Stimulation With 0.3-mg Recombinant Human Thyrotropin Prior to Iodine 131 Therapy to Improve the Size Reduction of Benign Nontoxic Nodular Goiter

A Prospective Randomized Double-blind Trial

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Background: Use of recombinant human thyrotropin increases the thyroid radiiodine (iodine 131 [131I]) uptake and may have a role in the context of 131I therapy of benign goiter.

Methods: In a double-blind, placebo-controlled trial, 57 patients with nodular nontoxic goiter (51 women and 6 men) were randomized to receive either 0.3 mg of recombinant human thyrotropin (n=28) or placebo (n=29) 24 hours before 131I therapy. The 131I dose was calculated based on thyroid size (measured by ultrasound), thyroid 131I uptake, and 131I half-life. The follow-up period was 1 year and included measurements of thyroid size and function and patient satisfaction.

Results: Baseline median goiter volume was 51 mL (range, 20-99 mL) in the placebo group and 59 mL (range, 25-92 mL) in the thyrotropin group (P=.75). At 12 months, the mean±SEM relative goiter reduction was 46.1%±4.0% in the placebo group and 62.1%±3.0% in the thyrotropin group (P=.002 between groups). The difference was most pronounced among patients with large goiters. Within each group, there was no significant correlation between retained thyroid 131I dose and goiter reduction. Adverse effects were significantly more frequent in the thyrotropin group (34 vs 12 events; P<.001). Permanent hypothyroidism developed in 3 patients (11%) in the placebo group compared with 16 patients (62%) in the thyrotropin group (P<.001). Patient satisfaction was high and uninfluenced by the use of recombinant human thyrotropin.

Conclusions: Stimulation with recombinant human thyrotropin prior to 131I therapy improves thyroid size reduction by 35%, with a 5-fold higher rate of hypothyroidism. These effects are, at least partially, mediated through mechanisms other than an increase in retained 131I thyroid dose. Further recombinant human thyrotropin dose-finding studies are warranted before routine use.

Trial Registration: clinicaltrials.gov Identifier: NCT00145366

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NONTOXIC NODULAR GOITER (NNG) is a frequent thyroid disorder with a high prevalence in areas with relative iodine deficiency.1 The clinical manifestations are related to those of growth and functional autonomy.

Treatment of NNG is controversial.1 Thyroid surgery and levothyroxine suppressive therapy has been considered the treatment of choice in several countries.2,3 Levothyroxine therapy has low efficacy4,5 and is increasingly disfavored by many clinicians.6 Surgery efficiently reduces goiter size but carries a risk of both surgical and anesthetic complications.6 As a nonsurgical alternative, radiiodine (iodine 131 [131I]) therapy results in a mean thyroid volume reduction of approximately 40% one year after treatment.1 However, in areas with a high dietary iodine intake, the thyroid 131I uptake (RAIU) is low, necessitating a relatively high amount of radiiodine. Furthermore, individual susceptibility to 131I and an irregular 131I uptake set an upper limit for the achievable goiter reduction. Therefore, it is of interest to explore strategies to enhance thyroid RAIU to augment thyroid volume reduction.

Use of recombinant human thyrotropin has been shown to approximately double the thyroid RAIU in patients with NNG7-11 and, when combined with 131I therapy, also to increase thyroid volume reduction.12-13 However, these studies have various shortcomings, and, to our knowledge, no placebo-controlled blinded trial has yet been published. The aim of the present study was to evaluate, in a double-blind, placebo-controlled set-up, the goiter-reducing effect and adverse effects of prestimulation with 0.3 mg of recombinant human thyrotropin 24 hours prior to 131I therapy, in a homogeneous well-characterized group of patients with NNG.

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METHODS

SUBJECTS AND STUDY DESIGN

From January 2002 through April 2004, 712 patients with NNG were examined at our endocrine outpatient clinic (Figure 1). All patients lived in a moderate iodine-deficient region. The diagnosis was obtained by clinical examination, ultrasonography, and sodium pertechnetate 99mTc thyroid scintigraphy. In case of a scintigraphically dominant hypoactive nodule, fine-needle aspiration biopsy was performed to exclude malignancy.

