Original Article

Observational Study on Outcomes after Radioiodine Ablation in Hyperthyroid Patients

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Abstract

Introduction: Radio-active Iodine (RAI) is a safe, definitive, and cost-effective modality of treatment that is used as the first line of treatment for Graves' hyperthyroidism by most endocrinologists. Very few reports are available from India, observational follow-up data is needed to determine the meaningful prognostic outcomes of RAI ablation in the Indian population. **Aims:** To study the outcomes in hyperthyroid patients undergoing RAI ablation. **Materials and Methods:** This observational cohort study was conducted at Department of Endocrinology at Indraprastha Apollo Hospital, New Delhi. A total of 82 hyperthyroid patients who underwent RAI ablation between June 2014 to June 2018 were enrolled. RAI dose was calculated arbitrarily in most cases; often by an empirical fixed dose based on the goiter size and RAIU. The patients were reviewed at 1, 3 and 6 months post-RAI ablation. During follow-up, along with a detailed clinical examination, free T4, free T3 and TSH were checked. **Results:** The dose of I-131 varied from 6 mCi to 14 mCi. Most of the patients were given RAI in the dose of 7.1-10 mci. About 63.4% of patients achieved hypothyroidism in 6 months, 6.1% in 1 month, 37.8% in 3 months, and 19.5% in 6 months. Gender, age, etiology of hyperthyroidism, baseline thyroid function, goiter, and ophthalmopathy did not affect outcomes after RAI ablation. Those who were not treated with antithyroid drugs prior to RAI therapy were found to have higher rates of conversion to a hypothyroid state. **Conclusion:** RAI can be given safely as the first line of treatment in Graves' disease and antithyroid drug naïve patients respond better to therapy.

Keywords: Goitre, Graves' disease, hyperthyroidism, radio-active iodine

Introduction

Hyperthyroidism is characterised by increased thyroid hormone synthesis and secretion from the thyroid gland, whereas Thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source.

The prevalence of hyperthyroidism is 0.8% in Europe and 1.3% in the USA.[1,2] Hyperthyroidism increases with age and is more frequent in women. In a review of several large studies, the incidence of hyperthyroidism was approximately 0.4 cases per 1000 women per year; the incidence in men was 25% or less than the incidence in women.[3] In an epidemiological study from Cochin, subclinical and overt hyperthyroidism were present in 1.6% and 1.3% of subjects participating in a community survey.[4] In a hospital-based study of women from Pondicherry, subclinical and overt hyperthyroidism was present in 0.6% and 1.2% of subjects, respectively.[5] More than a third of community-detected hyperthyroid cases have positive anti-TPO antibodies, and about 39% of cases have a goitre.[5] The most common cause of hyperthyroidism in iodine sufficient areas is Graves' disease (GD) whereas toxic multinodular goitre and toxic adenoma account for 50% of all cases of hyperthyroidism in iodine-deficient areas and are more predominant in elderly people.[6,7] Treatment options for GD include anti-thyroid drugs, radioiodine ablation and surgery (thyroidectomy).

Radioiodine (RAI) is the preferred first-line therapy for GD in the United States and the United Kingdom because

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.ijem_29_22

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Submitted: 13-Jan-2022 **Revised:** 12-Feb-2022
Accepted: 30-Mar-2022 **Published:** 06-Jun-2022

How to cite this article: Pamnani H, Jindal R, Khare J, Sharma M, Siddiqui A, Wangnoo SK. Observational study on outcomes after radioiodine ablation in hyperthyroid patients. Indian J Endocr Metab 2022;26:149-53.

it is associated with a higher cure rate and lower relapse rate compared with ATDs.[8] In India, however, there is a reluctance to use RAI as the first line of treatment because of its limited availability, unrealistic risk perception in both the general public and some medical practitioners and the lack of prospective trials in the Indian setting to evaluate the efficacy of different modalities of treatment to produce lasting effects. The medical literature is replete with reports of its efficacy, failures and complications, but most of these studies have been conducted among Caucasian persons and in relatively affluent societies. Very few reports are available from developing countries like India regarding radioiodine ablation where thyroid disorders are common. Hence, observational follow up data is needed to determine the meaningful prognostic outcomes of radioiodine ablation in the Indian population. The aim of this study is to present Indian data regarding radioiodine ablation outcomes in hyperthyroidism, in terms of conversion to hypothyroidism.

