

Factors Affecting and Outcome of Radioactive Iodine Therapy in Hyperthyroidism: A study at Institute of Nuclear Medicine & Allied Sciences (INMAS), Sylhet

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ABSTRACT

Objective: Radioactive iodine therapy (RIT) is the most commonly used modality to treat hyperthyroidism and is indeed in most cases, the treatment of choice. The aim of this study was to assess the clinical outcome one year after radioactive Iodine-131 (RAI -131) therapy and to identify the factors associated with response of the therapy.

Patients and Methods: A total 107 hyperthyroid patients were included in this study. All patients were pre-treated with anti-thyroid drugs (ATD). A fixed dose of 8 mCi of radioiodine was given to the patients with Graves' disease, 12 mCi to patients with single toxic adenoma and 15 mCi to patients with toxic multi-nodular goiter . The patients were done serum FT4 initially and followed up with serum T3, T4, and TSH at three months , six months and one year of RAI therapy . The clinically and biochemically euthyroid and hypothyroid patients were considered as cure of the disease.

Results : The cure rate was about 94.7% seen in female patients and 93.8% in male (P=0.92), 93.6% in younger age group (below 40 years) and 95.0% of the older patients (P=1.51), 95.5% of the patients who were taking ATD for more than one year and 92.7% of the patients who were taking ATD for less than one year before therapy(P=1.95), 95.4 % of the patients who had initial FT4 level less than 35 pmol/L and 92.7 % of the patients who had high initial FT4 (P=1.54). Cure rate of Graves' disease was 45/53 (92.5%), multi-nodular goiter 41/43 (95.3%) and for single toxic adenoma was 11/11 (100%) (P= 0.65). The incidence of radioiodine induced hypothyroidism was 6.5 % at three months, 13.1 % at six months and 15.0 % at one year. Overall incidence of cure rate of RAI therapy after one year was 101 (94.4 %).

Conclusion: No statistically significant difference was found in the cure rate when sex, age, duration of pretreatment with antithyroid drug, initial FT4 level and cause of hyperthyroidism were considered.

From this study it can be concluded that cure rate of RAI therapy is quite good and the pretreatment factors have little influence on the final outcome.

Key words: Radioiodine therapy, Hyperthyroidism.

INTRODUCTION

Hyperthyroidism is a state of increased function of the thyroid gland leading usually to a clinical state of thyrotoxicosis which is characterized by excessive production of thyroid hormones T3 and T4 by the thyroid which causes an increase in metabolic activity of the body. It is a common endocrine condition which presents in a number of different forms, the three most common being Graves' disease, toxic multi-nodular goiter and hyper-functioning follicular adenoma. Graves' disease (GD) is by far the most common form of overt hyperthyroidism accounting for about 80% to 90% of all cases (1, 2, 3, 4). It is an autoimmune disorder in which thyroid-stimulating hormone receptor antibodies cause the thyroid gland to synthesize and release large amounts of thyroid hormones (5).

Toxic nodular goiter is less common than Graves' disease, but its prevalence increases with age and in the presence of iodine deficiency. Hence, toxic nodular goiter might be more common than Graves' disease in older patients especially in iodine deficient regions (6).

The modes of treatment for hyperthyroidism available are antithyroid drugs, surgery and radioiodine (RAI) and although each of these is highly successful in controlling or curing hyperthyroidism but none leads to permanent euthyroidism on a consistent basis (7).

Radioactive iodine was introduced as a means for treatment of hyperthyroidism in 1941 by Hertz and Roberts in the United States and it has since been widely accepted as the gold standard for treatment of hyperthyroidism and is preferred over surgery or anti-thyroid medications (8). It has been established as an effective treatment modality of the patients with various etiologies of hyperthyroidism. It is less expensive, highly effective, easy to administer, tissue specific and safety has been proven in all age groups (9). The goal of radioactive iodine (RAI) treatment is to cure the hyperthyroidism and achieve the long-term control (10). The treatment is highly effective with a cure rate approaching 100% after one or more treatments, depending on the dose administered and various other factors (6).

