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Original Article

Efficacy of Radioiodine in the Treatment of Primary Hyperthyroidism

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Abstract

Background: Radioiodine (RI) is a commonly used treatment modality for primary hyperthyroidism. A single dose of RI has been reported to cure hyperthyroidism in the range of 50%–90% of the treated cases. The efficacy of RI treatment has not yet been investigated in the local population. **Objectives:** To assess the efficacy of RI therapy in patients with primary hyperthyroidism treated at Tawam Hospital, Al Ain, UAE. **Patients and Methods:** The electronic medical records of hyperthyroid patients who received RI treatment at Tawam Hospital between January 2009 and March 2017 were reviewed. The diagnosis was verified by reviewing clinical, laboratory, and imaging data. Following RI therapy, a cure was defined as the development of hypothyroidism or euthyroid status without the aid of antithyroid drugs (ATDs) within 6 months post-RI therapy. Multivariate analysis was used to assess predictors of RI response. **Results:** A total of 125 patients (68.8% women) met the study criteria. The mean age ± standard deviation (SD) at RI therapy was 40 ± 15.1 years. The etiology of hyperthyroidism was available for 121 patients; Graves' disease (GD) (n = 83, 68.6%), toxic multinodular goiter (TMNG) (n = 31, 25.6%), and toxic adenoma (TA) (n = 7, 5.8%). The majority of patients (109, 87.2%) were pretreated with ATDs; 70.3% of those were treated for a period exceeding 18 months. Almost quarter of the patients were referred to RI due to other compelling medical reasons including ATDs intolerance, neutropenia, and hepatotoxicity. The mean ± SD administered RI activity was 14.6 ± 3.7 mCi (range: 8–25). Treatment response evaluation was possible in 97 cases. Post a single dose of RI treatment, 91.8% of patients achieved either euthyroid or hypothyroid status. Patients with GD developed hypothyroidism more frequently than TMNG or TA (80.6% vs. 65.2% vs. 33.3%, respectively). The time to cure was within 3 months in 21% and 3–6 months in 79% of the patients. The given dosage of I^{131} was the only predictor of cure rate. No major adverse effects were reported. **Conclusion:** We found that there is a delay in referring potential patients with hyperthyroidism for RI treatment and the cure rate of a single dose of I^{131} is 91.8% within 6 months of posttreatment; patients with TA may require higher doses of I^{131} therapy. Further studies are needed to explore the patient–physician barriers in utilizing RI as a timely mode of treatment for appropriately selected patients.

Keywords: Efficacy, Graves' disease, hyperthyroidism, primary hyperthyroidism, radioactive iodine, toxic multinodular goiter, treatment

Introduction

Hyperthyroidism is frequently encountered in general clinical practice with an estimated prevalence of 0.75%.[1] The most common causes of hyperthyroidism are Graves' disease (GD), toxic multinodular goiter (TMNG), and toxic adenoma (TA). The management options include the use of antithyroid drugs (ATDs), radioiodine (RI) ablation, or surgery. All of these modalities are effective in controlling hyperthyroidism, and each has its pros and cons.

While ATDs are popular in Europe, RI therapy is the first choice in North America.[2,3] In addition to patient preference, current guidelines favor RI for patients with ATDs-related side effects or resistance, post thyroid surgery and as curative therapy for GD, TA, or TMNG.[4] Except for small risk of worsening Graves orbitopathy (GO) in a subset of patients, RI is generally safe and well tolerated.[5]

The efficacy of RI has been reported in several studies with a cure rate ranging between 50% and 90% after a single therapeutic dose.[6-10] In addition to other established factors, a

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recent report from New Zealand suggested that ethnicity may influence RI therapy outcomes.[11] To the best of our knowledge, to date, no studies have evaluated the use and efficacy of this modality of treatment in the UAE. Such information is valuable when counseling our patients and will help the informed decision process.

This study aims to assess the clinical characteristics and treatment outcomes of patients with hyperthyroidism treated with RI therapy.

