The outcome of ^{131}I treatment in Graves' patients pretreated or not with methimazole

Abstract

Despite extensive use of iodine-131 (^{131}I) treatment for Graves' hyperthyroidism, the optimal regimen of pretreatment with antithyroid drugs is still a matter of discussion. Our aim was to evaluate the success of ^{131}I treatment in patients with Graves' disease without and with pretreatment with methimazole (MMI). In a prospective randomized study 156 patients with Graves' disease were treated with fixed activity of 550MBq ^{131}I. First group of 59 patients received only ^{131}I. The second group of 50 patients received MMI which was stopped seven days before ^{131}I. The third group of 47 patients received MMI until ^{131}I application. Patients were followed clinically and biochemically 1, 3, 6 and 12 months after ^{131}I treatment. Absorbed dose of ^{131}I and thyroid volume were measured in each patient. Our result showed that ^{131}I treatment success after twelve months was equally effective in the first and second group (96.6% and 96%, respectively), while in the third group, success was significantly lower (63.8%). Accordingly, the absorbed dose of ^{131}I was significantly higher in the first and in second group (144±104Gy and 164±107Gy, respectively), and lower in the third group (105±58Gy) Thyroid volume gradually decreased without any significant difference between the three groups. In conclusion, our study provides evidence that application of ^{131}I is equally effective in the nonpretreated with MMI group and in the group discontinuing MMI one week before ^{131}I treatment, and it is more effective in these two groups as compared to the group in which pretreatment with MMI was administered till the day of ^{131}I application.

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Edvard Pirnat MD, PhD,
Katja Zaletel MD, PhD,
Simona Gaberšček MD, PhD,
Sergej Hojker MD, PhD

Department of Nuclear Medicine, University Medical Centre, Ljubljana, Slovenia

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Correspondence address:
Edvard Pirnat, Department of Nuclear Medicine, University Medical Centre, Ljubljana, Slovenia,
E-mail: edi.pirnat@kclj.si,
Tel: +386 1 230 19 71,
Fax: +386 1 522 22 37

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Introduction

Radioiodine (^{131}I) is extensively used for the treatment of Graves' hyperthyroidism. In spite of recently published data showing no increase of thyroid hormone levels after ^{131}I application [1-3], antithyroid drugs are frequently prescribed before ^{131}I treatment in order to prevent worsening of hyperthyroidism [4, 5]. On the other hand, data representing the influence of pretreatment with antithyroid drugs on the efficacy of ^{131}I treatment are controversial. Some studies reported a higher rate of ^{131}I treatment failure after pretreatment with antithyroid drugs [6-10], which others confirmed the opposite [11-16]. However, results are not easy to compare since studies substantially differ with respect to design, (prospective vs retrospective studies), cause of hyperthyroidism, regimen of pretreatment with antithyroid drugs and doses of the applied ^{131}I. The aim of our prospective randomized clinical study was to evaluate the success of treatment with the fixed activity of 550MBq ^{131}I in patients with Graves' disease without pretreatment compared to patients receiving different regimens of methimazole (MMI) pretreatment in an iodine sufficient region of Slovenia [17].

Patients and methods

Patients

We included 156 patients with the first reccurence of Graves' disease diagnosed by clinical and biochemical hyperthyroidism, estimated by the presence of thyroid stimulating hormone (TSH), thyroid receptor antibodies (TSAb), and diffuse goiter with hypoechogenic ultrasound (US) pattern. We excluded patients who were previously treated with radioiodine or thyroidectomy. The study was conducted at the Department of Nuclear Medicine of the University Medical Centre Ljubljana between January 2002 and May 2005. Local ethics committee approved the study. All patients gave their informed consent before ^{131}I treatment.

Methods

We measured TSH, free thyroxine (fT_4) and free triiodothyronine (fT_3) with direct chemoluminiscent immunoassay (Bayer Diagnostics, Tarrytown, New York, USA; normal values, 0.35-5.5mU/L, 11.5-22.7pmol/L and 3.5-6.5pmol/L, respectively). TSAb were measured by the first generation TRAK Assay (Brahms, Hennigsdorf, Germany; value >13U/L was considered positive). Goiter volume was estimated by US using standard formula a x b x c x 3,14 (pi value)/6 (a = length, b = depth, c = width of each lobe and isthmus in cm) [18]. Uptake of ^{131}I after 2, 4 and 24h was evaluated using tracer activity of 1.85MBq. For each patient, absorbed dose of ^{131}I was measured using a method of cumulated activity [19], and effective half life of therapeutic activity of ^{131}I, which was calculated by monoexponential decay function.