A single dose of radioiodine therapy has a success rate of 85-100% in patients with toxic nodular goiter. Radioiodine therapy may reduce the size of the goiter by up to 40% (11, 12).

PATIENTS AND METHODS

Initially 122 patients were selected but only 107 patients completed the follow-up. The study population was randomly selected from the patients referred to the Institute of Nuclear Medicine and Allied Sciences, Sylhet for RAI therapy with the indications of Graves' disease, toxic multi-nodular goiter, or single toxic adenoma. Exclusion criteria were pregnancy, lactation and severe Graves' ophthalmopathy. The likely consequences of the treatment, the usual precaution of radiation protection, necessity of follow up were fully explained to the patients and attendants, and informed written consent were taken before administering radioiodine. All patients were pre-treated with anti-thyroid drugs (ATD) to make them euthyroid or borderline hyperthyroid and discontinued medication at least five days before RIT. A fixed dose of eight mCi of radioiodine was given to the patients

with Graves' disease, 12 mCi was given to patients with single toxic adenoma and 15 mCi of radioiodine was given to patients with toxic multi-nodular goiter. The patients were done serum FT4 initially and followed up with serum T3, T4, and TSH at three months, six months and one year of RAI therapy. The clinically and biochemically euthyroid and hypothyroid patients were considered as cure of the disease. The patients who remained hyperthyroid after six months of RAI therapy, the second dose was given to them. All patients were followed up at one year to see the final outcome. The patients who remained hyperthyroid after one year of radio-iodine therapy considered not cure and recommended for the subsequent RAI therapy.

RESULTS

Baseline characteristics of the study subjects were shown in Table 1. Among the 107 study population 75 patients (70.1 %) were female and 32 patients (29.9 %) were male. About 94.7% cure rate was seen in female patients and 93.8% cure rate was seen in male patients, but the difference was not statistically significant ($P=0.92$). The age range was between 18 to 72 years with mean age 43.45 ± 14.93 years. The study population was divided into two age groups. 47 patients (43.9%) were below 40 years and 60 patients (56.1%) were above 40 years. The cure rate was 93.6% of the patients aged less than 40 years and 95.0% of the patients aged above 40 years; the difference was not statistically significant ($P=0.51$). The etiologies of hyperthyroidism were Graves' disease 53 (49.5%), single toxic adenomas 11 (10.3 %) and toxic multi-nodular goiter (40.2 %). The cure rate was 95.5% of the patients who were taking ATD for more than one year and 92.7% of the patients who were taking ATD for less than one year before the therapy, the difference was not statistically significant ($P=1.95$). The cure rate was 95.4 % of the patients who showed FT4 level less than 35 pmol/L and the cure rate was 92.7 % of the patients who

showed FT4 level more than 35 pmol/ , the difference was also not statistically significant (P=1.54). The cure rate after one year for Graves’ disease was 45/53 (92.5%), for multi-nodular goiter 41/43 (95.3%) and for single toxic adenoma was 11/11 (100%). The difference was also not statistically insignificant (P=0.65). The incidence of radioiodine induced hypothyroidism was 6.5 % at three months, 13.1% at six months and 15.0% at one year and the overall incidence of cure rate of RAI therapy after one year was 101 (94.4 %) (Table 2).

Table 1: Baseline characteristics of the study subjects with cure rate, total cure and p value.

