

Radioactive Iodine Therapy in Graves' Hyperthyroidism : A Prospective Study from a Tertiary Referral Centre in North India

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Abstract

Background : Radioactive iodine has gained widespread acceptance as the first-line therapy for Graves' hyperthyroidism and is the preferred treatment option in most situations.

Objective : A prospective study was conducted to look at the therapeutic practice of use of radioactive iodine in the treatment of Graves' hyperthyroidism, to determine whether the expected or desired therapeutic outcome is achieved.

Settings : A tertiary referral centre in north India, Delhi that caters to patients with thyroid disorders.

Methods : One hundred and seventy four consecutive subjects with Graves' hyperthyroidism, who were given radioactive iodine were followed up.

Results : There were 59 (33.9%) males and 115 (66.1%) females. The mean age was 41.8 ± 9 years. The dose of radioactive iodine ranged from 2 mCi to 15 mCi and the mean dose administered was 5.2 ± 1.9 mCi. After one year following radioactive iodine therapy, 29 (16.7%) subjects were euthyroid, 51 (29.3%) were hypothyroid and the remaining 94 (54%) had persisting hyperthyroidism. Those subjects with persisting hyperthyroidism at one year after radioactive iodine had received a significantly lower dose compared to the groups who had achieved cure (either euthyroidism or hypothyroidism).

Conclusion : The study shows that the current practice of empirical low dose radioactive iodine therapy to avoid hypothyroidism results in majority of patients having persisting hyperthyroidism. There is a need to take a new look at the current practice to increase the cure rate. ©

INTRODUCTION

Graves' disease is a common endocrine disease.¹ There are three forms of treatment – antithyroid drugs, radioactive iodine and surgery – each of which is not exclusive of the other. The choice of therapy may be influenced by its cost, convenience, history of recent exposure to iodine, availability of skilled surgical expertise, local cultural factors, size of goitre, severity of disease, personal biases, as well as more objective data reflecting the risks and benefits of each of these. Radioactive iodine (RAI) therapy for Graves' hyperthyroidism is safe and definitive, although post-treatment hypothyroidism and the need for lifelong thyroxine are to be expected.² Since 1941, when the first

patient was treated with ¹³¹I,³ the use of RAI therapy as the first line of treatment has gradually but steadily been increasing over the years and is presently considered to be the treatment of choice for most patients with Graves' hyperthyroidism.⁴

In India, the Institute of Nuclear Medicine and Allied Sciences (INMAS) at Delhi is a tertiary referral centre and caters to patients with thyroid disorders. It was possibly one of the first centres in the country where RAI was used for both diagnostic and therapeutic purposes. This article evaluates the outcome in patients who received RAI therapy for Graves' hyperthyroidism.

MATERIAL AND METHODS

One hundred and seventy four consecutive patients who received RAI therapy for Graves' hyperthyroidism were followed up. The study was conducted between the years 1996 and 1999. The basis of diagnosis of Graves' disease was the initial thyroid hormone and thyrotropin levels, radioactive iodine uptake values at 6 and 24 hours and thyroid scan at 24 hours. The detail of

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antithyroid drug therapy received was also noted.

The patients were reviewed at three monthly intervals for at least one year. During each follow up, clinical examination and laboratory measures of serum thyroxine, triiodothyronine and thyrotropin were carried out. Patients who were found to have developed hypothyroidism were given appropriate therapy; those with persisting hyperthyroidism were either followed up on beta blockers or were given antithyroid drugs and this decision was left to the treating physician. Some patients were given another dose of radioactive iodine, but not before 6 months of the previous RAI therapy.

Thyroid hormone assays were done by radio immuno assay and TSH estimation was done by immuno radiometric assay (IRMA). Immunoassay kits were obtained from Bhabha Atomic Research Centre, Mumbai.

Radioactive iodine uptake (RAIU) was carried out with 25 µCi dose of ¹³¹iodine and uptake measurements were done at 2, 6 and 24 hours. Scan was done at 24 hours. The RAI dose was calculated arbitrarily in most cases; often by an empirical fixed dose based on the goitre size and uptake values.

RESULTS

Total of 174 subjects were studied. There were 59 (33.9%) males and 115 (66.1%) females. The mean age was 41.8 ± 9.0 years. The youngest was an 18 year old young man and the oldest was a 60 year old woman.

