year of LT-MMI therapy (Fig. 2). After 6 years of continuous MMI therapy, none of the patients had TRAb levels above 1.7 IU/ml.

Table 2
Serum concentrations of fT4 and T3 in Graves' patients during 24 years of continuous long-term MMI treatment

	Baseline	Years of very long-term MMI treatment					
		1	5	10	15	20	24
Number	27	27	27	27	27	16	11
Serum fT4 (pmol/L)*	39.1 ± 9.2	16.9 ± 2.3	16.3 ± 2.3	16.2 ± 2.4	16.1 ± 2.5	16.3 ± 2.4	16.2 ± 2.2
Serum T3 (ng/dL)*	401 ± 126	135 ± 18	127 ± 18	129 ± 21	125 ± 18	123 ± 17	124 ± 17

*Values are mean ± standard deviation.

fT4, free thyroxine; T3, triiodothyronine; MMI, methimazole.

Mean dose of MMI was 9.8 ± 1.0 mg daily after three months of therapy and decreased to 5.4 ± 1.6 mg per day by the end of the first year of MMI treatment. Daily doses of MMI to maintain euthyroidism were gradually lowered to ≤ 5 mg by 10 years after the start of study in all patients. Mean daily dose of MMI decreased to 2.8 ± 1.7 mg daily after 24 years of LT-MMI treatment (Fig. 2); 5 of 11 patients required ≤ 2.5 mg daily MMI to remain euthyroid. None of the subjects showed recurrence on therapy. Except for minor adverse reactions in the first few months of therapy, no adverse reaction related to MMI occurred during 24 years of follow-up.

Discontinued MMI group : Twenty-two females and 10 males, aged 49.7 ± 12.4 years who were on LT-MMI for 12.8 ± 4.0 years, decided to discontinue MMI treatment. Trends of changes in serum concentrations of fT4, T3, TSH, TRAb and MMI dosage during 12.8 years of MMI treatment was not different from patients who decided to continue MMI treatment. Of these 32 patients, one left follow-up; overt hyperthyroidism relapsed in six patients during 6 years of follow-up. Two, two, one and one patients recurred at 6, 12, 32 and 50 months after discontinuation of MMI treatment. Other 25 (78%) patients in this group had normal serum concentrations of fT4, T3 and TSH and serum TRAb < 1.7 IU/ml during 6 additional years of follow-up. Figure 3 shows Kaplan-Meier curve for relapse of hyperthyroidism in patients who continued and those who discontinued MMI after 6 years of follow-up. There was no relapse in the first group and 19% relapse in the second group (log rank p = 0.019).

Discussion

The present study demonstrates continuous decline in serum fT4 and T3 concentrations and rise in serum TSH during 24 years of MMI treatment accompanied by continuous normalization of serum TRAb

and gradual decrease in daily doses of MMI to maintain euthyroid state. We have not found any episode of exacerbation of hyperthyroidism during 24 years of follow-up in patients treated with continuous LT-MMI treatment. In addition, no adverse events occurred after the first year up to 24 years of continuous MMI treatment; findings in agreement with a recent systematic review on safety of long-term ATD treatment [15].

Several studies have reported that in patients who experience relapse of hyperthyroidism after 12–18 months of ATD therapy, remission may be attained by additional 5 to 10 years of treatment [8, 11, 14] Therefore, some patients may prefer continuous lifelong MMI therapy for management of Graves' hyperthyroidism. In the present study, majority of patients who discontinued treatment after mean 12.8 years of continuous MMI stayed euthyroid during 6 years of follow-up; only 19% experienced relapse of hyperthyroidism. Results are similar to other studies reporting increased remission rates in Graves' hyperthyroidism after long-term MMI therapy, compared to the conventional 12–18 month ATD therapy [11]. A proposed justification for the observed results of LT-MMI therapy is related to immunomodulatory properties of MMI, an effect which is not yet fully understood [16].

Strengths of this study are the longest follow-up of patients with continuous MMI therapy and demonstration of the point of normalization of TSH in all treated patients. In addition, findings emphasize the fact that many patients require < 2.5 mg MMI daily to remain euthyroid and there is paucity of adverse events on low dose LT-MMI treatment. Following limitations are noteworthy; first, study arm was selected by each patient choice; therefore, study enrollment was not randomized and possibilities of biases may exist. Second, the study population is from an iodine-sufficient west-Asian country which may not be generalizable to other regions. Third, those who continued very LT-MMI treatment were already 2.8 years more on MMI than patients who discontinued medication.