Baseline characteristics	No of patients	Cure after 03 months	Cure after 06 months	Cure rate after 1 yr	P-Value
Age Group					
< 40 years	47	24 (51.1%)	38 (80.9%)	44 (93.6%)	0.92
>40 years	60	34 (56.6%)	50 (83.3%)	57 (95.0%)	
Sex					
Female	75	45 (60.0%)	63 (84.0%)	71(94.7%)	0.51
Male	32	13 (40.6%)	12 (78.1%)	30(93.8%)	
Use of ATD before RIT					
More than 1 year	66	36(54.5%)	57(86.4%)	63(95.5%)	1.95
Less than 1 year	41	22(53.6%)	31(75.6%)	38(92.7%)	
Free FT4					
<35 pmol	65	40 (61.5%)	59(90.8%)	62(95.4%)	1.54
>35 pmol	42	18 (42.9%)	29(69.0%)	39(92.8%)	
Etiology of hyperthyroidism					
Graves’ disease	53	33(62.3%)	45(84.9%)	49(92.5%)	0.65
Toxic MNG	43	19(44.2%)	45(81.4%)	51(95.3%)	
Single toxic adenoma	11	06(54.5%)	08(72.7%)	1(100%)	

Table 2: Thyroidal status among the study population at 3 months , 6 months and 12 months (n = 107):

Follow-up	Euthyroid	Hypothyroid	Hyperthyroid
3 months	51 (47.7%)	7 (6.5%)	49 (45.8%)
6 months	74 (69.2%)	14 (13.1%)	19 (17.8 %)
12 months	85 (79.4%)	16 (15.0%)	6 (5.6%)
Total cure 101 (94.4%), Persistent hyperthyroidism 06 (5.6%)			

DISCUSSION

Radioactive iodine treatment is an effective modality for definitive treatment of hyperthyroidism with

long-term cure. Conflicting results have been produced in several studies that have attempted to predict outcome following RAI therapy by correlating cure rate with various pre-treatment factors including age, gender, aetiology of hyperthyroidism, goitre size, use of antithyroid drugs, free thyroxine levels at diagnosis and thyroid antibody status.

In this study, males and females showed similar response to RAI therapy and no significant association was observed between sex and cure rate (P=0.92). This result is consistent with the outcome of many other studies that did not show gender to be a significant prognostic factor in patient responses to RAI therapy. In contrast, Allahabadia et al (13) found that after single dose of RAI therapy males had a lower cure rate than females (67.6% vs. 76.7%, P value 0.02).

The authors found a cure rate was 93.6% of the patients aged less than 40 years and 95.0% of the patients aged above 40 years. Compared to Allahabadia et al (13) study where younger patients (< 40 years) had lower cure rate (68.9% vs. 79.3%) than patients over 40 years of age, this study showed higher percentage of good response in the younger age group .

In our study, 49 patients (92.5%) had Graves’ disease (GD), 43 (40.2%) had toxic multi-nodular goiter and 11 (10.3%) had a single autonomous nodule where cure rate was 92.5% in GD, 95.3 % in toxic multi-nodular goiter and 100% in single autonomous nodule after one year. Cure rate was also not significantly associated with etiologies of hyperthyroidism (p=0.65) but Graves' patients had a significantly higher incidence of hypothyroidism (p< 0.01). In contrast, incidence of euthyroidism was significantly increased in toxic nodular goiter than those of the patients with GD (p < 0.05). The incidences of hyperthyroidism, euthyroidism, cure rate, and persistent hyperthyroidism did not vary significantly between females and male. But Wisam

K et al. showed 80% of the patients had diffuse goiter, 13.5% had multinodular goiter, while 6.5% had a single autonomous nodule and showed significant differences in the response rate: hypothyroidism at six months was 58%, 48.1% and 42.9 % (14) Other reports showed there was no difference in cure rate between the groups with Graves' disease and those with toxic nodular goiter (69.5% vs. 71.4%; P, not significant), but Graves' patients had a higher incidence of hypothyroidism (54.5% vs. 31.7%, $P < 0.0001$) like our findings.

