Success Rate of Radioactive Iodine Therapy in Graves' Disease Using Dose Corrected for Thyroid Gland Size

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ABSTRACT

Objective: Dose corrected for thyroid gland size is one of the methods used to determine I-131 activity for patients with Graves' disease. This study aimed to find the success rate of this method and the predictors for successful I-131 treatment.

Methods: This retrospective descriptive study conducted was in patients with Graves' disease who received the first dose of radioactive iodine (RAI) therapy. Patients received a fixed RAI dose of either 10, 15, 20, 25, or 30 mCi for corresponding thyroid gland size of ≤ 50, 51-100, 101-150, 151-200, and >200 grams, respectively. The treatment outcome assessed was between 6 to 9 months after the therapy based on serum free thyroxine and serum thyroid stimulating hormone. Successful treatment was defined as euthyroid and hypothyroid.

Results: A total number of 179 patients (126 females; mean age: 40.8 years) were enrolled. There was one patient exclusion from the outcome analysis due to undetermined laboratory results. The success rate of RAI therapy was 50% (95% CI: 42.4-57.6). Patients with gland size ≤ 50 gm had the highest success rate of 59.6%. Multivariable analysis showed no significant association between sex, thyroid gland size, prior antithyroid drug use and successful treatment.

Conclusion: First RAI therapy using dose corrected for thyroid gland size had a modest success rate of 50% in patients with Grave's disease. Sex, thyroid gland size, and prior antithyroid drug use were not significantly associated with the treatment outcomes.

Keywords: Radioactive iodine; Graves' disease; hyperthyroidism; success rate (Siriraj Med J 2021; 73: 108-113)

INTRODUCTION

Graves' disease is an organ-specific autoimmune disease and the most common cause of hyperthyroidism. The annual incidence is 20 to 30 cases per 100,000 individuals with approximately 3% and 0.5% lifetime risk in women and men, respectively.[1-3] Untreated or partially treated Graves' disease can lead to serious complications such as atrial fibrillation, neuropsychiatric symptoms, thyroid storm, or even death.[4,5] Thus, an appropriate treatment is the key to success for controlling hyperthyroidism symptoms and prevention of serious complications.

Radioactive iodine (RAI) therapy using the beta particle-emitting isotope, I-131, is the definitive treatment for Graves' disease by destroying thyroid follicular cells.[3,6]

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The goal of RAI therapy is to use sufficient activity of RAI to render the patient's hypothyroid.[4] There are two main methods to determine the RAI activity in clinical practice: estimation (the so called "fixed dose") and calculation of radioiodine uptake measurement and thyroid gland size.[7,8] The systematic reviews and meta-analyses showed equally successful treatment outcomes between the two methods.[9] However, the fixed dose regimen is simpler and more cost-effective.[10,11] Another approach to find an optimal I-131 activity in Graves' disease is dose corrected for thyroid gland size method by prescribing RAI activity according to the estimated thyroid gland size.[12] The advantages of this method are similar to the fixed dose in terms of cost and procedure. However, the treatment outcome of this method is not been well studied. Thus, we primarily aimed to find the success rate of first RAI therapy using dose corrected for thyroid gland size method in patients with Graves' disease. Moreover, we also evaluated predictive factors associated with the successful treatment.

MATERIALS AND METHODS

Patient selection

This retrospective descriptive study was approved by the Khon Kaen University Ethics Committee for Human Research (Reference number: HE601393) and the requirement for the informed consent was waived. From January 2012 to April 2017, patients enrolled for research had confirmed Graves' disease and had received first RAI therapy at Srinagarind Hospital. Patients were stratified into five groups according to thyroid gland size. Those with a history of thyroid surgery, received repeated doses of RAI therapy prior to first treatment outcome evaluation, or had undetermined laboratory results during the follow-up period because of recent thyroid hormone or antithyroid medication use were excluded.

