

ORIGINAL ARTICLE

The Outcome Of A Calculated Radioiodine Dose Based On Pertechnetate Thyroid Uptake Ratio In Treatment For Hyperthyroidism

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ABSTRACT

Introduction: There are two dosing methods for radioiodine dose administration including empirical fixed dose and calculated dose. Recent meta-analysis supported that dose calculation is better than empirical fixed dose. However, dose calculation by dosimetry or 24 hours radioiodine uptake ratio can be tedious. Pertechnetate thyroid scintigraphy is a simple nuclear imaging that can be completed on the same day and pertechnetate thyroid uptake ratio determined from the scintigraphy can be used to calculate the radioiodine dose. This research is done to measure the efficacy of the calculated dose regime. **Methods:** Hyperthyroidism patients referred for first radioiodine therapy were recruited. Pertechnetate thyroid scintigraphy was done and pertechnetate uptake ratio used for dose calculation. The outcome of the treatment was determined at six months. **Results:** A total of 95 patients were recruited. Six months after treatment, 82.1% of the calculated dose cohort achieved euthyroid or hypothyroid state. Participants with multinodular goitre had higher failure rate than those with Graves' disease ($p=0.032$) although there was no difference in the median RAI dose given ($p=0.866$). **Conclusion:** This calculated dose method showed good outcome with 82.1% cure rate at six months post treatment.

Keywords: Hyperthyroidism, Nuclear Medicine, Radionuclide imaging, Pertechnetate, Sodium iodide

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It has been a routine practice to give an empirical fixed dose of 15 mCi in Hospital Pulau Pinang due to the dispensing convenience. In 2015, by using the fixed dose of 15mCi, 40% of the patients treated for hyperthyroidism in Nuclear Medicine Department, Hospital Pulau Pinang required repeated treatment.

INTRODUCTION

Although radioactive iodine-131 (RAI) therapy is a mainstay of treatment for hyperthyroidism, various dosing methods of administering RAI have been used in different centres and there is no consensus as to which method offers the greatest efficacy in treating hyperthyroidism patients, while keeping the radiation exposure to the minimum. A recent meta-analysis did support that dose calculation is better than empirical fixed dose (1).

However, dose calculation by dosimetry or radioactive iodine thyroid uptake (ITU) ratio at 24 hours can be tedious and time consuming. It is especially challenging in local setting where we have very limited facilities and resources, as Nuclear Medicine services are not available in every tertiary hospital. Patients may have difficulty in terms of logistics and finances, especially if repeated treatments are needed.

A calculated dosing method by using pertechnetate thyroid uptake ratio (TcTU) algorithm rather than ITU offers greater convenience to the patients and potentially increase the treatment efficacy. Thus, this study is done to measure the efficacy of a calculated dose based on TcTU.

MATERIALS AND METHODS

A prospective cohort study for hyperthyroidism patients above 18 years old was carried out in the Department of Nuclear Medicine, Hospital Pulau Pinang, Pulau Pinang, Malaysia from March 2016 to September 2017 by using the calculated dose regime.

Patients with history of thyroid surgery and prior RAI therapy were excluded. Participants were asked to withhold anti-thyroid drugs (ATD) for a week and avoid substances with high iodine content for two weeks

prior to the appointment date (2). Blood for thyroid function test (TFT) was taken and pertechnetate thyroid scintigraphy was performed on the same day prior to RAI treatment at the same institution. Follow-up reviews were done at three months and six months post therapy. Outcome of participants who achieved euthyroidism or hypothyroidism at six months after RAI therapy was defined as treatment success. Euthyroidism was defined as having serum TSH and free T4 level within normal range without ATD. Hypothyroidism was defined as having elevated TSH with low/normal free T4 level or requiring ATD.

Thyroid Size Estimation

Thyroid gland size was estimated by physical examination (visual assessment and clinical palpation) based on World Health Organization (WHO) classification (3); Grade 0: No palpable or visible goitre, Grade 1: Goitre that was palpable but not visible when neck was in normal position and Grade 2: Goitre that was clearly visible when neck was in normal position.

Thyroid Scintigraphy and Pertechnetate Uptake Ratio

Technetium-99m (Tc-99m) in the form of pertechnetate was used as the radiopharmaceutical tracer and five mCi injected intravenously. Planar images were acquired 20 minutes after the injection using single photon emission computed tomography scintillation gamma camera equipped with a low-energy, high-resolution and parallel-hole collimator (E.CAM, Siemens Medical Solutions) with energy peak at 140 keV and 20% energy window. Scan was done in supine position with neck extended and supported by pillow placed under shoulder. Pre-injection syringe and post-injection syringe counts as well as anterior images of the neck were acquired for 200 seconds. The TcTU was calculated by camera-based method using standard software. The counts in the thyroid gland are determined by a region of interest (ROI) drawn along the borders of the gland and subtracted off the background counts by another ROI drawn just below the thyroid. The TcTU was calculated according to the ratio of background subtracted thyroid counts to the difference of post-injection syringe and pre-injection syringe counts. This method for the calculation of TcTU was as previously described by Ramos et al. (4).