All the 174 subjects had received antithyroid drug therapy prior to radioactive iodine therapy. The duration of antithyroid drug therapy varied and the mean duration was 31.7 + 30 months.

There was no goitre in 11 (6.3%) subjects whereas the remaining 163 (93.7%) had goitre; grade I in 23 (13.2%), grade II in 109 (62.6%) and grade III in 31 (17.8%)

At 12 months follow up after radioactive iodine therapy, 29 (16.7 %) subjects were euthyroid, 51 (29.3 %) were hypothyroid and the remaining 94 (54 %) continued to have persisting hyperthyroidism. The total number of hypothyroid patients is the cumulative one at the end of one year. Subjects detected to have hypothyroidism were given thyroxine replacement therapy on confirmation of diagnosis. The gender-wise breakdown is given in Table 1. Status in the table and the text means the thyroid functional status of the subjects.

The mean radioactive iodine dose given was 5.2 ± 1.9 mCi for the whole study group of 174 subjects. Patients

Table 1 : Status at one year follow up after RAI

Gender	Status at 12 months after RAI therapy			Total
	Euthyroid	Hypothyroid	Hyperthyroid	
Males	08	18	33	59
Females	21	33	61	115
Total	29	51	94	174

Table 2 : RAI dose, number of subjects and the status at one year

RAI Dose	No of subjects	Euthyroid	Hypothyroid	Hyperthyroid
2	1	0	0	1
2.5	15	1	2	12
3	15	0	1	14
4	16	3	2	11
5	78	17	23	38
5.6	1	1	0	0
6	9	2	2	5
6.2	1	0	1	0
6.5	1	0	1	0
7	20	1	12	7
7.5	4	1	3	0
8.2	6	1	3	2
10	6	1	1	4
15	1	1	0	0
Total	174	29	51	94

who were hypothyroid at one year follow up had received a mean dose of 6.168 ± 1.6 mCi and this was significantly higher than the mean dose of 5.2 ± 1.9 mCi that was given to all subjects. The mean dose given in subjects according to their status at one year end is given in Table 2.

Of the 174 subjects studied, 125 (71.8%) of the subjects received either 5 mCi or less. Of the 94 subjects with persisting hyperthyroidism at the end of one year after radioiodine therapy, 76 (81.3%) had received either 5 mCi or less radioiodine and only 5 of these 94 subjects had received more than 7 mCi radioactive iodine.

On the other hand, of the subjects who had become either euthyroid or hypothyroid at the end of one year, 59% of the subjects who had become hypothyroid, and 39.9% of the subjects who had become euthyroid had received more than 5 mCi radioactive iodine.

Total of 47 subjects received less than 5 mCi. Of these 38 (80.9%) of the subjects had persistent thyrotoxicosis at the end of one year. The remaining had either euthyroidism or hypothyroidism. Seventy eight subjects had 5 mCi. Of these 38 (48.7%) had persistent thyrotoxicosis with the remaining becoming either euthyroid or hypothyroid at the end of one year. 12 subjects had more than 5 mCi and less than 7 mCi. Of these 5 (41.7%) subjects had persistent thyrotoxicosis with the remaining becoming either euthyroid or hypothyroid at one year end. Twenty subjects had 7 mCi. Of these 7 (35%) subjects had persistent thyrotoxicosis. 17 subjects had more than 7 mCi. Of these 6 (35.3%) had persistent thyrotoxicosis.

Table 3 shows the initial T4 levels, the duration of antithyroid drug therapy, the RAIU values at 2 and 24 hours and the dose of radioactive iodine. All these variables with the exception of RAIU were found to be different between the groups of patients who were cured compared to those with persisting hyperthyroidism.