The outcomes for patients who have received RAI have differed from study to study. In our study, incidence of hypothyroidism was 13.1% at six months, and 15.0% at one year, which was lower than the findings of the Wisam K, et al (13) where cumulative incidence of hypothyroidism was 55.5% at six months and 67.9% at one year. Shintu et al (15) showed hypothyroidism in 74.2% of subjects, mostly in the second trimester post therapy. Similarly, in a study by Nebesio et al (16) hypothyroidism was observed in 75% patients 40-to-90 days after RAI. By comparison, Ahmad et al (17) reported that the cumulative incidence of hypothyroidism following RAI treatment was 38.2% after six months. The incidence increased to 55.8% after one year and to 86.1% at 10 years. According to Kendall-Taylor et al (18) the modal time to hypothyroidism was three months and 64% of patients were hypothyroid at one year.

The cure rate was 95.5% of the patients who were taking ATD for more than one year and 92.7% of the patients who were taking ATD for less than one year before the therapy. In subjects who received ATD more than one year showed good response but this association was not statistically significant ($P=1.95$). The cure rate was 95.4 % of the patients who showed FT4 level less than 35 pmol/L and the cure rate was 92.7 % of the patients who showed FT4 level more than 35 pmol/L, the difference was also not statistically significant ($P=1.54$).

Y Khalid, et al (19) showed one year following RAI

treatment, 543 (93%) patients were either euthyroid (162;28%) or hypothyroid (383;65%) and considered "cured"; 39 (7%) patients remained hyperthyroid and required further doses of RAI, with 34(6%) patients requiring two doses and 5(1%) patients three doses. At three months, 484 out of 571 (85%) patients, and at six months, 490 out of 549 (89%) patients were "cured". On uni-variate analysis no correlation could be established between the failure to respond to the first dose RAI and age, gender, aetiology or use of antithyroid medication ($p = ns$ for all) although the rate of hypothyroidism was significantly higher at the end of one year in patients with Graves' disease as compared to those with toxic nodular disease (77.1% vs. 50.3%, $p < 0.01$). In this study, patient's cure rate was higher (94.4%). The high rate might have been contributed by two factors: low sample size and higher RAI absorption in this patients due to regional iodine insufficiency compared to iodine sufficiency in regions where other studies were conducted.

In another study, only 16% of the subjects (20/79) who received a five 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 pre-treatment thyroid hormone values had no influence on outcome, but size of goiter had a direct relationship, larger goiters were associated with higher treatment failure (9, 20).

As a final consideration, it is essential to close follow up and management of these patients. It is possible to avoid long term debilitation and sequelae involved with hypothyroidism (21) and manage this condition closely, so the patient can live a normal life without comorbidities caused by iodine-131 therapy.

CONCLUSION

The goal of therapy for hyperthyroidism is to achieve a non-hyperthyroid status—either euthyroidism or iatrogenic hypothyroidism that has been completely compensated to the euthyroid state with oral levothyroxine. Follow up is necessary for both

management of hypothyroid patients and also for selection of the patients for subsequent RAI therapy. From this study it can be concluded that cure rate of RAI therapy is quite good and the pretreatment factors have little influence on the final outcome.