Patient preparation and treatment

Patients treated at our center followed strict patient preparation as per our center's standard protocol. Antithyroid Drug (ATD) either methimazole (MMI) or propylthiouracil (PTU), was discontinued three to seven days prior to RAI therapy. Patients had an advice to take low-iodine diet for one week before the therapy. Pregnancy tests done potentially on all pregnant females on the day of treatment. The thyroid gland size estimation of each patient performed by one of four expert nuclear medicine physicians. The recorded thyroid gland size was used to determine RAI activity according to our center' standard protocol. Patients received a fixed RAI dose of either 10, 15, 20, 25, or 30 mCi orally for corresponding thyroid gland size of ≤ 50, 51-100, 101-150, 151-200, and >200 grams as assessed by palpation. Beta-blockers and/or restarting ATD allowed for controlling symptoms after RAI therapy. Then, clinical outcomes evaluated between 6 to 9 months after first I-131 administration. Thyroid function tests including serum free thyroxine (FT4) and serum thyroid stimulating hormone (TSH), clinical symptoms, and thyroid gland size assessed at the follow-up time point.

Outcome measurement

Successful RAI therapy was defined as patients with euthyroid (normal FT4 and TSH), subclinical hypothyroidism (normal FT4 and high TSH), or overt hypothyroidism (low FT4 and high TSH) 6 to 9 months after the treatment. The patients who had subclinical hyperthyroidism (normal FT4 and low TSH) or overt hyperthyroidism (high FT4 and low TSH) had classified as treatment failure. The normal reference range of serum FT4 is 0.78-2.11 ng/dL and serum TSH is 0.2-4.2 μIU/mL.

Statistical analysis

The success rate of RAI therapy presented as the number and percentage of patients with euthyroid, subclinical hypothyroid and overt hypothyroid divided by the numbers of all patients. The categorical data (sex, group of gland size, type of ATD use) presented the number and percentage. The continuous data (age, follow-up time, serum FT4, serum TSH) presented as mean ± standard deviation (SD) or median (with interquartile range). Univariable analysis and multivariable analysis by multiple logistic regression used to test association between sex, prior ATD use, thyroid gland size and successful treatment. All the statistics two-sided and p values of less than 0.05 considered statistically significant. Accompanying 95% confidence intervals (95% CI) were reported where appropriate. Statistical analysis carried out was using STATA 10.1 (StataCorp LP, College Station, TX, USA).

RESULTS

A total number of 179 patients enrolled with a mean age of 40.8±13.6 years. Most of the patients were female (n = 126, 70.4%). When patients were grouped by thyroid gland size, 52 (29.1%), 52 (29.1%), 39 (21.8%), 22 (12.2%), and 14 (7.8%) had gland size of ≤ 50, 51-100, 101-150, 151-200, and ≥ 200 grams, respectively. Regarding the ATD, most of the patients used MMI prior to RAI therapy (n = 131, 73.2%). Only five patients (2.8%)

did not receive ATD before I-131 administration. The median follow-up time after treatment was 6.6 (6.1-7.5) months. The patient's demographic and clinical data are as shown in Table 1.

After the 6- to 9-month follow-up, there was one patient with indeterminate laboratory results (low serum FT4 and TSH). Thus, the success rate of treatment in 178 patients analyzed. Eighty-nine patients (50%) achieved successful treatment, among which 30 (16.9%) were euthyroid, 30 (16.9%) were subclinical hypothyroid, and 29 (16.2%) were overtly hypothyroid. The remaining 89 patients (50%) had treatment failure, among which 51 (28.7%) were subclinical hyperthyroid and 38 (21.3%) were overtly hyperthyroid. The details of treatment outcomes are as shown in Table 2.

Regarding the treatment outcomes based on the thyroid gland size, patients with gland size equal or less than 50 grams had the highest success rate of 59.6% (95% CI: 45.1-73.0), while patients with larger gland size tended to have lower success rate. Patients with gland size of 151-200 grams had the lowest success rate, 22.7% (95% CI: 7.8-45.4). The success rate in each group of thyroid gland size is as shown in Table 3.