Table 3. Initial thyroid function tests and response to radioiodine therapy

Tests	Initial TFT Values										
	All subjects		Euthyroid at 12 months			Hypothyroid at 12 months			Hyperthyroid at 12 months		
	Mean	SD	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE
T3	486.2	226.5	538	253	63.3	445.9	198.9	33.1	498.3	235.7	33
T4	24.4	9.3	24.0	7.0	1.6	22.3	7.4	1.2	27.9	9.2	1.1
TSH	0.09	0.12	0.16	0.19	0.04	0.06	0.06	0.01	0.09	0.11	0.01
RAIU 2hrs	39.7	20.0	38.9	19.0	3.7	36.6	19.0	2.7	41.6	20.9	2.2
RAIU 24hrs	63.0	16.2	61.8	17	3.3	62.5	16.0	2.3	63.8	16.3	1.7
Duration of ATD therapy	31.7	31	31.3	28.1	5.3	29.1	22.0	3.2	36.3	35.5	3.8
RAI Dose	5.2	1.9	5.7	1.8	0.34	5.8	1.5	0.2	4.7	1.9	0.19

DISCUSSION

Graves' disease is a common endocrine disease. The essential goal in the management of thyrotoxicosis of Graves' disease is to reduce the hypersecretion of thyroid hormones. Of the three forms of therapy available, the use of radioactive iodine as the first-line of treatment has gradually but steadily been increasing over the years and is presently considered to be the treatment of choice for most patients. Although there has been widespread acceptance of radioactive iodine as therapy, there has been no general agreement on the dose. Lower doses were used in the past because of failure to recognize that most patients eventually become hypothyroid regardless of the dose selected.^{4,6} Since hypothyroidism is inevitable after treatment of Graves' hyperthyroidism with radioactive iodine, the goal should be cure of hyperthyroidism rather than avoidance of hypothyroidism, which should be attempted with a single large dose.^{7,8}

In the current series, less than half the patients who received radioactive iodine had achieved cure, which is defined as euthyroidism or hypothyroidism. Of the 174 patients who received radioactive iodine, only 80 subjects had cure at one year. In the remaining, there was biochemical evidence of persisting hyperthyroidism.

The mean dose of radioactive iodine was 5.2 ± 1.9 mCi. In 125 (71.3%) subjects the dose of radioactive iodine given was 5 mCi or less. Nordyke and Gilbert⁹ analyzed a series of 605 patients treated with radioactive iodine to find out the optimal dose to achieve cure. They concluded that cure was directly related to the dose of ¹³¹I administered and there was no significant relation between cure and age, gender, and > 30% radioactive iodine uptake. The study also concluded that the optimal ¹³¹I dose for curing hyperthyroidism is approximated by starting with 10mCi and increasing it for unusually large glands or for special patient circumstances.

The Royal College of Physicians in their guidelines¹⁰ for the use of radioactive iodine in the management of hyperthyroidism recommend a dose in the range of 10 mCi or more for a 'standard' case of Graves' hyperthyroidism. Seen in the light of these *evidence-based*

recommendations, the dose of radioactive iodine in the present series is much less. This is probably one of the reasons for the persisting hyperthyroidism in more than half the patients.

In our institute the concept of low-dose fractional radioactive iodine therapy used to be given in the eighties. Although this has been given up, many physicians continue to give an empirical low dose in the hope of preventing ensuing hypothyroidism. There is a trade off with radioactive iodine therapy; higher doses cure hyperthyroidism with great regularity, but cause more hypothyroidism, whereas low-dose therapy would result in persistent hyperthyroidism in the majority of patients.

Hypothyroidism is an inevitable consequence of the treatment of Graves' hyperthyroidism with radioactive iodine and almost certainly would occur in all patients if they lived long enough.^{11,12} Hypothyroidism that occurs in the first year following radioactive iodine therapy is related to dose, while the subsequent occurrence is due to a combination of radiation-mediated injury and underlying autoimmunity.¹³ Hence current practice guidelines, recommend large single dose because attempting to achieve permanent euthyroidism with radioactive iodine is nearly impossible.^{4,10} Gopinath *et al*⁴ on the basis of their experience in Indian population observed that the dose of radioiodine in the treatment of Graves' hyperthyroidism should be such that to achieve rapid control of hyperthyroidism and the long term incidence of hypothyroidism should not be a deterrent in deciding on the dose. In another study reported from Bombay,¹⁵ only 16% of the subjects (20/79) who received a 5 mCi fixed dose radioiodine for treatment of thyrotoxicosis were hypothyroid at the end of one year after therapy. This study also noticed that age, sex and pretreatment thyroid hormone values had no influence on outcome, but size of goiter had a direct relationship, larger goiters were associated with higher treatment failure.

