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Comparison of Fixed versus Calculated Activity of Radioiodine for the Treatment of Graves Disease in Adults

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Background: Radioactive iodine as a treatment modality has been shown in several studies to be a safe and effective therapy for Graves disease. However, there is still no uniformity regarding optimal dosing method. The aim of this study is to compare the efficacy of calculated and fixed dosing of radioiodine for the treatment of Graves disease.

Methods: A hundred twenty-two patients diagnosed with Graves disease were randomized to receive either fixed or calculated dose of radioiodine. Those randomized to fixed activity received either low fixed activity at 9.9 mCi for thyroid gland size <40 g or high fixed activity at 14.9 mCi for thyroid gland size 40 to 80 g, and those grouped to calculated activity received 160 μCi/g of thyroid tissue adjusted for 24 hours radioiodine uptake. Thyroid function tests (free thyroxine [T4] and thyroid stimulating hormone [TSH]) were monitored at 10, 16, and 24 weeks after radioactive iodine therapy. The primary outcome, treatment failure was defined as persistently elevated free T4 and low TSH.

Results: Of the 122 patients randomized, 56 in the fixed dose group and 56 in the calculated dose group completed the follow-up. At the end of 6 months, the percentage of treatment failure was 37.50% in the calculated dose group versus 19.64% in the fixed dose group with a relative risk of 0.53 (95% confidence interval, 0.28 to 0.98) favoring the fixed dose group.

Conclusion: Fixed dose radioiodine has a significantly lower incidence of persistent hyperthyroidism at 6 months post-radioactive therapy.

Keywords: Graves disease; Radioactive iodine; Hyperthyroidism

INTRODUCTION

Radioactive iodine therapy is a well-established definitive treatment of Graves disease. Despite the long experience with radioiodine for hyperthyroidism, controversy remains regarding the optimal method to determine the activity that is required to achieve an optimal radiation activity to the thyroid gland and a subsequent optimal clinical outcome [1]. Administration of high I-131 activities, aimed at a rapid cure of hyperthyroidism, may result in a high incidence of hypothyroidism, necessitating life-long hormonal substitution. On the other hand, low I-131 activities may cause a delay in achieving euthyroidism; thus, prolonging the period at risk of cardiovascular complications, and may lead to higher recurrence rates [2].

Planned dose varies according to the aim of treatment and ranges from 80 to 200 μCi/g in different centers. Possible outcomes are euthyroidism, persistent or recurrent hyperthyroidism and permanent hypothyroidism. Outcomes depend on the amount

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of radioiodine delivered and retained by thyroid tissue, thyroid gland size, previous anti-thyroid drug use and other factors [3].

Two general methods are used to determine activity: standardized activity using a fixed activity for all patients versus dosimetric calculation, which is based on radioiodine uptake (RAIU) and estimated weight of the thyroid gland determined by direct palpation or thyroid ultrasound [1,4].

The latest recommendation of the American Thyroid Association and American Association of Clinical Endocrinologists in the management of hyperthyroidism is to administer sufficient radiation in a single activity (typically 10 to 15 mCi) to render the patient with Graves disease hypothyroid [5].

The present protocol at the Section of Nuclear Medicine and Section of Endocrinology Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, is to give a calculated activity, aiming to deliver 160 μCi/g of thyroid tissue in order to render a patient either euthyroid or hypothyroid [6,7]. The general research objective is to compare the efficacy of fixed versus calculated radioiodine activity in achieving hypothyroidism or euthyroidism.

METHODS

Ethical consideration

Study protocol was submitted and approved by the University of the Philippines Manila-Research Ethics Board (UPM-REB). The study was monitored by the UPM-REB in its entire duration. Subjects were given consent forms upon explanation of the significance, objective and intervention to be done. All data collected including the identity of the person involved remained confidential.

Study design

This study is a randomized double-blind trial done at the Philippine General Hospital, University of the Philippines.

Study subjects

All patients referred to the Section of Endocrinology, Diabetes and Metabolism at Philippine General Hospital for a first radioiodine treatment of Graves disease were potentially eligible for the study. Graves disease was diagnosed on the basis of compatible symptoms of thyrotoxicosis, suppressed thyroid stimulating hormone (TSH) levels (normal value, 0.3 to 3.8 mIU/L), elevated serum free thyroxine (T4, normal value, 11 to 24 pmol/L) and/or free triiodothyronine (T3, normal value, 2.2 to 6.8 pmol/L), elevated RAIU, and diffuse gland enlargement (on palpation or ultrasonography). All patients underwent complete physical examination and assessment of comorbid conditions.