In conclusion, long-term low dose MMI treatment may be prescribed effectively, even throughout the patients' life for those with Graves' hyperthyroidism who do not desire ablation treatment. Low cost, safe and effective drugs are prescribed as lifelong therapy for some specific diseases, such as epilepsy, inflammatory bowel disease, hypothyroidism and Addison disease and MMI may be added to the list for lifelong control of Graves' hyperthyroidism. It is noteworthy that final decision to select mode of treatment in GD is according to physicians and patients decisions and some may prefer definitive therapy of hyperthyroidism by ablation over long-term A treatment.

Declarations

Ethics approval and consent to participate:

The study protocol was approved by the ethics committee of the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

All study subjects provided a written informed consent.

Consent to publish:

Written informed consent for publication was obtained.

Availability of data and materials:

The datasets generated and/or analysed during the current study are not publicly available due to repository at a private clinic but are available from the corresponding author on reasonable request.

Competing interests:

All authors have no conflicts of interest to declare.

Funding:

There is no funding support.

Authors’ Contributions:

F.A.: Study design, data collection, analyses and interpretation, and writing of the manuscript draft. A.A.: Data collection and interpretation, and writing of the final manuscript. H.A.: Data interpretation and writing of the final manuscript.

Acknowledgements:

Not applicable.