Treatment protocol

We divided Graves' patients into three groups. In the first group, 59 patients were treated only with ^{131}I (without MMI pretreatment), all receiving beta adrenergic blockers (propranolol 40-120mg per day). Patients treated for hyperthyroidism with MMI for 2-12 months (median value, 4 months and 5 months, respectively) before ^{131}I treatment were randomly divided in the second and third groups. In the second group of 50 patients, MMI (10mg per day) was stopped seven days before ^{131}I treatment. Forty seven patients in the third group received MMI (10mg per day) till the ^{131}I application.

All patients were treated with 550MBq of ^{131}I. Neither of the three groups received antithyroid drugs during the first month after ^{131}I. Patients were clinically examined and tested before ^{131}I treatment and following 1, 3, 6 and 12 months after. At each occasion, serum TSH, fT_3, fT_4 and TSAb were measured, while thyroid volume was estimated by US before and 1, 3 and 6 months after ^{131}I treatment. During follow-up failure of treatment was evaluated by the percentage of persistent hyperthyroidism. Euthyroid state (normal TSH, fT_3 and fT_4 levels) without antithyroid drugs, or hypothyroid state (increased TSH, normal or decreased fT_3 and fT_4 levels) were considered as a successful treatment outcome.

Statistical analysis

Clinical and biochemical characteristics of the three groups were compared with chi square test for qualitative variables or with Student's t test for quantitative variables. The outcome of ^{131}I treatment after 1, 3, 6 and 12 months was analyzed using chi square test. The relationship between the outcome of ^{131}I treatment and age, gender, TSH, fT_4, fT_3, TSAb before ^{131}I treatment, and absorbed dose of ^{131}I was assessed with Spearman's rank correlation procedure. We considered P was significant when <0.05.

Results

Characteristics of patients

Before ^{131}I treatment, the three groups did not differ with regard to age, gender, smoking habits, thyroid volume and TSAb (Table 1).

Treatment outcome

One month after ^{131}I application, no difference in ^{131}I treatment outcome between the three groups was observed (Fig. 1). Surprisingly, only 20% of patients treated with ^{131}I alone were still hyperthyroid one month after treatment. However, three months after ^{131}I we noticed significantly higher percentage of hyperthyroid patients in the third group receiving MMI till the ^{131}I application when compared with the second group chi square = 4.62, P = 0.03), but no significant difference between the first and the third group chi square = 1.72, P = 0.189). Additionaly, no difference in treatment success was observed between the first and the second groups of patients. Six months

Table 1. *Patients data before ^{131}I treatment*

Parameter	Group 1	Group 2	Group 3
No. of patients	59	50	47
No. of patients	51/8	42/8	42/5
Age, year (min - max)	46.8±13.8 (17-80)	43.5±11.0 (20-64)	47.1±13.1 (22-75)
Smokers %	32.2	29.8	27.1
fT4 before ^{131}I (pmol/L), mean±SD	38.0±17.8 *	20.4±9.1	18.9±13.2
fT3 before ^{131}I mean±SD	12.4±5.5 *	7.6±4.9	7.1±5.3
TSAb (U/L), median (min - max)	12.4±5.5 *	13 (1-101)	12 (1-102)
Goiter volume (mL), mean±SD	31.2±15.7	30.4±13.9	33.7±17.7

Group 1: without pretreatment; group 2: methimazole (MMI) stopped 7 days before ^{131}I application; group 3: MMI till the day of ^{131}I application; SD, standard deviation; AD, absorbed dose); *, P < 0.0001

As depicted in Table 2, ^{131}I-uptake after 2h was not significantly different between the three groups. After 4 and 24h, the ^{131}I-uptake was significantly lower in the third group (P < 0.05 and P < 0.01, respectively). Accordingly, the calculated effective half life of ^{131}I was significantly shorter in the third group than in the other two groups and absorbed dose of ^{131}I was significantly lower in the third group when compared with the other two groups (P < 0.001).

Table 2. *Uptake of ^{131}I after 2, 4, and 24h, effective t½. and absorbed dose of ^{131}I in the three groups*

Parameter	Group 1	Group 2	Group 3
^{131}I-uptake (%) after 2h	35.1 ±19.0	38.8±19.5	33.2±19.9
^{131}I-uptake (%) after 4h	48.0±20.1	50.8±18.4	39.8±19.6***
^{131}I-uptake 24h	69.6±18.9	73.4±15.3	54.1±20.3*
Effective $t_{½}$ (days) mean±SD	3.9±1.7	4.4±2.4	3.3±2.4**
AD of 131I mean±SD	144.1±104.8	164.5±107.3	105.5±58.7**

Group 1: without pretreatment; group 2: methimazole (MMI) stopped 7 days before ^{131}I application; group 3: MMI till the day of ^{131}I application; SD, standard deviation; Effective $t_{½}$, AD, absorbed dose); *, P < 0.0001;**, P < 0.01, ***, P < 0.05.

after ^{131}I treatment we observed significantly higher percentage of hyperthyroid patients in the third group when compared with the first and the second group chi square = 8.72, P = 0.0032, and chi square = 8.64, P = 0.0033, respectively).