Patients included were at least 18 years of age diagnosed with Graves disease. Excluded are pregnant patients or those planning pregnancy within the year, lactating patients, those with co-existing thyroid cancer or suspicion of thyroid cancer, individuals unable to comply with radiation safety guidelines, those with symptomatic compression or large goiters (>80 g), those with nodular goiters, those with previous thyroid surgery or had received radioactive iodine treatment, those with moderate to severe active Graves ophthalmopathy. Large goiters (>80 g) were excluded from this study, since it is a practice in our institution to refer patients with large goiters for thyroidectomy.

Sample size

Sample size (n=122) was calculated using the 83% success rate of calculated activity of radioiodine in treatment of Graves disease, based on the local data of Philippine General Hospital [7]. Sample sizes of 61 in group one, and 61 in group two achieved 95% power to detect a non-inferiority margin difference between the group proportions of 0.05. The reference group proportion is 0.83. The treatment group proportion is assumed to be 0.78 under the null hypothesis of inferiority. The power was computed for the case when the actual treatment group proportion is 0.5000. The test statistic used is the one-sided Z test (unpooled). The significance level of the test was targeted at 0.95. The significance level actually achieved by this design is 0.0526. Drop out rate was also included in the calculation (n=20). Sixty-one patients were randomized to each group of fixed and calculated activity of radioiodine.

Description of study procedure/experimental maneuver

Randomization list was generated from Microsoft Excel 2000 (Microsoft, Redmond, WA, USA) and kept by the primary investigator. The subjects, referring physician and nuclear medicine consultants were blinded to randomization and activity received by the subjects.

Radioiodine therapy was accompanied by standard radiation protection guidelines, information that permanent hypothyroidism was a likely outcome from radioiodine therapy with possible lifelong levothyroxine supplementation and verification that the patient will have a follow-up assessment with the referring endocrinologist after radioiodine treatment.

Methimazole and propylthiouracil were discontinued 5 days and 2 weeks respectively before the thyroid scan and radioiodine, and were not restarted unless there was evidence of per-

sistent or worsening hyperthyroidism at the initial visit 4 weeks post-treatment. β-Blockers were allowed for symptom control during the peri-radioiodine period.

Each subject underwent thyroid scan with uptake (2 and 24 hours after a tracer dose) after discontinuation of anti-thyroid medications.

Thyroid gland weight is computed using measurements from thyroid ultrasound with the following formula: thyroid gland weight (g)=[(length×width×width)×0.4 left lobe]+[(length×width×width)×0.4 right lobe)]. The length represents the longitudinal diameter in centimeter; the width is the measure of the transverse diameter.

Subjects were randomized and treated according to either fixed or calculated radioiodine activity. Those randomized to fixed activity received either low fixed activity at 9.9 mCi for thyroid gland size <40 g or high fixed activity at 14.9 mCi for thyroid gland size 40 to 80 g, and those grouped to calculated activity received 160 μCi/g of thyroid tissue adjusted for 24 hours RAIU. Dose is calculated using the following formula: dose (mci)=(0.16×thyroid gland weight)/24-hour uptake (%).

A pregnancy test was obtained within 48 hours prior to treatment in any female with childbearing potential. Subjects were advised to reduce dietary iodine intake for 1 week prior to and after uptake and therapy.

Data collection

The following clinical variables were collected: age, gender, duration of anti-thyroid drugs prior to radioiodine therapy, smoking history, family history of Graves disease, presence of complications (ophthalmopathy, thyrotoxic heart disease), estimated thyroid size (using the thyroid ultrasound measurements), initial thyroid function tests (without treatment) and 2- and 24-hour uptake.

Description of outcome measures

The same endocrinologists as those in the pre-radioiodine assessment were involved in clinical follow-up, and they served as the outcome assessors. Follow-up was scheduled at 4, 10, 16, and 24 weeks post-radioiodine, and as deemed necessary by the endocrinologist, who monitored for the following clinical outcomes: persistent/recurrent hyperthyroidism requiring anti-thyroid medications and/or additional radioiodine therapy; hypothyroidism, confirmed biochemically with elevated serum TSH on two occasions at least 4 weeks apart and requiring permanent levothyroxine treatment; and euthyroidism, a clinically and biochemically euthyroid state to the end of follow-up in the absence of further thyroid treatment. Patients were followed until the end of 6 months.

Data analysis

Profile of patients was reported with descriptive statistics using quantitative variables (mean±SD) and qualitative variables (frequency, percentage), with 95% confidence interval. Patient characteristics and outcome were compared in the calculated versus the fixed method. The study was analyzed using the Stata Software for a non-inferiority study.