Treatment indications were symptoms of cervical compression, cosmetic discomfort, and/or subclinical hyperthyroidism (serum thyroid-stimulating hormone [TSH] <0.10 mU/L and normal serum thyroxine [T4] and serum triiodothyronine [T3] levels). Exclusion criteria are listed in Figure 1. Patients with a 24-hour thyroid RAIU below 20% were excluded because we found it of concern to treat such patients suboptimally, in case they were randomized to the placebo group. Of the 142 eligible patients, 115 accepted 131I therapy, 66 of whom provided signed informed consent. Nine patients dropped out just prior to treatment, leaving 57 patients (6 men and 51 women) for the final analysis (Figure 1).

The study was performed in a randomized, placebo-controlled, double-blinded set-up, in which each patient received either 0.3 mg of recombinant human thyrotropin or isotonic sodium chloride solution injected intramuscularly in the gluteal region 24 hours prior to 131I therapy. Freeze-dried recombinant human thyrotropin (vials containing 0.9-mg recombinant human thyrotropin; Thyrogen; Genzyme Transgenics Corp, Cambridge, Mass) was reconstituted with 3 mL of isotonic sodium chloride solution. Of this dilution, 0.3 mg of recombinant human thyrotropin corresponds to 1 mL. Prior to 131I therapy, pregnancy was ruled out by a urinary test in all female patients of childbearing age not using a safe contraception. The follow-up period was 12 months. The study was approved by the local ethics committee of the county of Funen, Denmark (trial No. 2001-0002) and registered at http://www.clinicaltrials.gov (registration number: NCT00145366).

UPTAKE MEASUREMENTS AND 131I THERAPY

A baseline thyroid RAIU was determined at 24 and 96 hours after oral administration of a tracer activity of 0.5 MBq (14.0 µCi) 131I. Aiming at a thyroid dose of 10 000 rad (100 Gy), the administered therapeutic 131I activity was calculated based on the following algorithm:

\[
\text{Activity (MBq)} = \frac{\text{Thyroid Volume (mL)} \times 22.4 \times (\text{Days} \times \text{MBq/mL}) \times 100}{\text{Half-Life (Days)} \times 24-\text{Hour }^{131}\text{I Uptake} \%}
\]

The effective half-life was calculated from the 24- and 96-hour thyroid RAIU measurements.

Iodine 131 therapy was given orally, 10 to 14 days following the last tracer thyroid RAIU measurement. According to the official radiation regulation in Denmark, patients were treated on an outpatient basis, receiving a maximum activity of approximately 600 MBq (16.2 mCi) of 131I. The iodine was administered in a liquid suspension, and an SD of ±10% in administered 131I activity was accepted. After 131I therapy, 24- and 96-hour RAIU measurements were repeated to assess the actual retained thyroid 131I dose. For further details concerning the exact measurements, please see our previously published study.14

THYROID SIZE ESTIMATION

Thyroid size was estimated by ultrasonography before treatment and 3, 6, 9, and 12 months following 131I therapy by a precise and accurate planimetric ultrasonic scanning procedure, using a 3.5-MHz compound scanner (type 1846; Bruel & Kjær, Copenhagen, Denmark) mounted with a 5-MHz transducer on a static scanner arm. The average intraobserver variation of this method is around 5%, with a measurement error of 7%.15 The mean ± SD thyroid volume in an adult Danish population without clinically overt goiter is 18.6±4.5 mL (normal range, 10-28 mL).15 The ultrasound measurements were performed by experienced operators blinded toward the randomization (V.E.N., S.J.B., and L.H.).

THYROID FUNCTION

Thyroid function testing was performed before treatment; 3 and 6 weeks after 131I therapy; and 3, 6, 9, and 12 months after 131I therapy. This included serum TSH, serum total T4, and serum total T3 levels, which were measured at our Department of Clinical Chemistry, Odense University Hospital, Odense, Dan-
sured. In subjects who developed thyrotoxicosis after 131I therapy that persisted for more than 6 weeks, TSH receptor antibodies (values > 2 IU/L as positive) were measured to detect possible 131I-induced Graves disease. Before and 12 months after 131I therapy, and at the end of follow-up, each individual was asked to indicate on the visual analog scale, ranging from 0 to 10, their subjective benefit of the 131I therapy on goiter-related symptoms (ie, cervical obstructive symptoms and cosmetic discomfort). Of the randomized patients, 28 received recombinant human thyrotropin and 29 received placebo. No significant differences were found in any of the baseline variables. Of the randomized patients, 28 received recombinant human thyrotropin and 29 received placebo.