Calculation of RAI Dose

The RAI dose was calculated based on the formula incorporating Joseph's algorithm (1977) by Gotthardt et al. (5) that substitutes the thyroid volume and ITU with TcTU equations. The desired delivered activity was set at 200 μ Ci/g as it was found to be effective in achieving a high cure rate (6, 7).

$$\text{Dose (mCi)} = \frac{200 \times [8.33 \times \text{TcTU} (\%) - 6.67]}{67.5 \times \text{TcTU} (\%) + 67.5}$$

Data Analysis

Statistical analyses was performed using IBM Statistical

Package for Social Science software version 22 for Mac by using appropriate tests where applicable (8). P value of 0.05 and less was considered as significant.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments as well as Malaysian Guideline for Good Clinical Practice. This study had been approved by the Medical Research Ethics Committee (MREC) of the Malaysian Ministry of Health and registered with the Malaysia National Medical Research Register (NMRR ID: NMRR-15-1991-28409). This study had also been approved by the Jawatankuasa Etika Penyelidikan Manusia (JEPeM) of Universiti Sains Malaysia (USM JEPeM ID: USM/JEPeM/16020069).

RESULTS

Demographics and Clinical Data

The demographics of the participants are summarised in Table I. A total of 75 participants (79.0%) were biochemically toxic on the day of treatment with median TSH 0.005 mIU/l (0.005 to 0.010 mIU/l), median free T4 31.00 pmol/l (22.00 to 47.00 pmol/l). The rest were biochemically euthyroid with median TSH 0.718 mIU/l (0.340 to 1.105 mIU/l) and median free T4 14.92 pmol/l (12.25 to 17.75 pmol/l). The laboratory's normal range for TSH was given as 0.270 to 4.200 mIU/l and normal range for T4 was given as 12.00 – 22.00 pmol/l. Most of them were on oral carbimazole with median daily dose of 10mg (5mg to 15mg), seven were on oral propylthiouracil (mean daily dose 410 \pm 277mg) and there was one participant who was on oral lithium 600mg daily for the past one year as she developed allergic reaction to carbimazole and propylthiouracil.

TcTU and RAI Dose

The median TcTU was 18.0% (7.8% to 30.8%) and based on the TcTU, the median calculated RAI dose was 22.0 mCi (20.0 to 23.0 mCi). There was no significant difference in TcTU ($p=0.990$) and RAI dose ($p=0.866$) between Graves' disease and multinodular goitre (MNG).

Treatment Outcome

Out of all the participants, 17.9% were euthyroid, 56.8% were hypothyroid and 25.3% remained hyperthyroid after three months of RAI therapy. The overall success rate at three months post RAI therapy was 74.7%. At six months post RAI therapy, 14.7% of the participants were euthyroid, 67.4% was hypothyroid and 17.9% remained hyperthyroid. Thus, the success rate at six months post RAI therapy was 82.1%. There were four euthyroid participants and one hypothyroid participant at three months post treatment who relapsed after six months.

Table I: Demographics and clinical data of the study participants

	Frequency (%)	
Total subjects	95 (100.0%)	
Age (years) *	46.0 ± 13.6	
Gender	Male	22 (23.2%)
	Female	73 (76.8%)
	Malay	68 (71.6%)
Ethnic	Chinese	21 (22.1%)
	Indian	4 (4.2%)
	Others	2 (2.1%)
	Graves disease	64 (67.4%)
Diagnosis	MNG	29 (30.5%)
	Toxic adenoma	2 (2.1%)
	Indeterminate	0 (0%)
Duration of disease (months) †	48.0 (23.0 – 96.0)	
ATD	Carbimazole	87 (91.6%)
	Propylthiouracil	7 (7.4%)
	Lithium	1 (1.0%)
	Family history	Yes
	No	75 (78.9%)
Pretreatment goiter	Grade 0	15 (15.8%)
	Grade 1	30 (31.6%)
	Grade 2	50 (52.6%)
Pretreatment TFT	TSH †	0.008 (0.005 - 0.047)
	T4 †	26.26 (18.00 - 43.00)

* Mean ± s.d.