We defined non-inferiority as 5% difference in the failure rate of the treatment group compared to the standard. The relative risk for treatment failure will be computed for each arm.

RESULTS

Of the 122 study participants, 61 were randomized to the fixed dose treatment arm and 61 to the calculated dose arm.

Baseline characteristics are summarized in Table 1. Majority of the subjects were female, non-smokers and without a family history of thyroid disease. Few patients have ophthalmopathy (most were mild and inactive) and thyrotoxic heart disease (most belong to functional class I to II). Baseline TSH were 0.11±0.28 mIU/L for the calculated dose group and 0.05±0.01 mIU/L for the fixed dose group. There were no significant differences between the two groups with respect to the characteristics listed.

In the fixed dose group, 40 (65.57%) received 9.9 mCi and 21 (34.43%) received 14.9 mCi. Subjects in the calculated dose group received radioiodine dose of 3.71 to 14.9 mCi.

Table 2 summarizes the effects of radioiodine therapy for both study groups on follow-up at week 10, 16, and 24 post-therapy. Results were calculated using a per protocol analysis. At both weeks 10 and 16, results showed a trend toward benefit with fixed dose treatment but the results were not statistically significant. However, at the end of the 6-month follow-up, 45 (80.36%) achieved a successful outcome (hypothyroid or euthyroid) in the fixed dose arm compared to only 35 (62.50%) in the calculated dose arm.

Table 3 summarizes the effects of radioiodine therapy for both groups on follow up. However this time, the results were shown based on an intention-to-treat analysis.

In both per protocol and intention-to-treat analysis, the fixed dose protocol shows treatment benefit over the calculated dose protocol in week 10, 16, and 24 of follow-up with significant results favoring fixed dose protocol in week 24 of follow-up.

Table 1. Baseline Characteristics of Study Participants (n=122)

Characteristic	Calculated	Fixed	P value[a]
Number	61	61	
Age, yr	35.48±10.58	35.20±11.97	0.892
Sex, female:male	53:8	46:15	0.164
Anti-thyroid medication use	14±10	19±32	0.243
Smoking, yes:no	55:6	54:7	1.000
Family history, yes:no	9:52	8:53	1.000
Ophthalmopathy, %	18.03	34.43	0.063
TTHD, %	9.84	18.03	0.296
Baseline TSH, mIU/L	0.11±0.28	0.05±0.11	0.179
Baseline free T4, pmol/L	53.89±48.27	61.51±57.03	0.437
Thyroid gland weight, g	34.14±14.46	36.01±17.32	0.518
2-Hour uptake, %	49.51±20.33	48.91±19.14	0.866
24-Hour uptake, %	63.07±11.07	63.90±13.25	0.708
Mean dose received	8.46±3.18	9.9±14.9	-

Values are expressed as mean±SD.
TTHD, thyrotoxic heart disease; TSH, thyroid stimulating hormone; T4, thyroxine.
[a]Significant if P<0.05.

Table 2. Summary of Percentage of Treatment Failure of Calculated versus Fixed Dose of Radioiodine Treatment (per Protocol Analysis)

	Calculated	Fixed	Relative risk	P value
Week 10	27 (48.21)	23 (41.07)	0.85 (0.56–1.29)	0.447
Week 16	24 (42.86)	15 (26.79)	0.63 (0.37–1.06)	0.074
Week 24	21 (37.50)	11 (19.64)	0.52 (0.28–0.98)	0.037

Values are expressed as number (%) or relative risk (95% confidence interval).

Table 3. Relative Risk of Treatment Failure of Calculated versus Fixed Dose of Radioiodine Treatment (Intention-to-Treat Analysis)

	Relative risk	P value
Week 10	0.85 (0.55–1.31)	0.462
Week 16	0.63 (0.36–1.07)	0.081
Week 24	0.52 (0.27–0.99)	0.040

Values are expressed as relative risk (95% confidence interval).

DISCUSSION

Radioactive iodine has long been used to treat Graves disease because of its efficacy, safety, and cost effectiveness. The following approaches have been used: either a fixed dose was given to all patients (independent of gland size or iodine uptake) or a dose calculated to deliver a specific radiation dose based on gland size and iodine uptake and sometimes iodine turnover [4]. Studies have been done as well as a systematic review and meta-analysis but results has been conflicting and still no consensus has been reached regarding which method is optimal.