Materials and Methods

All Indian patients who underwent Radioiodine ablation therapy for hyperthyroidism between June 2014 to June 2018 at the Endocrine Department of Indraprastha Apollo Hospital, New Delhi were enrolled in the study. A total of 82 patients eligible were included in the study after explaining the purpose and investigations of the study and obtaining informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institute ethics committee. The exclusion criteria were patients who failed to give informed consent, were pregnant or planning pregnancy within 6 months, breast feeding, severe Graves' ophthalmopathy, aged under 10 years, with large and compressive goiters (≥150 g) or intrathoracic goiters, with a history of thyroidectomy and with thyroid nodules suspicious of malignancy.

The diagnosis of hyperthyroidism was based on clinical, biochemical and scintigraphic evidence. The subjects enrolled were subjected to detailed history with respect to demographic data (age, sex, residence), duration and nature of symptoms, presence of eye signs, presence of goitre, serum concentration of free T3, free T4 and TSH. The dose and duration of antithyroid drugs prior to Radioiodine ablation were noted. All antithyroid drugs were stopped 5 days prior to the I-131 dose and antithyroid drugs were not restarted immediately after radioiodine ablation therapy. All patients underwent 2 and 24-h RAIU tests before radioiodine therapy. Patients received a 5 μCi dose of sodium iodide (^{131}I-NaI) on an empty stomach, after a low-iodine diet for 15 days prior to RIT. Patients with mild to moderate ophthalmopathy were taken up for ablation under the cover of steroids. All females of child bearing potential underwent pregnancy testing within 48 hours prior to administration of RAI and were advised to take oral contraceptive pills for at least 6 months post-ablation. Radiation safety measures were explained to patients and their caregivers. They were advised to report any adverse drug reactions. An estimate of the dose needed to deliver an activity sufficient for complete gland ablation requires consideration of thyroid gland weight and the 24-hour radioactive iodine uptake. RAI dosing for GD is usually calculated by the formula

$$\frac{100200 \text{ mci} * \text{thyroid gland weight (gm)}}{24 \text{ hours RAIU (\%)}}$$

But in our centre, RAI dose was calculated arbitrarily in most cases; often by an empirical fixed dose based on the goitre size and radioiodine uptake values. The patients were reviewed at 1, 3 and 6 months post radioiodine ablation. During each follow-up visit, clinical examination (for any changes in goitre and ophthalmopathy) and laboratory measures of serum free T4, free T3 and TSH were carried out.

Hyperthyroidism was defined as serum TSH level less than 0.35 μIU/ml (reference; 0.35-5.5 μIU/ml) with increased serum free T3 (reference; 2.3-4.2 pg/ml) and/or increased free T4 (reference; 0.89-1.76 ng/dl). All thyroid hormone investigations were done using electrochemiluminescence immunoassay (ECLIA).

Statistical analysis was performed using SPSS Statistical Software version 22.0 and R.3.2.0. Clinical Parameters are presented in terms of Mean and SD for quantitative variable and frequency (%) for qualitative variables. Z Test of proportion was used to compare proportions between groups. Chi-Square test was used to observe the correlation between categorical variables like Goiter status and Hypothyroidism. The level of statistical significance will be taken as $P < 0.05$.

Results

There were a total of 23 males and 59 females (72%) in the study sample with the mean age of females being 41.8 ± 14.6 years and males being 39.1 ± 11.6 years.