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Figures

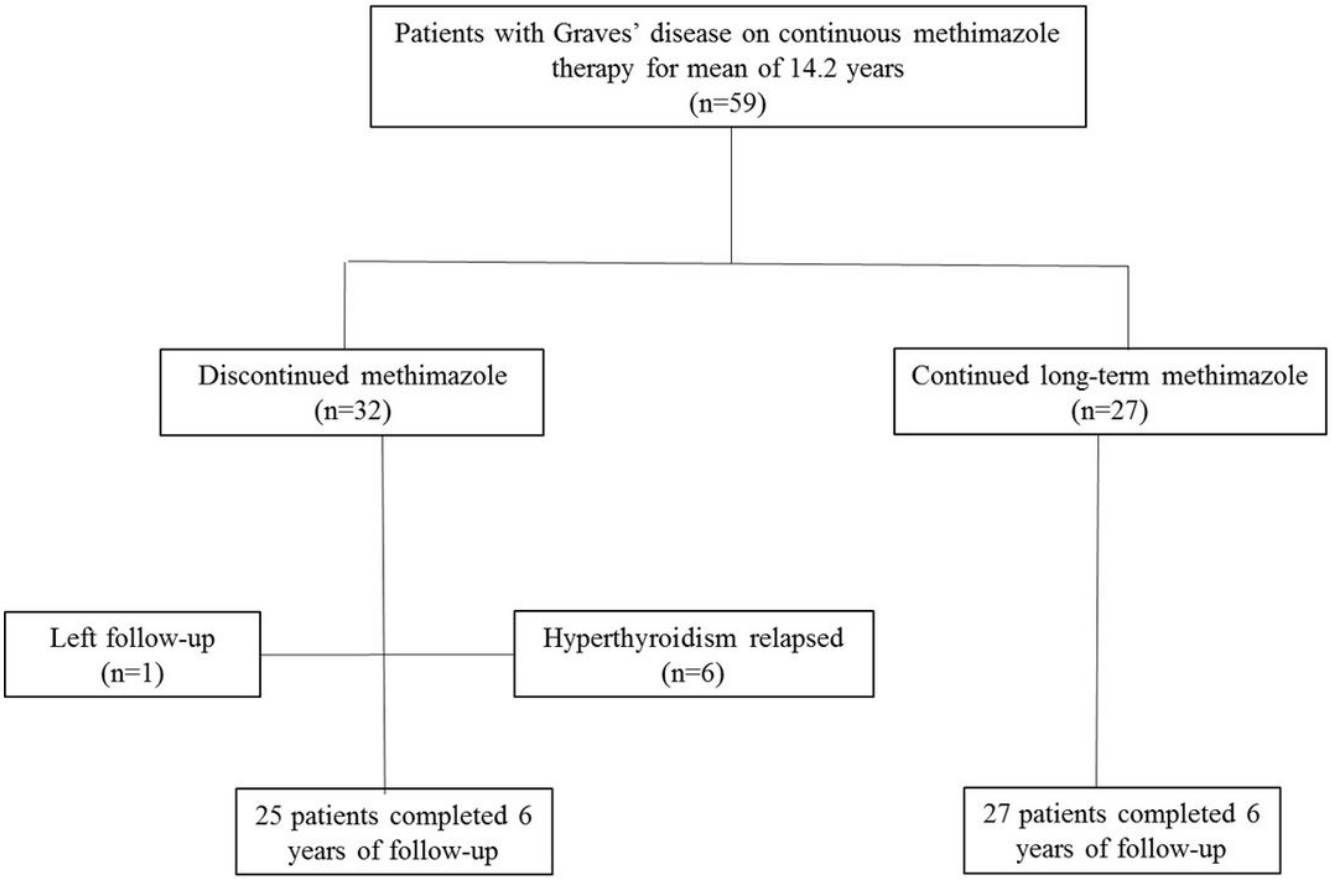
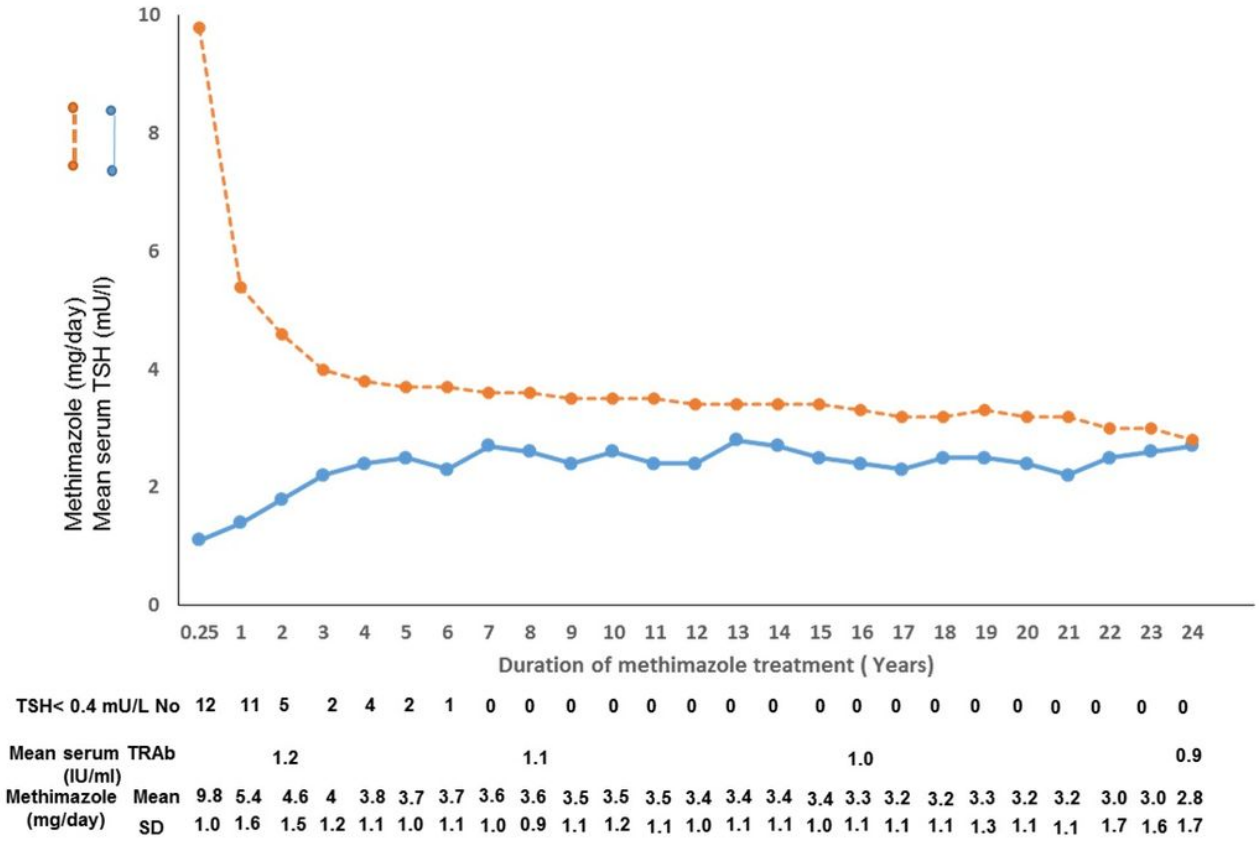


Figure 1

Figure 1

Enrollment and follow-up of study patients.