Twelve months after ^{131}I treatment, we observed even higher percentage of hyperthyroid patients in the third group than in the first and in the second group chi square = 19.11, P < 0.0001, and chi square = 13.94, P = 0.0002, respectively). There was no difference in the ^{131}I treatment outcome between the first and the second group of patients, with only 3% and 4% of persistent hyperthyroidism, respectively.

Because of persistent hyperthyroidism, six patients in the third group received a second dose of ^{131}I six to nine months after the first one.

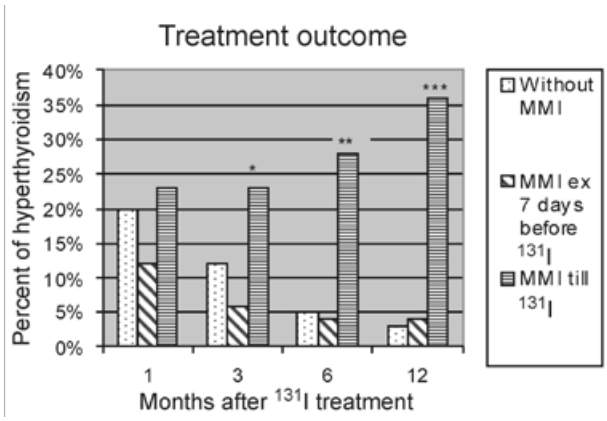

Figure 1. Treatment outcome in the three groups shown as a percent of hyperthyroid patients 1, 3, 6 and 12 months after ^{131}I. Asterisks represent significantly higher percent of hyperthyroidism in group 2 when compared with groups 1 and 2, *, P<0.05; **, P<0.005; ***, P<0.0005

When we estimated the relation between the absorbed dose and ^{131}I treatment outcome, more than 150Gy was proven to be successful in all patients as early as 6 months after treatment. With the absorbed dose between 100 and 150Gy, persistent hyperthyroidism was observed in 15% of patients, while the absorbed dose lower than 100Gy was associated with treatment failure in 25.4% of patients. The absorbed dose lower than 100Gy was more frequently measured in the third group compared to the first and second group (55.3%, 15%, and 15.4%, respectively; chi square = 4.89, P = 0.027).

Six months after ^{131}I application, treatment failure was associated with significantly lower absorbed dose (80.8±33.9Gy) and larger thyroid volume (44.6±19.9mL) compared to absorbed dose (148.9±97.6Gy) and thyroid volume (29.7±12.4mL) of successfully treated patients (P<0.001). No correlation between the outcome of ^{131}I treatment and age, gender, TSH, fT_4, fT_3 and TSAb before ^{131}I treatment in neither of three groups was found.

Thyroid volume

As shown in Figure 2, we observed a significant reduction of thyroid volume as soon as one month after ^{131}I application in all three groups (P<0.001). Afterwards, thyroid volume gradually decreased. Six months after ^{131}I application, the thyroid volume reduction was 73.3±14.3%, 78.1±7.7% and 76.3±12.8% in the first, second and third groups, respectively.

We found no correlation between the thyroid volume reduction and absorbed dose of ^{131}I or thyroid volume before ^{131}I treatment. Yet, in patients with successful ^{131}I treatment, a significantly higher volume reduction was observed six months after treatment than in patients with treatment failure (65.1±16.0% vs. 46.0±24.9%, P=0.025).

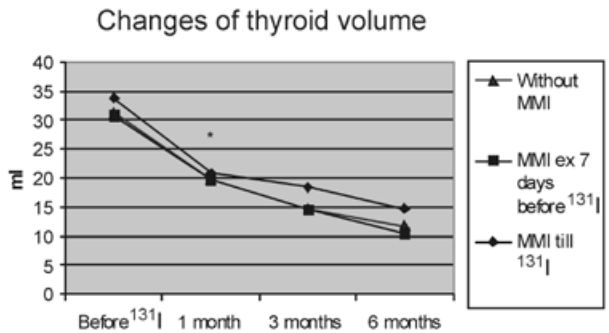

Figure 2. Changes of thyroid volume in the three groups, mean values are shown,* P<0.001 (compared with the value before ^{131}I application)

Discussion

Our results provide evidence that treatment with ^{131}I is highly effective and equally successful in patients not pretreated with MMI and in patients that discontinued MMI one week before treatment. In spite of being significantly more hyperthyroid before ^{131}I application, one month after treatment the percentage of hyperthyroidism in patients not pretreated with MMI did not differ significantly from that in MMI pretreated patients. As reported in our previous work no clinical exacerbation of hyperthyroidism was observed on the first month after application of **^{131}I** alone [3].