Out of 82 patients, 61 (74.4%) were diagnosed to have GD, 12 (14.6%) were diagnosed with toxic multi-nodular goitre (TMNG) and nine (11%) were diagnosed with toxic adenoma. The mean age of patients with GD was 40.1 ± 12.7 years, TMNG was 49.8 ± 14.9 years and toxic adenoma were 35.8 ± 15.7 years.

Before undergoing RAI ablation, goiter was present in 33 patients (40.2%) and mild to moderate (not severe) ophthalmopathy was present in eleven patients (13%). All patients with ophthalmopathy were started on steroids prior to RAI ablation.

53 cases (64.6%) were taking the antithyroid drug before RAI therapy. 51 cases (62.2%) were taking Carbimazole, 2 cases (2.4%) were taking Propylthiouracil (PTU) and no patient was taking Methimazole prior to Radioiodine therapy. Initially, all patients were started on Carbimazole, but two patients complained of fever and dizziness after starting Carbimazole and switched to PTU before coming to us.

All 82 patients were treated with I-131 and the dose varied from 6 mCi to 14 mCi. RAI dose regimen was divided into

three groups: Group A (6-7 mCi), Group B (7.1-10 mCi) and Group C (>10 mCi).

Five patients received an RAI dose of 6-7 mci (Group A), a majority of patients (n = 73) received RAI dose of 7.1-10 mci (Group B) and 4 patients received RAI dose greater than 10 mci (Group C), details are given in Table 1.

Overall 52 (63.4%) patients became hypothyroid and Levothyroxine was started in 6.1%, 37.8% and 19.5% of patients after 1, 3 and 6 months, respectively, after radioiodine in this study, described in Table 2.

Overall, the incidence of hypothyroidism was 3.8%, 94.2% and 1.9% in Group A, B and C group, respectively. A maximum number of people achieved hypothyroidism at three months in both A and B groups while hypothyroidism occurs at 6 months in Group C [Table 3].

At end of 6 months, out of 59 females, 36 (69.23%) converted to hypothyroidism while out of 23 males, 16 (30.77%) converted to hypothyroidism. The conversion of hypothyroidism was more in females in this study but that was not statistically significant (*P* value 0.471).

In this study, 66.7% of patients in the age group of 13-30 years attained hypothyroidism while 63.2% attained hypothyroidism in the 31-50 years age group and 60.9% attained in >50 years, age group. But the correlation between age group and hypothyroidism attained is not statistically significant (*P* value 0.922).

Maximum rates of hypothyroidism were seen in Graves' patient, followed by toxic adenoma and then multinodular goitre, but it was not statistically significant (*P* value 0.176).

Conversion to hypothyroidism after RAI ablation was less in presence of goitre and also it was less in presence of ophthalmopathy but it was not statistically significant (*P* value 0.367 and 0.183 respectively). Fifty-three patients (64.6%) were given antithyroid drugs prior to RAI ablation. Out of 53 patients, who were given antithyroid drugs, 54.7% (n = 29) of patients attained hypothyroidism. Out of 29 patients who were not given any anti thyroid drugs prior to RAI ablation, 79.3% (n = 23) attained hypothyroidism. In this study, those who were not treated with antithyroid drugs prior to Radioiodine therapy were found to have higher rates of conversion to hypothyroid state and it was statistically significant (*P* value 0.027) [Table 4].

Baseline thyroid hormone levels had no relation to the attainment of hypothyroidism [*P* value 0.883 (free T3), 0.659 (free T4) and 0.405 (TSH)].

Goiter was present in 40.2% (n = 33) of patients prior to RAI therapy and improvement in goiter size was noticed in 73% (n = 24) of patients and remained the same in 27% (n = 9) as reported by patients.

Mild to moderate ophthalmopathy was present in 13% (n = 11), and all patients with ophthalmopathy were started on steroids pre-procedure. In this study, ophthalmopathy improved in 64% (n = 7), deteriorate in 9% (n = 1) and it remained same in 27% (n = 3). Deterioration in ophthalmopathy was seen in form of worsening proptosis and lid retraction.

