Journal of Bangladesh College of Physicians and Surgeons
Vol. 26, No. 2, May 2008

Radioiodine (^{131}i) Therapy for Thyrotoxicosis Patients and their Outcome: Experience at Center for Nuclear Medicine & Ultrasound, Barisal

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Summary:

Radioiodine therapy appears to be an effective means in controlling thyrotoxicosis and it acts either by destroying functioning thyroid cells or by inhibiting their ability to replicate. The variable radiosensitivity of the gland means that the choice of dose is empirical. Unfortunately all attempts at dosimetry have thus far failed to reliably deliver a dose that avoids recurrence and does not ultimately lead to hypothyroidism. Ninety five patients (female 66 and male 29) with thyrotoxicosis treated with radioiodine at the Center for Nuclear Medicine & Ultrasound, Barisal and their outcome were analyzed from January 2000 to December 2004. Before radioiodine administration clinical features of the patients, palpation of the thyroid gland and ultrasonogram were performed.131$_I$ was given as fixed dose method and the dose ranged from 8-12 mCi. Higher doses were administered for larger goiter, multinodular goiter and in relapse cases. Hyperthyroid state was controlled in 85 (89%) patients after receiving single dose of radioiodine and 13 (13.6%) patients developed hypothyroidism within 3 months of therapy. Radioiodine therapy has proved to be cheap and effective method of treatment for thyrotoxicosis.

Key words: Thyrotoxicosis, Radioiodine therapy, Hypothyroidism.

(J Bangladesh Coll Phys Surg 2008; 26: 73-78)

Introduction:

Thyrotoxicosis is a clinical condition that results from high level of circulating thyroxine and triiodothyronine. These patients are usually restless, talk rapidly, and display emotional liability. Other classic signs and symptoms include sweating, heat intolerance, palpitations, insomnias, and worm, fine skin. Prominent eyes or a state may be produced by increased thyroid hormones level, but infiltrative eye signs signal the presence of Graves' disease. Graves' disease is the most common (70-85%) cause of thyrotoxicosis and occurs most frequently in young women.[1] Radioiodine therapy is a promising technique for the patients with thyrotoxicosis. The major attraction of radioiodine as a therapeutic agent for thyrotoxicosis lies in its simplicity, relatively low cost and absence of significant complications. [2] ^{131}I is administered orally as a single dose and is trapped and organified in the thyroid, the effects of its radiation is long lasting, with cumulative effects on follicular cell survival and replication. Carbimazole reduces the efficacy of ^{131}I therapy because it prevents organification of ^{131}I in the gland, and so should be avoided until 48 hrs after radio-iodine administration.[3] The majority of the patients eventually develop hypothyroidism and the incidence of hypothyroidism after radioiodine treatment varies, depending on the dose used, individual sensitivity to radioiodine and the length of follow up. The aim of the present study was to assess its effectiveness in controlling the disease as well as the incidence of hypothyroidism following radioiodine therapy.

Material and Methods:

Ninety five patients who received radioiodine therapy during a period of January 2000 through December 2004 at the Center for Nuclear Medicine & Ultrasound, Barisal were enrolled for this retrospective study. All patients were diagnosed hyperthyroidism on the basis of clinical features and thyroid hormone levels. Their total triiodothyronine (T_3) and thyroxine (T_4) level were raised with low

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Received: 8 July, 2007 **Accepted:** 27 February, 2008

thyroid stimulating hormone (TSH). Serum T_3 and T_4 were measured by radioimmunoassay (RIA) method and TSH was measured by immunoradiometric assay (IRMA). The normal range of T_3, T4 and TSH were 1.23-3.54 nmol/L, 54- 173 nmol/l and 0.3-5 mIU/L respectively in the studied laboratory.

All patients were referred by the physicians. Clinical features and body weight were recorded in a predesigned clinical proforma.Thyroid glands were palpated and ultrasonogram was performed for each individual using 5 MHz curvilinear probe. The parenchymal echotexcture and the volume of the thyroid gland were measured and noted accordingly. Radionuclide thyroid scan was performed with ^{99m}Tc pertechnate using gmma camera.

