Original Article

EMPIRICAL FIXED RADIOIODINE THERAPY FOR HYPERTHYROIDISM: A SENSIBLE OPTION AND ITS OUTCOME AT A LOCAL NUCLEAR MEDICINE REFERRAL CENTRE.

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ABSTRACT

Fixed empirical radioiodine therapy is one of the treatment options for hyperthyroidism. Although several methods to calculate administered radioiodine activity have been proposed previously, no clear advantages could be proven in using adjusted dosage over fixed dosage. Hence, our aim was to determine the outcome following fixed 15 millicurie (mCi) therapy among local hyperthyroidism patients and factors associated with euthyroid status post-treatment. Patients undergoing first-time radioiodine therapy and achieved pre-treatment urinary iodine level <50 µg/L following minimum of 1 week dietary restriction preparation were recruited (n=49). Majority were middle aged females with small to moderate goitre. Anti-thyroid drugs consumption was stopped for at least a week prior to empirical 15 mCi radioiodine therapy. Favourable treatment outcome includes euthyroid and hypothyroidism determined at 9th month follow-up post-therapy. Collected clinical data were analysed. Majority (88%) achieved favourable thyroid status (euthyroid, n=26 and hypothyroidism, n=17). None developed any major therapy complication. No significant association between age, gender, goitre classification and duration of illness with euthyroid post-treatment status. However, patients with optimised baseline free thyroxine, fT4 values within normal range were associated with euthyroid status (p<0.05). Multiple logistic regression analysis revealed that optimised baseline fT4 was the only factor associated with developing euthyroid status (OR 19.48, 95% CI 1.253-302.692, p<0.05). Majority of our hyperthyroidism patients achieved favourable outcome following empirical fixed 15 mCi radioiodine therapy. Optimised baseline fT4 was significantly associated with euthyroid status post-treatment.

INTRODUCTION

Hyperthyroidism can be defined as a state of hyper-functioning thyroid causing excessive circulating thyroid hormones. Various aetiologies such as Graves' disease, toxic thyroid adenoma and multinodular goitre lead to hyperthyroidism. Nuclear medicine therapy utilising radioactive Iodine-131 or radioiodine is an established treatment method for thyroid diseases. Oral administration of radioiodine and its role in the management of hyperthyroidism related benign disorders and thyroid malignancy have been well documented [1]. After being taken up by thyroid gland and processed similarly as dietary iodine, radioactive Iodine-131 will emit beta-radiation destroying thyroidal follicular cells and gradually leading to disease control [2].

At present, outpatient radioiodine therapy for hyper-thyroidism has become one of the feasible treatment options in Malaysia mainly available at several tertiary hospitals and referral institutions with nuclear medicine facilities [3]. Although majority of our hyper-thyroidism patients are medically treated with thionamide anti-thyroid drugs, some of them might be referred for radioiodine therapy. Reason for Iodine-131 administration among this subset of patients is essentially due to failure of medical treatment [4]. The aim of radioiodine therapy in hyperthyroidism is to achieve euthyroid state or iatrogenic hypothyroidism which require thyroxine supplement [1].

Most local nuclear medicine centres prescribe empirical fixed radioiodine dosage of generally <30 millicurie (mCi) for hyperthyroidism with consideration given to thyroid size based on physical examination [5]. Although several methods in calculating appropriate and almost accurate Iodine-131 dosage were previously proposed, no clear advantages could be proven in using adjusted over fixed dose regimen [6, 7]. Hence, our aim was to determine the outcome following common fixed 15 millicurie (mCi) therapy among local hyperthyroidism patients particularly euthyroid state post-therapy and factors associated with it.

METHODOLOGY

A prospective study was conducted, involving hyperthyroidism patients regardless of underlying of aetiologies referred for first-time radioiodine therapy between January and September 2014, at Nuclear Medicine Department, Hospital Pulau Pinang. The patients received briefing and written instruction on relevant preparation measures and pre-therapy dietary restriction. Anti-thyroid drugs consumption except for lithium was stopped for at least a week prior to and after radioiodine therapy. Subsequently, pre-treatment urinary iodine test was performed to ensure compliance towards the dietary preparation. Altogether, 49 patients who achieved urinary iodine level <50 µg/L following minimum of 1 week dieting were recruited.