Patients and Methods

Setting

The nuclear medicine electronic database at Tawam hospital, the largest tertiary care center in the city of Al Ain, UAE, was used. All patients treated with RI for hyperthyroidism between January 2009 and March 2017 were included in the study.

Patients' demographics, diagnosis, duration of disease, time to RI therapy, the dose of RI, treatment efficacy, and adverse effects were collected from the medical records. The diagnosis was verified using clinical, laboratory thyroid function tests, thyroid antibodies including thyroid receptor antibodies, and/or imaging (scintigraphy or ultrasound) data as per established guidelines.[4] As per the hospital protocol, following RI therapy, patients were followed 4–6 weeks initially and then every 2–3 months at the discretion of the treating physician to assess response to treatment. Treatment is considered efficacious if cure, defined as development of hypothyroidism (high thyroid-stimulating hormone [TSH] or low-free thyroxine [FT4]) or euthyroidism (normal FT4, normal TSH) off ATDs, is achieved within 6 months of therapy. The study was approved by Al Ain Medical District Ethical Committee (AAMDEC) (CRD 506/17).

Radioiodine dose

The dose of RI was decided by the treating nuclear medicine physician, and it was estimated according to goiter size, diagnosis, and percentage of RI uptake on the diagnostic thyroid scan.

Statistical analysis

Continuous data are presented as means and standard deviations (SDs) or median and range according to the studied variable. Categorical comparisons were performed with the Chi-Square test. Simple binary logistic regression was used to find the degree of association with independent and dependent variables. Statistical significance was considered if $P < 0.05$.

Results

Demographic and clinical characteristics

A total of 125 patients (68.8% women) were included in the study [Table 1]. The mean age at RI therapy was 40 years ± 15.1 (range: 10–71). The UAE nationals were 50.4% (n = 63) of the studied patients. About 32.8% of patients (n = 41) were referred from outside our center.

Table 1: Patients' demographic characteristics and indications for use of radioiodine therapy

Characteristics	Results*
Age at RI treatment	40±15.1
Gender	
Male	39 (31.2)
Female	86 (68.8)
Diagnosis (n=121)	
Graves' disease	83 (68.6)
Toxic multinodular goiter	31 (25.6)
Toxic adenoma	7 (5.8)
Orbitopathy before RI therapy (n=93)	
Yes	10 (10.8)
No	83 (89.2)
ATDs pre RI (n=114)	
Yes	109 (95.6)
No	5 (4.4)
Time from diagnosis to RI therapy (months)	
<18	33 (29.7)
>18	78 (70.3)
Reason for RI therapy (n=116)	
Patient/physician preference	83 (71.6)
Relapse after ATD withdrawal	18 (15.5)
Neutropenia	7 (6)
History of thyroid surgery	5 (4.3)
ATD-related hepatotoxicity	2 (1.8)
ATD intolerance (nausea and vomiting)	1 (0.9)

*Results are shown as n (%) or mean±SD. RI: Radioiodine, ATDs: Antithyroid drugs, SD: Standard deviation

The etiology of hyperthyroidism was available for 121 patients; GD (n = 83, 68.6%), TMNG (n = 31, 25.6%), and TA (n = 7, 5.8%). Only 9.8% of patients with GD patients had abnormal eyes' findings of GO. The three most common reasons for selecting RI therapy were patient/physician preference (71.6%), relapse of hyperthyroidism off ATDs (15.5%), and neutropenia (6%). The complete data on the status of ATDs pre-RI therapy were available in 114 out of 125 patients. Most patients (n = 109, 87.2%) were pretreated with ATDs, and 70.3% of these were treated for more than 18 months. The mean dose ± SD of RI for the whole cohort was 14.56 ± mCi (range: 8–25). The mean doses were 14.7 ± 3.7, 13.7 ± 3.5, and 16.7 ± 3.9 mCi for GD, TMNG, and TA, respectively. The median time from diagnosis to RI treatment was 30.6 months (range: 0.25–168) and 63% of the patients received RI after 18 months of the diagnosis.