PATIENT SATISFACTION

The subjective benefit of the 131I therapy on goiter-related symptoms (ie, cervical obstructive symptoms and cosmetic discomfort) were registered by a visual analog scale. Before treatment, 3 months after 131I therapy, and at the end of follow-up, each individual was asked to indicate on the visual analog scale, ranging from 0 to 10 (arbitrary units), the degree of cervical compression and cosmetic discomfort. The score of 0 represented no complaints and 10, the worst possible degree of compression and/or discomfort.

STATISTICAL ANALYSIS

Accepting a type I error of 5% and a type II error of 10% and assuming an SD of 20% on the percentage of goiter volume reduction,1 at least 21 patients in each randomization group were required to detect a difference of 20%. The STATA 8 (StataCorp, College Station, Tex) statistical software program was used, and data are presented as median (range) or mean±SD or SEM. Non-parametric or parametric statistical tests were used, depending on the normality of the data. A repeated-measure analysis of variance was performed to test for an overall difference between groups. A 1-way analysis of variance or the Friedman test was used to test within-group differences. Linear regression analysis was used to test for relationships between relevant variables. Visual analog scale score data were compared by use of the Wilcoxon test. To compare frequencies, the χ² test was used. The level of statistical significance was chosen as P<.05.

RESULTS

BASELINE DATA

Baseline clinical and laboratory data are given in Table 1. No significant differences were found in any of the baseline variables. Of the randomized patients, 28 received recombinant human thyrotropin and 29 received placebo. In 12 patients (7 received placebo and 5 received recombinant human thyrotropin), the 131I activity was limited to 600 MBq (16.2 mCi) owing to a significantly lower mean±SD thyroid RAIU (26.3%±9.2% vs 35.2±6.0%; P<.001 between groups) and a significantly higher median thyroid volume (67 mL [range, 41-99 mL] vs 51 mL [range, 20-83 mL]; P=.01 between groups) compared with the 45 patients given an unrestricted activity. Thus, the calculated 131I activity in the 12 patients was above 600 MBq (16.2 mCi) (median, 1232 MBq [range, 853-2062 MBq] [33.3 mCi [range, 23.1-55.7 mCi]] in the placebo group; median, 929 MBq [range, 789-1632 MBq] [25.1 mCi [range, 21.1-44.1 mCi]] in the thyrotropin group; P=.34). Because in-house therapy was not planned, they were only given approximately 600 MBq (16.2 mCi). Thus, the overall median 131I activity was 581 MBq (range, 241-666 MBq) (15.7 mCi [range, 6.5-18.0 mCi]) and 519 MBq (range, 173-658 MBq) (14.0 mCi [range, 4.7-17.8 mCi]) in the thyrotropin group and the placebo group, respectively (P=.55 between groups) (Table 2). For further details regarding the exact 131I kinetics after stimulation with 0.3 mg of recombinant human thyrotropin, please see our previously published study.11

GOITER VOLUME REDUCTION

Baseline median goiter volume was 51 mL (range, 20-99 mL) in the placebo group and 59 mL (25-92 mL) in the thyrotropin group (P=.75). At 12 months, the corresponding values were 27 mL (5-82 mL) and 20 mL (4-78 mL), respectively.
mL (6-59 mL), respectively (P<.001, within groups compared with baseline). In relative numbers, the mean±SEM goiter reduction at 3 months after 131I therapy was 21.0%±2.1% in the placebo group and 27.0%±3.0% in the thyrotropin group (P=.11); at 6 months, 36.0%±4.3% and 46.0%±3.0%, respectively (P=.04); at 9 months, 42.0%±4.1% and 55.0%±3.1%, respectively (P=.01); and at 12 months, 46.1%±4.0% and 62.1%±3.0%, respectively (P=.002) (Figure 2). Thus, compared with conventional 131I therapy, the goiter reduction was increased by 35% at 12 months when stimulating with 0.3 mg of recombinant human thyrotropin or placebo. Overall, those who developed hypothyroidism had a significantly higher mean±SD retained thyroid dose compared with those who remained euthyroid (14 800±5700 rad [148.0±57.0 Gy] and 94 300±4300 rad [94.3±43.0 Gy], respectively; P<.001). However, when stratifying according to randomization group, the difference was statistically insignificant (15 600±5800 rad [156.0±58.0 Gy] and 12 810±5610 rad [128.1±56.1 Gy] in the thyrotropin group [P=.17] and 10 710±3430 rad [107.1±34.3 Gy] and 78 200±2210 rad [78.2±22.1 Gy] in the placebo group [P=.13]), but this is most likely explained by lack of statistical power. It is worth noting that those