All patients received with empirical fixed 15 mCi radioiodine. They were then monitored and attended clinic sessions scheduled every 3 months. Favourable treatment outcome includes euthyroid and hypothyroidism determined at 9th month follow-up post-radioiodine therapy. Relevant clinical data including age, gender, duration of illness, pre-therapy free thyroxine (fT4) level, thyroid size based on the WHO/UNICEF/ICCIDD goitre grading as well as treatment adverse effect and outcome were collected. Statistical analysis was performed using SPSS version 19.0 for Windows. Written consents were obtained from all subjects prior to their enrolment in this study. This study has received ethical approvals from Medical Research Ethics Committee, Kementerian Kesihatan Malaysia and Human Research Ethics Committee, Universiti Sains Malaysia.

RESULTS

Out of 49 patients included in this study, 73% of them were females. Average age of patients was 45.5 ± 12.5 years. Mean duration of hyperthyroidism was 40.2 ± 29.8 months with 55% of patients having the illness for more than 24 months. Nearly 61% of patients presented with small to moderate sized goitre. Mean fT4 level pre-radioiodine therapy was 21.0 ± 14.2 pmol/L. Approximately 71% of patients had optimised pre-therapy fT4 values (within normal range of 12–22 pmol/L). At 9th month follow-up, majority of patients (88%) achieved favourable treatment outcome with overall no reported major adverse effects. Clinical characteristics and treatment outcomes are summarised in Table 1.

Among patients with favourable outcome, about 60% attained euthyroid state without thyroxine supplement post-radioiodine therapy. Patients with optimised pre-therapy fT4 level showed significant correlation with euthyroid status (p=0.037). However, there was no significant association found between euthyroid status and gender (p=0.625), age (p=0.551), duration of illness (p=0.204) as well as goitre classification (p=0.299). Furthermore, multiple logistic regression analysis revealed that optimised fT4 was the only significant factor associated with developing euthyroid (OR 19.478, 95%CI 1.253–302.692, p<0.05) as shown in Table 2.

Table 1: Clinical characteristics and treatment outcomes of the patients (n=49)

Variables		n (%)
Gender	Females	36 (73%)
	Males	13 (27%)
Mean Age		45.5 ± 12.5 years
Mean Duration of Illness		40.2 ± 29.8 months
Illness Duration	≤ 24 months	22 (45%)
	> 24 months	27 (55%)
Goitre Grading	Small to Moderate	30 (61%)
	Large	19 (39%)
Mean Baseline fT4		21.0 ± 14.2 pmol/L
Category of fT4	Deranged	14 (29%)
	Optimised	35 (71%)
Outcome	Euthyroid	26 (53%)
	Hypothyroidism	17 (35%)
	Hyperthyroidism	6 (12%)

DISCUSSION

Generally, radioiodine therapy for hyperthyroidism is relatively safe and has minimal adverse effects. However, the protocol for radioiodine therapy varied between centres and there were differences in the doses of Iodine-131 activity being used to cure hyperthyroidism [8]. Empirical fixed dose regimen for radioiodine therapy is being described as simple, more convenient to use and effective in achieving therapeutic goals compared to calculated dose method [2, 9]. Calculated dose regimen is associated with prolongation of treatment duration and has not been demonstrated to have significant benefits in terms of improving cure rates [10]. Fixed doses of radioiodine activity are generally in the range of 5–15 mCi which enable further incremental dose of Iodine-131 when the thyroid gland is large [11]. A Summary of Consensus for Management of Thyroid Disorders in Malaysia has highlighted the role of radioiodine therapy and fixed dose approach using 10–15 mCi Iodine-131 for hyperthyroidism [12].