Multiple logistic regression demonstrated that females tended to have successful treatment than males but there was no statistical significance (adjusted OR = 1.28, 95% CI: 0.62-2.64, p value = 0.51). Regarding the thyroid gland size, patients with gland size 151-200 grams seemed to have lower successful treatment than those with gland size ≤ 50 gm but there was also no statistical significance (adjusted OR = 0.35, 95% CI: 0.08-1.59, p value = 0.17). Furthermore, use of MMI or PTU prior to the RAI therapy showed no significant association with the successful treatment as shown in Table 4. In addition, we also evaluated the impact of different ATD use prior to the therapy on successful treatment and found that there was no statistically significant difference between either MMI or PTU and the treatment outcomes (adjusted OR = 1.83, 95% CI: 0.86-3.92, p value = 0.12).

TABLE 1. Patient's demographic and clinical data.

Variables	Total 179 n (%)
Sex	
Male	53 (29.6)
Female	126 (70.4)
Age (year)	
Mean	40.8
SD	13.6
Estimated thyroid gland size (gram)	
≤ 50	52 (29.1)
51-100	52 (29.1)
101-150	39 (21.8)
151-200	22 (12.2)
> 200	14 (7.8)
Antithyroid drug	
Methimazole (MMI)	131 (73.2)
Propylthiouracil (PTU)	42 (23.5)
Both MMI and PTU	1 (0.5)
None	5 (2.8)
Follow-up time (month)	
Median	6.6
Interquartile range	6.1-7.5

TABLE 2. Outcomes of RAI therapy at the 6 to 9-month follow-up.

Outcome	Total 178[a] n (%)
Success	89 (50)
Euthyroid	30 (16.9)
Subclinical hypothyroid	30 (16.9)
Overt hypothyroid	29 (16.2)
Failure	89 (50)
Subclinical hyperthyroid	51 (28.7)
Overt hyperthyroid	38 (21.3)

[a]There was one patient with thyroid gland size > 200 grams whose thyroid function test cannot be determined. Thus, the treatment outcomes were analyzed in 178 patients.

TABLE 3. Outcomes of RAI therapy at the 6 to 9-month follow-up based on thyroid gland size.

Thyroid gland size (gram)	Median size (IQR)	Success	Failure	Percent success rate (95% CI)
≤ 50	35 (30-40)	31	21	59.6 (45.1-73.0)
51-100	70 (60-80)	28	24	53.9 (39.5-67.8)
101-150	120 (120-145)	19	20	48.7 (32.4-65.2)
151-200	200 (200)	5	17	22.7 (7.8-45.4)
> 200	250 (250-287.5)	6	7	46.2 (19.2-74.9)
Overall	80 (50-130)	89	89	50.0 (42.4-57.6)

Abbreviation: IQR, interquartile range

DISCUSSION

We studied the success rate of RAI therapy by dose corrected for thyroid gland size method in 178 patients with Graves' disease who received first-dose I-131 administration. The treatment outcomes evaluated at 6 to 9 months after the therapy. We decided to determine the treatment outcomes at this time point because there was variation in the follow-up period in each patient and hypothyroid could achieve up to 12 months after the therapy.[13] Eighty-nine patients achieved successful treatment accounts for only 50% success rate (95% CI: 42.4-57.6). This figure was lower than reported in the previous studies using the estimation method to determine I-131 activity with the success rate between 60-85%.[10,11,14-18] Several factors affected our therapeutic outcome. The first important factor that affected the outcome was thyroid gland size, well known to be an independent predictor of the response to I-131 therapy.[13] The median thyroid gland size of our patients was higher than those in other studies (80 grams vs 35-70 grams)[10,11,14,17] and 71.35% of our patients had thyroid gland size larger than 50 grams. Thus, this could lower the overall success rate. However, the patients with thyroid gland size ≤ 50 grams could achieve higher success rate approximately at 60%. Second, we used the palpation method for thyroid gland size estimation which could underestimate the size of larger goiter (greater than 40 mL).[19] The study by Canto et al. used thyroid ultrasound for gland size estimation and found that the overall success rate was 80% even though there were one-third of patients with gland size between

TABLE 4. Univariable and multivariable analyses of successful treatment.