† median (interquartile range)

A total of 75 out of 95 participants in the cohort had a significant goitre size reduction, mostly occurred in the first three months (Fig 1). Total of 65 participants had a reduction in goitre size at 3 months post therapy. 19 participants had reduction from grade 2 goitre to grade 1 goitre, 23 participants had reduction from grade 2 goitre to grade 0 goitre and 23 participants had reduction from grade 1 goitre to grade 0 goitre. There was a significant further reduction of goitre size in 19 participants after 6 months of therapy when compared with their goitre size at 3 months post treatment. 5 participants reduced from grade 2 goitre to grade 1 goitre, 2 participants reduced from grade 2 goitre to grade 0 goitre and 12 participants reduced from grade 1 goitre to grade 0 goitre.

Interestingly, the treatment outcome at six months was statistically different between diffuse goitre and multinodular goitre (Table II). Both participants with solitary toxic nodule were successfully treated. There was no difference in outcome between participants taking carbimazole compared to propylthiouracil (Table II) and the only participant who was on lithium was euthyroid at six months after therapy.

DISCUSSION

This study shows good outcome from the treatment with calculated RAI dose. The success rate at three months for this study is higher than the published success rate of 64.2% by using graded doses of up to 30mCi in the West African population despite that the current cohort had more severe disease, based on the lower pretreatment

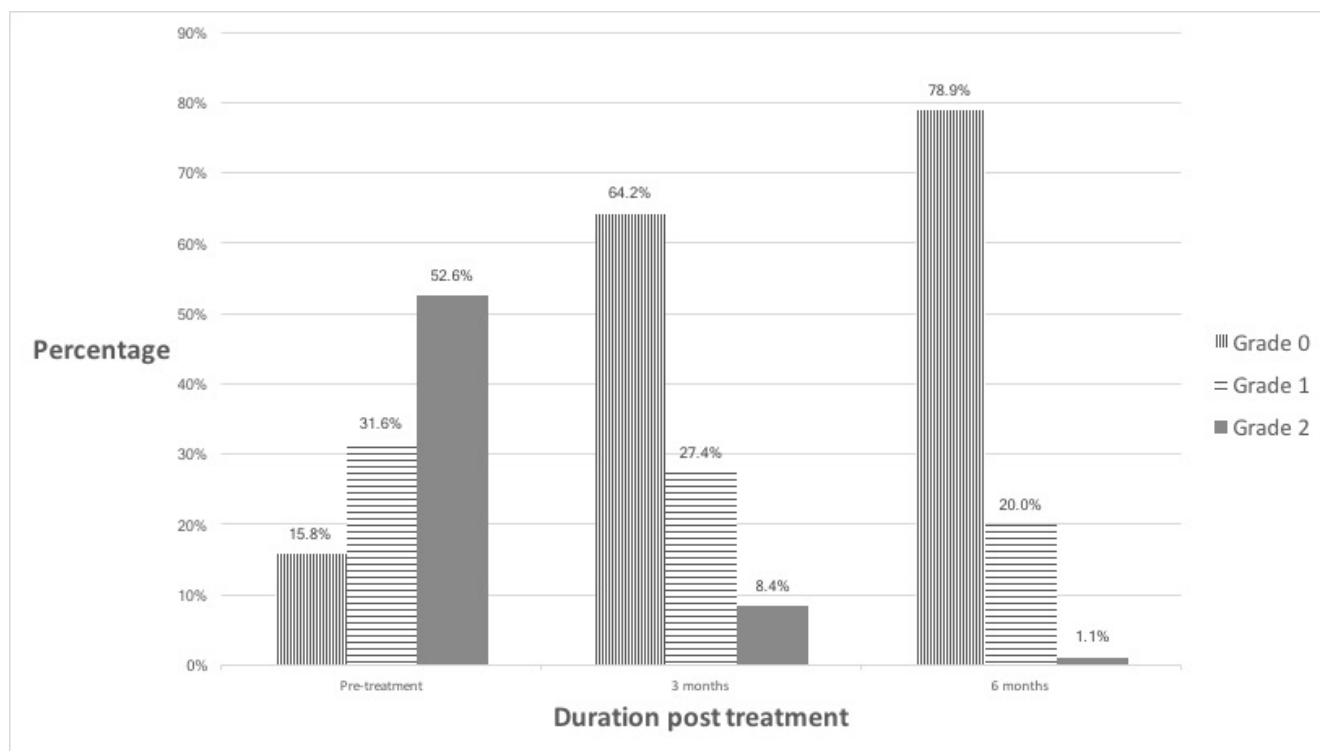


Figure 1: A graph showing the reduction in goitre size during the period of follow-up