REFERENCES

1. Tuttle RM, Becker DV, Hurley JR. Radioiodine Treatment of Thyroid Diseases. In: Sandler MP, Coleman RE, Patton JA, Wackers FJ, Gottschalk A, editors. *Diagnostic Nuclear Medicine*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2003:653-70.
2. Meier DA, Dworkin HJ, Bender JM. Therapy for Hyperthyroidism. In: Henkin RE, Bova D, Dillehey GL, Halama JR, Karesh SM, Wagner RH, Zimmer AM, editors. *Nuclear Medicine*. 2nd ed. Philadelphia: Mosby Elsevier; 2006:1567-75.
3. Susan J, Mandel SJ, Larsen PR, Davies TF. Thyrotoxicosis. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. *Williams Textbook of Endocrinology*, 12th ed. Philadelphia: Saunders Elsevier; 2011:362-405.
4. Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I et al. Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract*. 2011;17(3):456-520.
5. Solomon B, Glinoe D, Largesse R & Wartofsky L. Current Trends In the Management of Graves' Disease. *Journal of Clinical Endocrinology and Metabolism*. 1990;70:1518-24.
6. Douglas S. Ross, M.D. Radioiodine Therapy for Hyperthyroidism. *N Engl J Med* 2011;364 :542-50.
7. Pusuwan P, Tuntawiroon M, Sritongkul N. A Prospective Randomized Study of the Efficacy and Cost-Effectiveness of High and Low Dose Regimens of I-131 Treatment in Hyperthyroidism. *J Med Assoc Thai*. 2011;94(3):361-68.
8. Franklyn, J.A., Daykin, J., Drolc, Z. Long-Term Follow-Up of Treatment of Thyrotoxicosis by Three Different Methods. *Clin Endocrinol (Oxf)* 1991;34:71-76,
9. Zingrillo M, Urbano N, Suriano V. Radioiodine Treatment of Plummer and Multinodular Toxic and Nontoxic Goiter Disease by the First Approximation Dosimetry Method. *Cancer Biother Radiopharm* 2007;22(2):256-60.
10. Erkan ME, Demirin H, Asik M, Celbek G, Yildirim M, Aydin Y, et al. Efficiency of Radioactive I-131 Therapy in Geriatric Patients with Toxic Nodular goiter. *Aging Clin Exp Res* 2012; 24(6):714-7.
11. Reid JR and Wheeler SF. Hyperthyroidism Diagnosis and Treatment. *Am Fam Physician* 2005;72(4):623-30.
12. Franklyn JA. Drug Therapy: The Management of Hyperthyroidism. *N Engl J Med*. 1994; 330:1731-38.
13. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine Treatment of Hyperthyroidism-Prognostic Factors For Outcome. *J Clin Endocrinol Metab* 2001;86:3611-17.
14. Wisam K. Ghadban, Mahmoud A. Zirie, Daoud A. Al-Khateeb, Amin A. Jayyousi, Hassan M. Mobayedh, Ahmed S. El-Aloosy, Radioiodine Treatment of Hyperthyroidism Success Rate and Influence of Thyrostatic Medication. *Saudi Med J* 2003;24(4):347-51
15. Ajit S. Shintu, Leena Pacheb, and T. K. Sreekanth. Fixed Dose Radioactive Iodine Therapy in Hyperthyroidism : Outcome and Factors Affecting It In a Region in South India. *Thyroid Science* 2010; 5(60):1-7 .
16. Nebesio TD and Siddigui A R. Time Course to Hyperthyroidism After Dose Radioablation Therapy of Graves' Disease In Children. *J Pediatr* 2002;141(1):99-103.
17. Ahmad AF, Ahmad M and Young ET. Objective Estimates of The Probability of Developing Hypothyroidism Following Radioactive Iodine Treatment of Thyrotoxicosis. *Eur J Endocrinol* 2002; 146:767-775,
18. Kendall-Taylor P, Keir MJ and Ross WM. Ablative RAI therapy for hyperthyroidism: long term follow up study. *Br Med J (Clin Res Ed)* 1984;289(6441):361-63.
19. Y Khalid, D M Barton, V Baskar, H Kumar P Jones, T E T West and H N Buch. Efficacy of Fixed High Dose Radioiodine Therapy for Hyperthyroidism – a 14 years Experience: A Focus on Influence of Pre-treatment Factors on Outcomes. *BJMP* 2011;4(3):435
20. Nair N. Results of a Single 5 mCi Dose of Radioactive Iodine in Thyrotoxicosis. *Indian J Nucl Med* 1991;6:6-11.
21. Thientunyakit T, Thongmak S, Premprapha T. Comparative Evaluation of Two Different Dosage Calculation Protocols of Iodine-131 In the Treatment of Hyperthyroidism. *J Med Assoc*