**Table 2. Iodine 131 (131I) Kinetics at Baseline and After Therapy Following Prestimulation With 131I 0.3 mg of Recombinant Human Thyrotropin or Placebo**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Placebo (n = 29)</th>
<th>Recombinant Human Thyrotropin (n = 29)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h 131I tracer uptake, mean ± SD, %</td>
<td></td>
<td>34.0 ± 5.5</td>
<td>31.6 ± 11.0</td>
<td>.29</td>
</tr>
<tr>
<td>96-h 131I tracer uptake, mean ± SD, %</td>
<td></td>
<td>32.3 ± 5.6</td>
<td>31.0 ± 12.0</td>
<td>.53</td>
</tr>
<tr>
<td>24-h 131I therapy</td>
<td></td>
<td>47.0 ± 13.0</td>
<td>28.7 ± 9.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>uptake, mean ± SD, %</td>
<td></td>
<td>46.0 ± 13.0</td>
<td>27.4 ± 8.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>24-h 131I therapy</td>
<td></td>
<td>6.8 ± 1.4</td>
<td>6.9 ± 1.8</td>
<td>.89</td>
</tr>
<tr>
<td>uptake, mean ± SD, d</td>
<td></td>
<td>581 (241-666)</td>
<td>519 (173-658)</td>
<td>.55</td>
</tr>
<tr>
<td>Therapeutic 131I activity, median (range), MBq†</td>
<td></td>
<td>138 600 ± 55 800</td>
<td>80 600 ± 26 300</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Retained thyroid dose, mean ± SD, rad†</td>
<td></td>
<td>48.1 ± 11.0</td>
<td>0.2 ± 9.0‡</td>
<td>.002</td>
</tr>
</tbody>
</table>

*To convert to millicurie, divide by 37.
†To convert to gray, divide by 100.
‡95% Confidence interval, 26.0 to 70.0.
§95% Confidence interval, −19.0 to 19.0.

**Figure 2.** The percentage mean change in thyroid volume following stimulation with 0.3 mg of recombinant human thyrotropin or placebo 24 hours prior to iodine 131 [131I] therapy. *P=.04 between groups. †P=.01 between groups. ‡P=.002 between groups. §P<.001 compared with baseline. Error bars indicate SEM.

**Figure 3.**

**Figure 4.**

**THYROID FUNCTION**

Overall, 25 patients had subclinical hyperthyroidism before treatment (14 in the placebo group and 11 in the thyrotropin group; P=.60). Three weeks after 131I therapy, 37 patients (20 in the thyrotropin group and 17 in the placebo group; P=.15) showed a transient decrease in serum TSH level below 0.30 mU/L. Thereafter, the thyroid function of these patients either normalized or decreased. No significant changes in serum levels of free T4 and free T3 indexes were observed 3 weeks following 131I therapy in either group (132.0±69.3 nmol/L in the thyrotropin group and 130.0±46.0 nmol/L in the placebo group) compared with baseline values.

Permanent hypothyroidism (Figure 4) developed in 16 patients (62%) in the thyrotropin group compared with 3 patients (11%) in the placebo group (P<.001), and consequently these patients were given levothyroxine. Overall, those who developed hypothyroidism had a significantly higher mean±SD retained thyroid dose compared with those who remained euthyroid (14 800±5700 rad [148.0±57.0 Gy] and 94 300±4300 rad [94.3±43.0 Gy], respectively; P<.001). However, when stratifying according to randomization group, the difference was statistically insignificant (15 600±5800 rad [156.0±58.0 Gy] and 12 810±5610 rad [128.1±56.1 Gy] in the thyrotropin group [P=.17] and 10 710±3430 rad [107.1±34.3 Gy] and 78 200±2210 rad [78.2±22.1 Gy] in the placebo group [P=.13]), but this is most likely explained by lack of statistical power. It is worth noting that those
who developed hypothyroidism experienced a greater mean ± SD goiter reduction compared with those remaining euthyroid (69.0% ± 11.5% and 52.0% ± 16.0%, respectively; \( P = .005 \)).