An empirical fixed dose regimen of 15 mCi was selected and administered for all patients in this current study. Overall success rate at 9th month follow-up following fixed empirical 15 mCi radioiodine therapy among our cohort of patients was 88% with 26 patients achieving euthyroid status and 17 patients noted to be hypothyroid requiring thyroxine supplement. An early analysis of 478 hyperthyroidism patients showed 44% of them developed euthyroid and 35% became hypothyroid at four months after 15 mCi of Iodine-131 therapy [10]. In another study, Lewis *et al*. (2013) reported favourable outcome with 74% of subjects became hypothyroid and 19% developed euthyroid at one year follow-up post radioiodine therapy with approximately 15 mCi for 449 hyperthyroidism patients with Graves' disease, toxic MNG and indeterminate aetiology [8].

Majority of patients in this study were middle aged females having hyperthyroidism with small to moderate sized goitre for more than 2 years prior to radioiodine therapy. Apart from radioiodine dosage, there are several other parameters such as age and gender of the patients, goitre size as well as disease severity that may influence Iodine-131 treatment outcome in hyperthyroidism [13]. Lower cure rates were associated with males, young patients, large goitre and higher disease severity [14, 15]. The statistical analysis revealed that patients with optimised pre-therapy fT4 level were significantly associated with post-treatment euthyroid status while age, gender, duration of illness and goitre classification showed no significant correlation. Optimised pre-therapy fT4 level was the only significant factor associated with developing euthyroid based on the multiple logistic regression analysis.

A retrospective study by Khalid *et al.* (2011) involving 584 hyperthyroidism patients receiving approximately 15 mCi radioiodine therapy revealed that 93% of subjects achieved favourable outcome and their pre-treatment fT4 level was the only factor which independently influenced therapy outcome. High fT4 level of >45 pmol/L predicted a lower cure rate [16]. Although Lewis *et al.* (2013) reported that patients with medium to large sized goitre were found to have persistent hyperthyroidism (14.7%, p=0.001) than those with small or no goitre, the influence of goitre size was not significant in the logistic regression model after inclusion of baseline fT4. Moreover, patients with markedly high baseline fT4 level (>80 pmol/L) in that study were

Table 2: Association between clinical parameters and euthyroid state post-radioiodine therapy by Multiple Logistic Regression model (n=43)

Variables	Regression coefficient (b)	Adjusted Odd Ratio (95% CI)	Wald statistic	Significance value
Age (years)	-0.019	0.98 (0.87, 1.10)	0.10	0.753
Illness duration (months)	0.002	1.00 (0.96, 1.05)	0.01	0.920
Gender				
Female	0	1		
Male	0.501	1.65 (0.25, 10.86)	0.27	0.602
Goitre				
Small to medium	0	1		
Large	0.248	1.28 (0.19, 8.49)	0.07	0.797
Baseline fT4 category				
Deranged	0	1		
Optimised	2.969	19.48 (1.25, 302.69)	4.50	0.034

demonstrated to have increased failure rate (16.7%, p=0.003) compared to those with lower ranges of fT4 [8].

Limitations of this study included the small sample size and short duration of follow-up compared to other previous studies. Long term effect especially hypothyroidism might manifest later with permanent hypothyroidism seemed to be unavoidable in Graves' disease [13, 17]. Additionally, information on the exact aetiologies of hyperthyroidism was not evaluated due to limited data available, while test for thyroid autoantibodies, ultrasonography and radioiodine uptake study were not routinely done for all patients. Another study limitation was determinant of goitre grading done by physical evaluation which could be subjected to observer variation and less accurate compared to ultrasonography. However, estimation of goitre by similar clinical method and grading have been utilised in other previous studies [9, 10].

CONCLUSION

Empirical fixed common dosage of 15 mCi radioiodine therapy could well be utilised for hyperthyroidism treatment. Majority of patients from our cohort of predominantly females with small to moderate goitre achieved favourable outcome at 9th month follow-up. No major therapy complications observed. Optimised pre-therapy fT4 level was significantly associated with developing euthyroid status post Iodine-131 treatment. Future study with larger cohort and longer monitoring period is recommended.

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