A meta-analysis by de Rooij et al. [2] compared the effect of estimated versus calculated activity of radioiodine in hyperthyroidism, and showed that estimation and calculation of applied I-131 activities resulted in similar rates of successful treatment outcome (i.e., achieving persistent euthyroidism) and cure of hyperthyroidism (i.e., achieving euthyroidism or hypothyroidism). The weighted mean relative frequency of successful treatment outcome was 1.03 (95% confidence interval [CI], 0.91 to 1.16), and cure of hyperthyroidism was 1.03 (95% CI, 0.96 to 1.10) [2]. Subgroup analysis showed a relative frequency of euthyroidism of 1.03 (95% CI, 0.84 to 1.26) for Graves disease [2]. This meta-analysis involved studies with large clinical heterogeneity and only included a small number of randomized

controlled trials. Differences included: methods used to determine radioactive iodine activities, formulas used to calculate activity, causes of hyperthyroidism (Graves disease, toxic multinodular goiter, and toxic adenoma), methods to determine thyroid gland weight (palpation, ultrasound, and nuclear imaging), definition of a successful outcome with some studies using euthyroidism as a successful outcome.

A randomized double blind comparison was published by Miranda-Padua et al. [6]; where 27 patients were given a fixed dose and 18 patients given a calculated dose. At 6-month post-radioiodine therapy, failure rates were observed in 11 versus 22% in fixed versus calculated dose group respectively with a relative risk of 0.67 favoring the fixed dose group [6]. The authors reported that the study can be influenced by its small population size and the variation in the patient drop outs [6].

Although radioactive iodine treatment is relatively inexpensive, the need to determine thyroid gland size and iodine uptake measurements, the calculated dose regimen adds a level of complexity and additional costs. In our hospital, the combined cost for performing RAIU measurement and thyroid ultrasound exceed/equals the cost of the treatment itself and performance of these may even delay the administration of treatment. Given the limited resources and economic considerations in our hospital, the use of fixed-dose regimen may be more cost-effective for the patients in our setting. Therefore the use of a fixed activity method can possibly simply our approach to treatment of Graves disease with potential cost savings.

The basis for the use of 160 μCi/g for the calculated dose is the study done by Aniel-Quimpo et al. [7], comparing low and high activity radioiodine (80 μCi/g vs. 160 μCig), which showed that at 4 years, 1/7 from the low activity and 7/9 from the high activity group were hypothyroid.

Our study was a randomized, double blind, controlled prospective trial comparing the two protocols: calculated versus fixed dose. Treatment goal was to render the patient either euthyroid or hypothyroid at the end of week 24 with treatment failure designated as persistence of hyperthyroidism at the end of follow up period. The outcome of our study showed advantage of fixed dose regimen with a higher success rate and a lower incidence of persistent hyperthyroidism. Our results were in an agreement with the results of the study done by Miranda-Padua et al. [6].

Studies have addressed the response to radioiodine therapy in relation to the radioiodine uptake and generally a high radioactive iodine uptake value is considered as a favorable factor for the success of radioiodine therapy [8]. However, studies by Damle et al. [8] and Walter et al. [9] have yielded conflicting results that showed an inverse correlation of pre-therapeutic iodine uptake level and therapeutic outcome. Standards regarding fixed doses were mainly based on studies done in iodine-replete countries, which may cause a lower radioactive iodine uptake value. Filipinos may have higher uptake values because of the relatively iodine-deficient state [6].

Because of financial reasons, patients in our setting may be exposed longer to anti-thyroid drugs before undergoing radioiodine therapy. Anti-thyroid drugs may cause a relative radio-resistant state [10]. A meta-analysis of the effects of anti-thyroid drugs on radioiodine treatment by Walter et al. [11] showed increased risk of treatment failure (persistent hyperthyroidism) of 1.48 and a lower risk of hypothyroidism (risk ratio, 0.76) when anti-thyroid drugs were given before radioiodine treatment.

Our patients are symptomatic of thyrotoxicosis longer before seeking first consult. Patients in our study have a lower baseline TSH and a higher mean free T4 and/or free T3. Lewis et al. [12] in their study showed that a higher free T4 at presentation was associated with an increased failure rate of radioiodine [10]. Thyroid gland size also influences outcome as patients with a larger thyroid size are more likely to fail after a single dose of radioiodine [10,12].

Although 80% of patients achieve permanent hypothyroidism at the end of 6 months, rates of hypothyroidism can still increase; in our study, because follow-up is limited to only until the end of 6 months post-radioiodine therapy, some patients who may still achieve hypothyroidism may have been missed. Although permanent hypothyroidism was diagnosed when serum TSH was elevated on two occasions, 4 weeks apart, it is still possible that some of these cases represented transient hypothyroidism.

In conclusion, the study showed a significant advantage of the fixed dose radioiodine therapy compared with the calculated dose with a higher success rate and a lower incidence of persistent hyperthyroidism.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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