Variable	Univariable analysis Crude OR (95% CI)	p value	Multivariable analysis Adjusted OR (95% CI)	p value
Sex				
Male	1		1	
Female	1.31 (0.69-2.49)	0.41	1.28 (0.62-2.64)	0.51
Thyroid gland size (gram)				
≤ 50	1		1	
51-100	1.36 (0.40-4.61)	0.62	1.15 (0.31-4.21)	0.84
101-150	1.11 (0.31-3.90)	0.87	0.97 (0.27-3.56)	0.97
151-200	0.34 (0.08-1.50)	0.16	0.35 (0.08-1.59)	0.17
> 200	1.72 (0.51-5.85)	0.38	1.63 (0.44-6.08)	0.47
Antithyroid medication				
None	1		1	
MMI	1.78 (0.29-10.98)	0.54	2.90 (0.43-19.38)	0.27
PTU	0.87 (0.13-5.78)	0.88	1.58 (0.22-11.37)	0.65

Abbreviations: Crude OR, crude odds ratio; Adjusted OR, adjusted odds ratio, MMI; methimazole, PTU; propylthiouracil

40-80 grams.[10] Third, we did not perform radioiodine uptake test (RAIU) that might identify patients with rapid I-131 turnover Graves' disease that maybe found in up to 15% of all Graves' disease patients and needed a higher I-131 activity or other therapeutic intervention such as lithium carbonate.[20] Fourth, although with a one-week low-iodine diet intake advised to the patients before RAI therapy, the actual amount of iodine intake is difficult to quantify. The study by Meller et al. found that there was 2-fold increased iodine excretion prior to the therapy corresponded to a decrease of the radioiodine uptake by 25%.[21] However, the prospective study by Santarosa et al. showed no difference in the rate of hypothyroidism 6 months after RAI therapy between patients with Graves' disease patients who consumed low-iodine diet and patients who took regular diet (86.7% vs 82.6%, p value = 0.74).[22] Lastly, since most of the patients had been referrals from other hospitals, some patients who had a higher chance to be cured with a single dose of I-131, such as patients with small gland size or mild hyperthyroidism, had been referred back to their primary hospitals for further follow-up. Thus, the assessment count of successful treatment numbers was difficult to achieve in our study results of this group of patients and this could lead to underestimation of treatment success.

Regarding the predictors for the therapeutic outcome, sex showed no significant association with successful treatment which was in line with most studies. There was no exact reason to explain the difference in the biological response to radioiodine between male and female.[13] For thyroid gland size, it was also no significant association with the treatment outcomes. This maybe explains the method to determine I-131 activity. We used dose correction for thyroid gland size; the larger gland size received the higher prescribed radioiodine activity. In addition, prior MMI or PTU use before RAI therapy, although known to have radioprotective effect[13], showed no significant association with successful treatment in our study. The result was consistent with a randomized clinical trial by Bonnema et al. which demonstrated no difference between failure rate of RAI therapy among Graves's disease patients who were and were not pretreated with PTU (40.0% vs 30.8%, p value = 0.81).[23] The prospective randomized study by Pirnat et al. also showed equally effective outcomes in Graves' disease patients who did not receive MMI and patients who had discontinued MMI seven days before RAI therapy (99.6% vs 99.0%).[24]

There were some limitations of our study. First, due to being a retrospective study, other potential predictive

factors such as pretreatment serum FT4 and TSH, duration of disease, duration of ATD use, and thyroid autoantibodies were difficult to evaluate. Second, the thyroid gland size was assessed by different nuclear medicine physicians could cause variation in estimating gland size. Thus, this could affect the prescribed I-131 activity in each patient. Third, the follow-up duration was varied among the patients ranging from 6 to 9 months which can affect the treatment outcomes.

An issue that needs clarification is the strategy to improve success rate of RAI therapy by using dose corrected for thyroid gland size method. Higher prescribed I-131 activity for each stratum of thyroid gland size needs consideration and further prospective study is required.

CONCLUSION

First RAI therapy using dose corrected for thyroid gland size had a modest success rate of 50% in patients with Grave's disease. Sex, thyroid gland size, and prior antithyroid drug use showed no significant association with the successful treatment.

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