Regarding the outcome six and twelve months after treatment, similar success rates of more than 95% were observed in groups I and II. Comparable report by others on a smaller group of 61 patients with Graves' disease similarly showed equal outcome in patients treated only with ^{131}I and in patients were MMI was stopped four days before ^{131}I application [14]. However, the failure rate was 15.6% and 13.8%, respectively, which is much higher compared to our study (3% and 4%, respectively). Others in a very small group of 34 patients with Graves' disease showed that stopping MMI six days before ^{131}I treatment had similar success as no MMI pretreatment on one year success rate of ^{131}I treatment [16].

In concordance with previous studies, our group of patients treated with MMI till the day of ^{131}I application also presented with significant rate of treatment failure. A large prospective clinical study of 385 Graves' patients confirmed that stopping MMI two days before ^{131}I treatment resulted in a 50% increase of treatment success as compared to ^{131}I treatment carried out under MMI [20]. Earlier prospective clinical study of 78 Graves' patients revealed significantly lower uptake of ^{131}I and lower treatment success in a group of patients receiving MMI than in patients without treatment [21]. Also recently published meta-analysis confirmed that antithyroid drugs potentially increase rates of failure if they are given in the week before or after ^{131}I treatment [22].

Methimazole has been shown to influence ^{131}I kinetics by diminishing ^{131}I uptake and blocking ^{131}I organification, resulting in shortened ^{131}I effective half life and reduced absorbed dose of ^{131}I [6, 23]. Our data showed that MMI significantly reduces ^{131}I uptake, effective half life and absorbed dose. Others showed that the effective half life of ^{131}I was 1.6 days shorter and the absorbed dose of ^{131}I 22% lower in patients treated with MMI when compared with patients not receiving MMI [13]. Similarly, a retrospective clinical study including 555 hyperthyroid patients with Graves' disease or toxic nodular goitre showed significantly shorter effective half life of ^{131}I in patients treated with antithyroid drugs than in patients without such treatment [23]. Several studies indicate that stopping MMI few days before ^{131}I diminishes the effects of MMI. In a prospective clinical study including 77 patients with Graves' disease, effective half life of ^{131}I increased on average for 2.5 days after stopping MMI [24]. Significant increase of ^{131}I uptake and effective half-life was observed 3 days after withdrawal of MMI treatment in Graves' patients [25]. It has been indicated that three days of stopping MMI is long enough to restore the success of ^{131}I treatment and short enough to avoid the risk of exacerbation of hyperthyroidism [26]. Those data were confirmed by this study, since we demonstrated comparable percentage of ^{131}I uptake, effective half life of ^{131}I, absorbed dose of ^{131}I and a similar outcome of ^{131}I treatment in the group of patients where MMI was stopped seven days before ^{131}I application as in the group without MMI pretreatment.

Absorbed dose has proven to influence importantly on ^{131}I treatment success since positive outcome was observed in all patients receiving more than 150Gy. In previous studies higher absorbed dose has been reported to be required for successful outcome [27, 28]. As showed by others, the absorbed dose of 200Gy was associated with 80% success of ^{131}I treatment [27, 29]. Others reported 94% success of ^{131}I treatment in a group of 226 patients with Graves' disease without carbimazole treatment and with target absorbed dose of 250Gy [30]. Better success of ^{131}I treatment in our study at the lower absorbed dose compared to previously cited studies [27, 29, 30] could be attributed to higher iodine supply in our country. Since 1999, kitchen salt in Slovenia is iodinated with 25-30mg of potassium iodide per kilogram of salt, classifying our country as an iodine sufficient region [17]. Insufficient iodine supply is responsible for the development of thyroid autonomy [31] and autonomous thyroid tissue is more radioresistant compared to thyroid tissue in Graves' disease [4]. Therefore, we presume that higher absorbed dose is necessary for successful treatment of Graves' disease in iodine-insufficient areas.

As for thyroid volume, our data indicate that the reduction after ^{131}I treatment is not associated with the outcome. The data in the literature are scarce. However, the thyroid reduction has been also observed in a prospective randomized clinical study of 92 Graves' disease patients treated with 555MBq of ^{131}I or an activity calculated basis, in order to deliver 100Gy to the thyroid. Volume reduction was more than 70% one year after treatment and the bulk of this reduction was found within the first six months [32].

In conclusion, our study indicates that application of ^{131}I alone is equally effective with a cure rate of more than 95% in the nonpretreated group and in the group stopping MMI one week before ^{131}I treatment. Pretreatment with MMI till the day of ^{131}I application reduces the success of ^{131}I treatment by more than 30%. Application of **^{131}I** alone may be applied in most patients with Graves' hyperthyroidism.

The authors declare that they have no conflict of interest

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