Radioiodine response and treatment outcomes

Proper follow-up after RI therapy was available for 97 patients. Of those, 89 (91.8%) patients achieved cure [Table 2]. Patients with GD developed hypothyroidism more frequently than TMNG or TA (80.6% vs. 65.2% vs. 33.3%, respectively). In contrast, patients with TA were more likely to develop euthyroid status and be free off thyroxine replacement [33.3%; Figure 1]. Data on time to achieve cure were available in 76 patients. Of those, 16 (21%) patients were cured within 3 months and 60 (79%) patients between 3 and 6 months. There were eight patients out of 97 (8.3%) who remained

Table 2: Doses and response to radioiodine therapy

Details	Results*
Radioiodine dose	
Graves' disease	14.7±3.7
Toxic multinodular goiter	13.7±3.5
Toxic adenoma	16.7±3.9
Cure rates (*n*=97)	
Yes	89 (91.8)
No	8 (8.2)
Time to cure (*n*=72), months	
<3	19 (26.4)
3-6	53 (73.6)

*Results are shown as *n* (%) or mean±SD. SD: Standard deviation

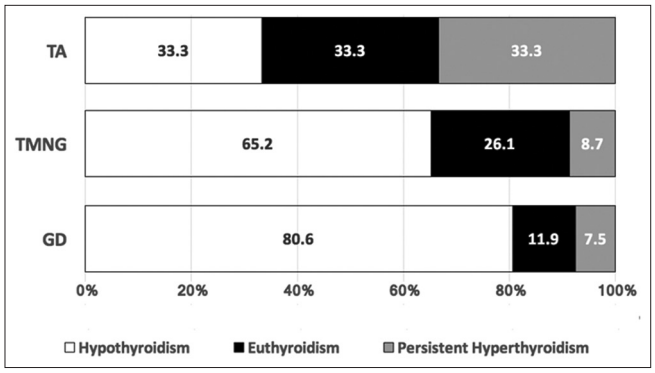

Figure 1: Response rates to radioiodine therapy by etiology. X-axis shows the rates and type of response as percentages and Y-axis indicates the etiology of hyperthyroidism. TA: Toxic adenoma, GD: Graves' disease, TMNG: Toxic multinodular goiter

thyrotoxic 6 months post-RI therapy. Of those, five patients needed a 2nd dose of RI, and all were rendered hypothyroid, two patients continued on ATDs, and one patient developed hypothyroidism 7 months post-RI therapy.

Predictive factors of treatment response

Predictors of cure in response to RI treatment were analyzed using a logistic regression model. The variables included age, gender, nationality, diagnosis, time to RI Therapy, RI dose, pretherapy ATDs' use, presence of GO, percentage of RI uptake on diagnostic scan, and thyroid hormone levels. Out of these parameters, only RI dose was higher in the cured group (14.7 ± 3.7 SD vs. 11.9 ± 3.2 SD; $P < 0.05$) with an odds ratio of 1.26 (confidence interval: 1.01–1.62); each 1 mCi increase of RI dose (above 8 mCi) will increase the chance of cure by 26%. Age did not show any statistically significant association with cure rate, and data on other variables were not enough to perform further analysis.

Radioiodine adverse events

Three patients presented shortly after RI therapy with worsening symptoms of hyperthyroidism and biochemical evidence of further elevation thyroid hormones. Of those, one was treated with ATD, prednisone was added in another, and one required short hospital admission and was treated with steroids and had an uncomplicated course. One patient developed new orbitopathy and needed intravenous steroids followed by surgical intervention. Two patients with mild orbitopathy were treated with prednisone before RI treatment, and none of those has any worsening of the preexisting condition.