In this study, significant improvement in goiter was seen at 3 months after radioiodine ablation (*P* value 0.005) as compared to 1 month. More improvement in ophthalmopathy was noted at 1 month than at 3 months after radioiodine ablation but it was not statistically significant (*P* value 0.342).

Table 1: Different doses of Radioiodine as per sex distribution

RAI Dose	Female	Male	Total number of patients
6-7 mci	5 (8%)	0 (0%)	5 (6.1%)
7.1-10 mci	50 (85%)	23 (100%)	73 (89%)
>10 mci	4 (7%)	0 (0%)	4 (4.9%)
Grand Total	59 (100%)	23 (100%)	82 (100%)

Table 2: Patients became hypothyroid and Levothyroxine started at different months after radioiodine ablation

LT4 RX Started at month after Ablation	Number of patients	%
1 month	5	6.1%
3 months	31	37.8%
6 months	16	19.5%
Not attained Hypothyroidism	30	36.6%
Grand Total	82	100.0%

Table 3: Hypothyroidism in different groups according to doses of RAI

RAI Dose	Hypothyroidism achieved (*n*=52)			
	1 month	3 months	6 months	Grand Total
6-7 mci	0 (0%)	2 (100%)	0 (0%)	2 (3.8%)
7.1-10 mci	5 (10.2%)	29 (59.2%)	15 (30.6%)	49 (94.2%)
>10 mci	0 (0%)	0 (0%)	1 (100%)	1 (1.9%)
Grand Total	5 (9.6%)	31 (59.6%)	16 (30.8%)	52 (100%)

Table 4: Conversion to hypothyroidism after RAI ablation in patients who were on antithyroid drugs prior to RAI ablation

Neomercazole	Hypothyroidism			
	Attained	Not attained	Grand Total	*P*
Not Given	23 (79.3%)	6 (20.7%)	29 (35.4%)	0.027
Given	29 (54.7%)	24 (45.3%)	53 (64.6%)	
Grand Total	52 (63.4%)	30 (36.6%)	82 (100%)	

Discussion

GD is the common condition encountered in clinical practice. Apart from its contraindications (viz: Pregnancy and breast feeding), radioiodine ablation can be offered as a treatment

option for GD. In the majority of the cases, a single dose leads to lifelong hypothyroidism, which is the hallmark of treatment of Graves'. Several studies have shown comparable results of both fixed and calculated doses, fixed-dose regimen has the advantage of being more convenient with lower cost. As of now, there are no definitive data, that provides evidence of increased rates of malignant potential, reproductive issues or any other serious long term issues.[9] In India, antithyroid drugs are main stay in the management of GD and the same was shown by a study by Mithal *et al*.[10] Radioiodine has been the most popular treatment for hyperthyroidism in the United States, although the use of thionamides may be increasing.[11] Radioiodine is less popular outside of the United States.[12,13] Antithyroid drugs have to be given for a long time, the advantage of radioiodine is that it can be given as a single oral dose and most patients need only a single dose to become euthyroid or hypothyroid. Radioiodine therapy as a definitive treatment is safe and cost-effective. Radioiodine therapy is gaining acceptance as the form of treatment mainly in North America and is also picking up in other regions. The uptake of radioiodine therapy as a treatment is gradually picking up in our country with increased access to radioiodine and its awareness.

RAI is the preferred treatment option but may have a few side effects like delayed control of symptoms; transient neck soreness; flushing, decreased taste sensations, worsening of ophthalmopathy and infiltrative dermopathy. In addition, radiation thyroiditis may occur in 1% of patients. Radioiodine in the doses used to treat hyperthyroidism usually does not cause infertility or birth defects in the offspring of treated patients. Malignancy is one concern with RAI however, in more than seven decades in which RAI has been in use, no increased prevalence of thyroid or other carcinomas in treated patients has been noted. Meta-analysis suggests that the risk of radiation-induced cancer following RAI therapy for hyperthyroidism is small and, in observational studies, may only be detectable at higher doses. Additional studies are needed on the risks and advantages of radioiodine in the treatment of hyperthyroidism.[14]