Table II: Comparison of treatment outcome according to various factors

	Failure, Frequency	Success, Frequency	P value
Scan morphology *			
Diffuse goitre	8	56	0.032
MNG	9	20	
Gender †			
Male	4	18	>0.995
Female	13	60	
Goitre size			
Grade 0	0	15	0.126
Grade 1	6	24	
Grade 2	11	39	
Thyroid status †			
Non toxic	3	17	>0.995
Toxic	14	61	
ATD †			
Carbimazole	14	73	0.109
Propylthiouracil	3	4	
TcTU (%)	27.0 (12.6-39.2)	16.6 (7.6-27.2)	0.055
Dosage (mCi)	23.0 (21.0-24.0)	22.0 (19.8-23.0)	0.064
Duration of disease (months)	60.0 (12.0-78.0)	48.0 (24.0-96.0)	0.830
Pretreatment TSH (mIU/l)	0.005 (0.005-0.033)	0.009 (0.005-0.073)	0.354
Pretreatment free T4 (pmol/l)	32.00 (19.50-59.50)	26.10 (17.93-40.00)	0.503
Age (years) §	44.5 ± 13.9 ¶	46.2 ± 13.3 ¶	0.629

* Chi-square test

† Fisher-Exact test

‡ Mann-Whitney test

§ independent t-test

|| median (IQR)

¶ mean ± s.d

TSH of this cohort (9). The pretreatment TSH in that study group was 0.015 mIU/l, which was higher than this cohort.

At the study endpoint, the overall success rate of 82.1% is in concordance with the outcomes in other literatures on RAI therapy as well. In a study by Schiavo et al. in 2015, The RAI treatment outcome for MNG using calculated dose based on 24-hour ITU was also 82% after six months of treatment (10). On the other hand, the success rate was slightly higher at 88.3% for a study using calculated dose by ITU method for Graves' disease in a study done by Nwatsok et al. in 2012 (11). This may be due to the difference in the disease severity as only 42.6% of that cohort had goitre and the higher mean pretreatment TSH of 0.94 mIU/l. The success rate for calculated dose based on ITU in another study by Schneider et al. in 2014 was only 77.2% although that study group had similar characteristics with the current cohort (12). Overall, this suggests that calculation using TcTU algorithm is comparable to using ITU.

As shown in this study, the success rate for MNG and Graves' disease is significantly different, with MNG having a higher failure rate of 31.0% compared to 12.5% for Graves' disease, despite no differences in TcTU and RAI dose. This is in agreement with a study comparing the outcome between MNG and Graves' disease by Kurber et al. in 2001 (13). The authors also reported that ATD has negative effect on outcome in MNG but not in Graves' disease (13). This may be due to the steal phenomenon in MNG where the effect of pretreatment with ATD causes the rise in TSH which diverts the RAI from the autonomous nodules to the rest of the thyroid tissue (14). This cause a greater drop of efficacy in multinodular goitre than in Graves' disease. Also, the dose calculation for MNG may be more complicated than Graves' disease due to the polyclonal nature of the autonomous nodules (5) as well as the presence of other non-functioning nodules and stromal tissues in MNG (14). Thus, the algorithm used in this study might need adjustments in MNG and further research in this area is recommended.

However, there was no difference of outcome between those taking carbimazole and those on propylthiouracil in this current study. Pretreatment with ATD (carbimazole and propylthiouracil) are known to reduce RAI treatment efficacy even if the ATD was discontinued for a week before RAI treatment (15, 16). Interestingly, as mentioned in a study by Shivaprasad and Prasanna Kumar in 2015, the success rate in the pretreated group was 82.3%, which is similar with the outcome in the prospective cohort of this current study (15).

Therefore, the likely factors that contribute to the lower efficacy of this RAI treatment than expected are due to the pretreatment with ATD as well as the worse disease severity of this cohort, as evidenced by the large goitre size, high dose of the prior ATD therapy and the low pretreatment TSH.

One of the limitations of this study was the narrow time frame that did not allow for prolonged follow up of the participants. The study outcome was defined as the success rate at six months while certain literatures followed patients for up to one year and yielded better outcome rates (17, 18). However the time frame for follow-up of six months was adequate as the ATA guideline suggests repeating RAI dose if patients remain hyperthyroid after six months of initial RAI therapy (19). Other confounding factors such as smoking, concurrent illnesses, concurrent medications, compliance to diet restriction and withholding ATD prior to RAI therapy might interfere with the results of this study (14). Non-parametric statistical tests had to be used due to the skewed data distribution with small sample size in certain subgroups leading to low statistical power. Future study with a larger sample size is recommended to further validate the result of this study.

CONCLUSIONS

This calculated RAI dose therapy based on the TcTU algorithm showed fairly good outcome with 82.1% cure rate at six months post therapy. Patients with MNG were more likely to relapse after RAI therapy although there was no difference in the TcTU and RAI dose compared to Graves' disease.

Based on this study, the calculated dosing method may be used as a routine clinical practice. However, as the MNG had higher failure rate compared to Graves' disease, the algorithm may need to be adjusted and further research should be done in this area.

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