Discussion

RI is an important modality for the treatment of hyperthyroidism and has been in clinical use for about 80 years.[10] It is the first-line therapy for hyperthyroidism in North America in contrast to Europe and Asia where ATDs are popular. In our study, the time from diagnosis of hyperthyroidism to receiving RI therapy was more than 18 months in the majority of patients. This may suggest that RI is not the preferred treatment modality in our patients or by our physicians. This finding is in keeping with a recent survey of physicians treating GD in the Middle East and North Africa region, 40% of participants from UAE, showing that 60% would use ATDs as their first-line therapy.[12] Since there is a delay in resorting to RI treatment, future studies are needed to explore the patient–physician barriers to utilizing RI as a mode of treatment.

In addition to patients' preference, RI therapy is used for patients developing agranulocytosis or derangement of liver enzymes on ATDs.[4] In this study, about a quarter of the patients were referred to RI due to other compelling medical reasons including ATDs intolerance, neutropenia, and hepatotoxicity.

The cure rate after a single dose of RI treatment in our cohort was slightly higher (91.8%) than in many other studies.[6-10] This difference could be attributed to other factors such as patients' characteristics, the definition of cure, RI dose, or its method of calculation. In general, there are two ways of selecting the treatment of RI; fixed or calculated dose. There is no definitive evidence that one is superior to the other.[4] In our center, using semicalculated method by a single treating nuclear medicine physician, almost for the entire study period, may have resulted in such a higher cure rate.

The majority of our patients achieved cure 3–6 months after RI therapy while some made it earlier. Furthermore, all the five patients treated with the 2nd dose of RI were cured. Our findings are in agreement with the current guidelines that recommend monitoring thyroid functions test 4–6 weeks after RI therapy and advice repeating RI therapy at 6 months mark for those with persistent hyperthyroidism.[4] In our study, hypothyroidism developed more commonly in GD patients following RI while euthyroid status was seen more frequently in patients with TA and TMNG. This differential response to RI therapy has been reported in other studies and is attributed to the sparing effect of RI therapy on the suppressed nontoxic normal thyroid tissue in TA and TMNG.[5,13]

In our study, only the higher RI dose predicted a favorable response to RI therapy. Similarly, other studies showed that higher RI dose was not only associated with higher cure rate but also reduced time to achieve cure.[14] Data on other known

predictors of successful RI such as goiter size and levels of thyroid receptors antibodies were not available in our study. Identification of those patients is essential so that a proper RI dose can be selected, and careful follow-up posttherapy is considered primarily for elderly patients or those with cardiovascular disease. It is critical to develop structured clinical practice guidelines in following up patients post-RI treatment for short- and long-term adverse effects.

De novo or worsening GO is one of the main limiting factors when considering RI therapy. It has been reported to occur in 7.5%–15% of patients with GD following RI.[15] In our study, only one patient developed severe GO requiring surgery and radiation therapy. This low risk could be due to preselection of patients with no or mild GO to undergo RI therapy. In a landmark study, Bartalena L *et al*. demonstrated in a prospective randomized controlled trial that steroid coverage mitigates the adverse effects of RI on GO.[5] Two of our patients with established GO were pretreated with steroids before RI and none developed worsening of GO.

The limitations of our study include its retrospective nature with inadequate documentation of variables predictive of treatment response such as goiter size and thyroid receptor antibodies for many of the patients. Besides, response to RI treatment lacked in a proportion of the referred cases due to loss of structured follow-up.

Conclusions

The present study showed that a single dose of RI is highly effective in controlling hyperthyroidism in our cohort. The prolonged duration of hyperthyroidism from the diagnosis to RI therapy suggests that ATDs remain as the primary modality of choice for the majority of our patients. Hence, further studies are needed to explore the patient–physician barriers in the delay of utilizing RI as the mode of treatment in hyperthyroidism in the appropriately selected patients.

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Author's contributions

KA: Study design, ethical approval, data collection, data entry, data analysis, and drafting the manuscript; BA: Study design, data verification, data analysis, and revising the manuscript; MA: Data collection and data cleansing; JS: Statistical analysis; and KA, BA, SY, JA reviewed and edited the manuscript.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

The study was approved by AAMDEC (CRD 506/17). Patients in our hospital provide a general consent allowing the anonymized use of their data for education, quality assurance, and research without the need for specific consent.

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