Before treatment, thyroid peroxidase antibodies were present in 6 patients (5 in the thyrotropin group) and were found in an additional 8 patients 1 year after \(^{131}\)I therapy (4 in the thyrotropin group). Of these 14 patients, 6 developed hypothyroidism during the observation period (all were pretreated with recombinant human thyrotropin). None had TSH receptor antibodies before treatment, but these appeared in 2 patients (both were in the thyrotropin group) during the follow-up period.

**ADVERSE EFFECTS**

Adverse effects were significantly more frequent in the thyrotropin group (34 events occurred in the thyrotropin group and 12 events in the placebo group; \( P < .001 \)). These were especially related to hyperthyroid symptoms and thyroid growth (Table 3). No patient experienced any respiratory problems, and any complaints of cervical compression and/or pain remitted within 1 to 2 weeks after \(^{131}\)I therapy, while hypothyroid symptoms had disappeared within 3 weeks after \(^{131}\)I therapy in nearly all cases. One patient in the thyrotropin group developed Graves disease and mild and transient thyroid-associated ophthalmopathy, which was treated successfully with methimazole and prednisolone for a short period.

**PATIENT SATISFACTION**

No significant correlation was found between the individual visual analog scale scores and the initial goiter size (\( r = 0.003; P = .93 \)). In both groups, the goiter-related symptoms were significantly improved 3 months and 1 year after \(^{131}\)I therapy (Table 4). No significant difference was found between the 2 randomization groups, neither at 3 months nor 1 year after therapy.
A few previous clinical studies have suggested that recombinant human thyrotropin prestimulation augments the effect of 131I therapy in patients with NNG. However, all of these studies have shortcomings related to either dose calculation, an inhomogeneous study population, lack of a control group, a short follow-up period, or a small study population (unpublished study). To our knowledge, our study is the first large-scale, double-blind, placebo-controlled trial investigating the effects and adverse effects of pre-treatment with recombinant human thyrotropin prior to 131I therapy in patients with benign NNG. We found a mean thyroid volume reduction of 62% in the thyrotropin group compared with 46% in the placebo group, corresponding to an increase of 35% in thyroid size reduction. Furthermore, we found that patient satisfaction was high, independent of whether recombinant human thyrotropin or placebo was given, which could be owing to a poor correlation between thyroid size and symptoms or perhaps a lack of sensitivity of the visual analog scale.

In concert with other studies not using recombinant human thyrotropin, we found an inverse correlation in the placebo group between the initial goiter volume and the relative goiter reduction after 1 year, which was not found in the thyrotropin group. That dose restriction was slightly higher in the latter group does not change this fact. Thus, recombinant human thyrotropin–augmented 131I therapy may be independent of goiter size, possibly because of a more homogeneous distribution of 131I. This indicates that recombinant human thyrotropin may have a particular role in patients with large goiters. Furthermore, patients with a low thyroid RAIU seem to benefit more from recombinant human thyrotropin prestimulation, and we most likely underestimated the effect of recombinant human thyrotropin because patients with a thyroid RAIU below 20%—the very patients we anticipate to have the greatest benefit—were excluded.

We have previously shown that 0.3-mg recombinant human thyrotropin use 24 hours prior to 131I therapy increases the retained thyroid dose by 75% compared with placebo. Although a positive correlation between the retained thyroid dose after recombinant human thyrotropin stimulation and goiter volume reduction 6 months after 131I therapy was recently suggested, our study offers no confirmation of this. Consequently, the effect of recombinant human thyrotropin on goiter volume reduction cannot solely be explained by an increase in the applied thyroid dose but may be dependent on other factors mediated by recombinant human thyrotropin. In fact, we found that patients in the thyrotropin group achieved a fairly comparable goiter reduction irrespective of whether 8000 rad (80 Gy) or 25 000 rad (250 Gy) was retained. This could be due to a recombinant human thyrotropin–induced reactivation of dormant thyroid tissue, increased thyroid sensitivity to ionizing radiation, or perhaps a higher rate of apoptosis of the thyrocytes.