In this study, those who were not treated with antithyroid drugs prior to Radioiodine therapy were found to have significantly higher rates of conversion to hypothyroid state (79.3% vs 54.7%; *P* value 0.027). Studies in the past evaluating the effect of administration of antithyroid drugs prior to RAI therapy have given conflicting results.[15-19] Antithyroid drugs increased the rate of treatment failure when they were given in the week before RAI treatment, shown in a recent meta analysis.[20]

Overall, 63.4% of patients achieved hypothyroidism in 6 months in this study. 6.1% of patients achieved hypothyroidism in 1 month, 37.8% in 3 months and 19.5% in 6 months. Maximum conversion to hypothyroid state was found with RAI dosing of 7.1-10 mci and was variable by dose of radioiodine administered and duration of follow up as studied by others.[19,21-24]

In this study, it was also found that for those who were rendered either euthyroid or hypothyroid at 3-6 months, TSH levels remained suppressed later on in some, but we had collected data till 6 months only. These patients need to be followed closely for a longer period to look for relapse in the future. Uy HL, *et al*.[25] also reported that transient hypothyroidism can occur following RAI therapy with subsequent recurrent hyperthyroidism.

Gender, age, baseline thyroid function test and etiology of the hyperthyroidism did not significantly affect rates of conversion to hypothyroidism after radioiodine ablation, in concordance with findings of Sanyal D, *et al*.[26] and Nair N[22] and others.[27,28]

In this study, goitre had no relationship with response rate. This might be due to the fact that in our study goiter was graded visually according to the new WHO classification and also no quantification of the volume was done. This was in concordance with the findings of Banzal *et al*.[24] and discordant with the findings of Sanyal *et al*.[26] Nair[22] and Nwatsock *et al*.[23]

In this study, baseline ophthalmopathy did not affect the rates of hypothyroidism after radioiodine ablation. There was no worsening of ophthalmopathy except in one patient, who had to be treated with corticosteroids, this was because of prespecified exclusion criteria of active and severe ophthalmopathy in our study. We found that the patient in whom ophthalmopathy worsened had attained hypothyroidism at 3 months, but in other patients who attained hypothyroidism even at 1, 3 and 6 months, ophthalmopathy remained static or improved. Nwatsock *et al*. found that Radioiodine ablation was associated with 3.7% of GO occurrence mainly in those who developed an early (1–2 months after radioiodine) and prolonged (1–4 months) hypothyroid period. The occurrence or worsening of GO after radioiodine therapy should be more related to radioiodine-induced hypothyroidism.[29] Perros *et al*.[30] found that Radioidine ablation was not associated with deterioration of GO in patients with minimally active eye disease when post radioiodine hypothyroidism is prevented. Systemic corticosteroid treatment prevents the exacerbations of Graves' ophthalmopathy that occur after radioiodine therapy in a substantial proportion of patients with hyperthyroidism who have some degree of ocular involvement before treatment.[31]

Our present study demonstrated that RAI can be given safely as the first line of treatment for patients with GD as the definitive therapy. It was also seen in a study conducted by Vuayakumar *et al*.[32] and Karyampudi *et al*.[19] that radioiodine is safely tolerated by newly diagnosed GD patients.

The strength of the present study is the low dropout rate of the study subjects. The patient numbers were good in number and there was regular follow up. There are very few studies in India evaluating the efficacy and safety of RAI. The main limitations of the study are the short duration of follow up and our inability to assess the iodine status and thyroidal volume status of the study subjects.

Conclusion

RAI can be given safely as the first line of treatment for patients with GD. It is not essential to give antithyroid drugs before Radioiodine ablation and in fact, Radioiodine naïve patients respond better to therapy. Much longer follow up is needed to ensure that recurrence of disease or hypothyroidism can be treated after 6 months.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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