TSH< 0.4 mU/L No		12	11	5	2	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean serum (IU/ml)	TRAb			1.2						1.1								1.0							0.9
Methimazole (mg/day)	Mean	9.8	5.4	4.6	4	3.8	3.7	3.7	3.6	3.6	3.5	3.5	3.5	3.4	3.4	3.4	3.4	3.3	3.2	3.2	3.3	3.2	3.2	3.0	3.0	2.8
	SD	1.0	1.6	1.5	1.2	1.1	1.0	1.1	1.0	0.9	1.1	1.2	1.1	1.0	1.1	1.1	1.0	1.1	1.1	1.1	1.3	1.1	1.1	1.7	1.6	1.7

Figure 2

Figure 2

Serum concentrations of TSH and TSH receptor antibody (TRAb) and mean daily doses of methimazole during 24 years of continuous methimazole treatment. All 27 patients continued therapy for at least 15 years, 16 patients until 20 years and 11 patients until 24 years. Daily doses of methimazole to maintain euthyroidism decreased to mean of 3.4±1.0 and 2.8±1.7 mg daily, by 15 and 24 years of therapy; suppressed serum TSH was not seen in any patient after 7 years of treatment. Serum TRAb was normal in all patients during methimazole treatment.

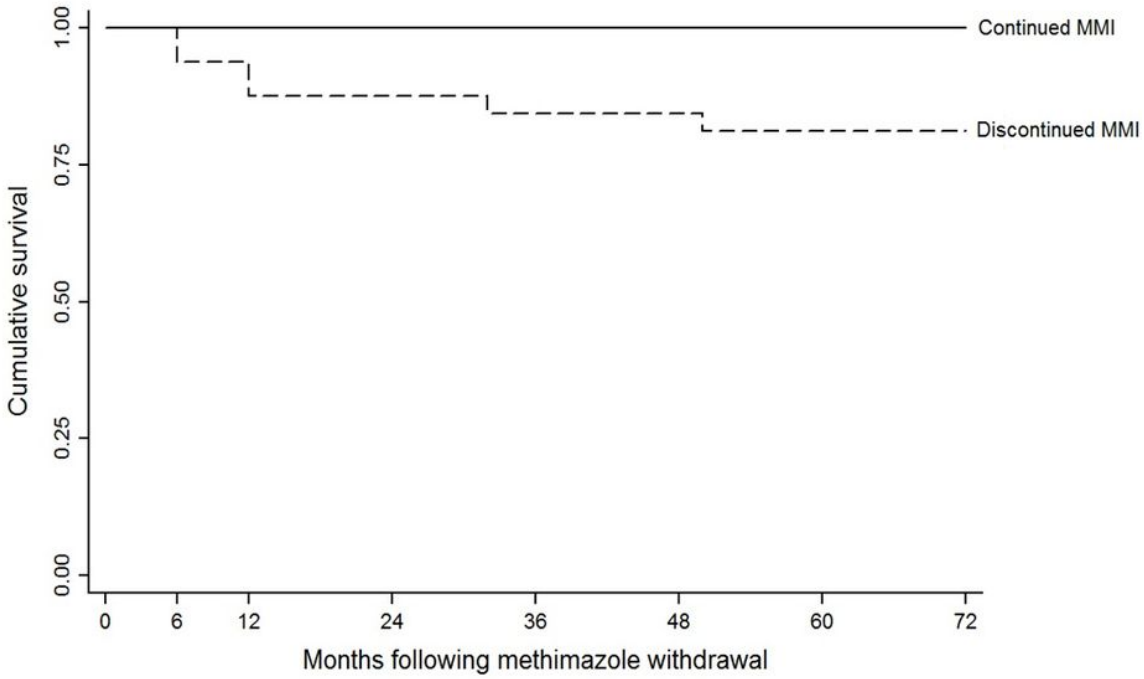


Figure 3

Figure 3

Kaplan-Meier curve for relapse of hyperthyroidism in patients with Graves' disease after long-term methimazole (MMI) treatment. No recurrence was observed in patients who continued MMI; hyperthyroidism relapsed in 19% of those who discontinued MMI therapy.

Supplementary Files

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- CONSORT2010Checklist.doc