In line with the findings of others, we demonstrated that early adverse effects were significantly more frequent in the thyrotropin group, especially those related to thyroid hyperfunction, thyroid growth, and thyroid pain. Unless very low recombinant human thyrotropin doses are used, we know that recombinant human thyrotropin combined with 131I therapy results in a more pronounced increase in the serum thyroid hormone levels within the first week compared with conventional 131I therapy. It was not our focus to evaluate the early changes in thyroid hormones, but none of our patients were hospitalized and none developed tachycardia or tachyarrhythmias necessitating treatment during the follow-up period. The various adverse effects may be due to the higher 131I dose retained in the thyroid, a local reaction to recombinant human thyrotropin, or a combination of these factors. It is likely that recombinant human thyrotropin and 131I may act in an additive or even synergistic fashion because adverse effects were more frequent in the thyrotropin group.

From our previous investigation of the impact of 0.9-mg recombinant human thyrotropin use on thyroid volume in healthy nongorotic individuals and of 0.3-mg recombinant human thyrotropin use in patients with NNG, we know that recombinant human thyrotropin causes an acute and temporary increase in thyroid size by approximately 35% and 24%, respectively. Considering that 131I therapy in some cases causes a transient goiter growth of 15% to 25% within the first week, its combination with recombinant human thyrotropin use may potentially lead to severe tracheal compression in susceptible individuals. In the present study, none of our patients experienced any respiratory problems, but whether there was an impact on the trachea is unknown because we did not perform tracheal imaging (computed tomography or magnetic resonance imaging).

### Table 4. Visual Analog Scale*

<table>
<thead>
<tr>
<th>Time After Iodine 131 Therapy</th>
<th>0.3-mg Recombinant Human Thyrotropin</th>
<th>Placebo</th>
<th>P Value (Between Groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cervical Compression</td>
<td>Cosmetic Complaints</td>
<td>Cervical Compression</td>
</tr>
<tr>
<td>Baseline</td>
<td>4.0 (0.0-9.0)</td>
<td>1.0 (0.0-10.0)</td>
<td>5.0 (0.0-9.0)</td>
</tr>
<tr>
<td>3 Months</td>
<td>3.0 (0.0-6.0)</td>
<td>1.0 (0.0-5.0)</td>
<td>2.5 (0.0-8.0)</td>
</tr>
<tr>
<td>12 Months</td>
<td>0.0 (0.0-4.0)</td>
<td>0.0 (0.0-4.0)</td>
<td>0.0 (0.0-8.0)</td>
</tr>
</tbody>
</table>

*Data are given as median (range) visual analog scale score (with 0 representing no complaints and 10, the worst possible degree of compression and/or discomfort) unless otherwise specified.
ing) or pulmonary function tests. An early measurement of the acute changes in goiter size after radioiodine therapy would have been informative but was not performed to avoid radiation exposure of the personnel.

A late adverse effect of \(^{131}\text{I}\) therapy is the development of hypothyroidism.\(^{1,20,24,25}\) In the present study, a 5-fold higher incidence was found, most likely due to a higher retained thyroid \(^{131}\text{I}\) dose and a more homogenous distribution of \(^{131}\text{I}\).\(^{1,21}\) Because levothyroxine replacement therapy is usually straightforward, this should not be a major argument against recombinant human thyrotropin–augmented \(^{131}\text{I}\) therapy. A point favoring recombinant human thyrotropin use is that those patients who developed hypothyroidism also had a greater goiter reduction.

From this randomized, placebo-controlled, double-blind trial, we conclude that the use of 0.3 mg of recombinant human thyrotropin 24 hours prior to \(^{131}\text{I}\) therapy results in a more effective goiter volume reduction at the expense of a 5-fold higher frequency of hypothyroidism, a higher frequency of adverse effects, and lack of evidence of an improved patient satisfaction. Future studies should focus on including patients with large goiters and low thyroid RAII because they may benefit the most from recombinant human thyrotropin prestimulation. Finally, the optimal dose and timing of recombinant human thyrotropin use in relation to \(^{131}\text{I}\) therapy remains to be determined, with the aim being the best balance between beneficial and adverse effects.

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