In the present study all patients had been pre-treated with carbimazole for varying duration and radioactive iodine therapy has rather been provided as a second-line therapy in these patients. Adjunctive drug therapy

requires higher doses of radioactive iodine due to the induction of radio-resistance by antithyroid drugs.¹⁶⁻¹⁸ This is another important factor that could have contributed to the low cure rate. The use of antithyroid drug prior to and /or following radioactive iodine therapy has to be individualized based on the age of the patient, the severity of thyrotoxicosis and other co-morbid conditions.

At a time, when research enhanced health care (some prefer this to evidence-based practice) is taking a prominent role, it is important for institutions to audit their practice and find out how good we are with reference to evidence-based recommendations. The above series clearly show that there is a need to increase the average dose of radioactive iodine with clear understanding that higher doses result in more hypothyroidism.

REFERENCES

- Burman KD. Hyperthyroidism. In: Becker KL, Ed. Principles and practice of endocrinology, 1st ed. Philadelphia: Lippincott; 1990;331-347.
- Beierwaltes WH. Treatment of hyperthyroidism with iodine 131. *Semin Nucl Med* 1978;8:95-103.
- Sawin CT, Becker DV. Radioiodine and treatment of hyperthyroidism: The early history. *Thyroid* 1997;7:163-176.
- Solomon B, Glinoe D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. *J Clin Endocrinol Metab* 1990;70:1518-24.
- Malone JF, Cullen MJ. Two mechanisms for hypothyroidism after ¹³¹I therapy. *Lancet* 1976;2:73.
- Sridama V, McCormick M, Kaplan E, Fauchet R, DeGroot LJ. Long term follow up study of compensated low dose ¹³¹I therapy for Graves' disease. *N Engl J Med* 1984;311:426-31.
- Wise PH, Burnet RB, Ahmad A, Harding PE. Intentional radioiodine ablation in Graves' disease. *Lancet* 1975;1:1231-32.
- Safa AM, Skillern PG. Treatment of hyperthyroidism with a large initial dose of sodium iodide ¹³¹I. *Arch Intern Med* 1975;135:673-75.
- Nordyke RA, Gilbert FI Jr. Optimal Iodine-¹³¹dose for eliminating hyperthyroidism in Graves' disease. *J Nucl Med* 1991;32:411-16.
- Guidelines for the use of radioiodine in the management of hyperthyroidism : A summary. Prepared by the radioiodine audit subcommittee of the Royal College of Physicians Committee on diabetes and endocrinology and the research unit of the Royal College of Physicians. *J R Coll Physicians London* 1995;29:464-69.
- Alevizaki CC, Alevizaki-Harhalaki, Ikkos DG. Radioiodine -131 treatment of thyrotoxicosis :dose required for and some factors affecting the early induction of hypothyroidism. *Eur J Nucl Med* 1985;10:450-54.
- Cevallos JL, Hagen GA, Maloof F, Chapman EM. Low-dosage ¹³¹I therapy of thyrotoxicosis(diffuse goiters). A five-year follow-up study. *N Eng J Med* 1974;290:141-44.
- Becker DV, McConahey WM, Dobins BM , et al. The results of thyrotoxicosis therapy follow up study.In:Fellinger K,Hofer R (eds).Further advances in thyroid research. Vienna:*G Gitsel und Cie* 1971;1:603-609.
- Gopinath PG, Prasanna Kumari KM, Padhy AK, Aggarwal SL. Thyroid status 10 years after I-131 therapy for toxic diffuse goiter. *Indian J Nucl Med* 1989;4:8-10.
- Nair N. Results of a single 5 mCi dose of radioactive iodine in thyrotoxicosis. *Indian J Nucl Med* 1991;6:6-11.
- DunnJT. Choice of therapy in young adults with hyperthyroidism of Graves'disease : a brief case -directed poll of fifty-four thyroidologists. *Ann Intern Med* 1984;100:891-93.
- Lundell G, Holm LE, Ljunggren JG, Wasserman J. Incidence of hypothyroidism after ¹³¹I therapy for hyperthyroidism. *Acta Radiol* 1981;20:225-30.
- Lundell G, Holm LE. Hypothyroidism following ¹³¹I therapy for hyperthyroidism in relation to immunologic parameters. *Acta Radiol Oncol* 1980;19:449-54.

Announcement

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Announcement

The Indian Association for Bronchology is conducting its 11th Indian Congress on Bronchology on 20th – 22nd January 2006 at GRT Grant Days in Chennai.

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