Before administering radioiodine, the nature of the treatment and its radiation risk, cost benefit ratio, the importance of precautionary measures and the necessity of subsequent follow up were explained to the patients. In case of female of reproductive age, menstrual history was taken carefully and pregnancy was excluded before radioiodine therapy and the rule of 10 days were followed.

The dose of ^{131}I was given to the patients as a fixed dose method. The dose given at first time ranged from 8-12 mCi with a mean (± SD) of 10.6 ± 1.54 mCi. Higher dose was given for very large and multinodular goiter. Similarly lower dose was required for relatively smaller and / or diffuse goiter. Clinical features also considered carefully before estimating the dose. In case of 2nd or subsequent therapy higher doses were required. Antithyroid drugs (Crbimazole) and β blockers were given to patients who had marked features of thyrotoxicosis, very ill health, and in old age group. Antithyroid drugs were usually given for 4-6 weeks and stopped 3 days prior to radioiodine therapy. That was resumed after 3 days and advised to continue for another 4-6 weeks according to symptoms.

Patients were advised to attend the center as required or after 3 months whichever is earlier. Next follow up was performed at three months interval for first year and six monthly for subsequent years. In each follow up clinical features and thyroid hormone levels were assessed. When the 1st dose seemed to be ineffective 2nd or subsequent dosage were considered at least 6 months after the first dose. Patients who developed hypothyroidism, managed with thyroxine replacement as long as needed.

Results and observations:

Ninety five thyrotoxicosis patients treated with radioiodine (^{131}I) from January 2000 through December 2004 were available for the analysis of therapeutic outcome. Among 95 patients, female were 66 and male 29 with the age ranged from 18-75 years (Fig-1). The mean (± SD) age of the patients was 41.65 ± 11.48 years and the female to male ratio was 2.2:1. Most of them had history of weight loss, palpitation, sweating and tremor (Fig-2), and out of ninety five, thirty six patients had exophthalmos. On ultrasonogram 90 patients (94.73 %) had diffuse

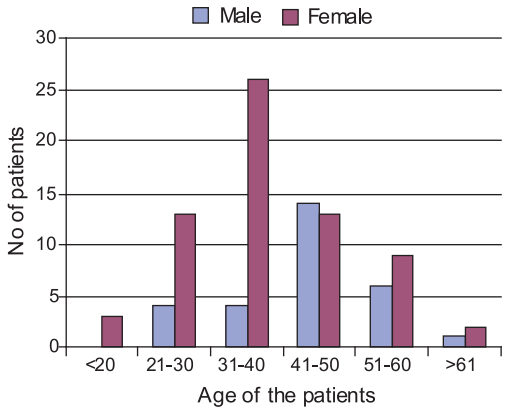

Fig.1: *Age and sex distribution of the patients with thyrotoxicosis.*

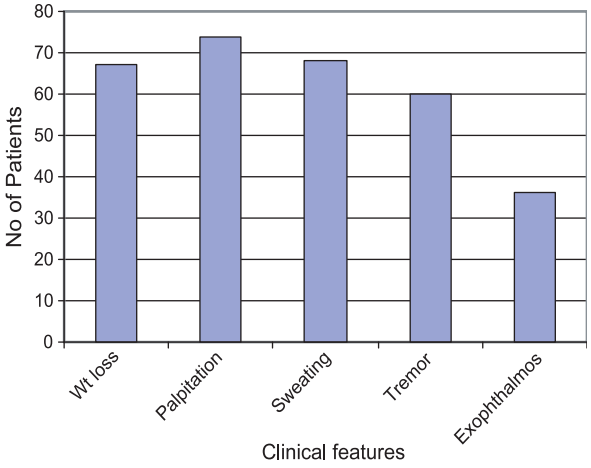

Fig.2: *Common clinical features among the patients with thyrotoxicosis.*

goiter, 3 (3.15 %) had single nodular goiter and 2 (2 %) had multinodular goiter. Their mean (± SD) T_3 level was 7.75 ± 2.85 nmol/L, mean (± SD) T_4 level was 272.75 ± 42.39 nmol/L and mean (± SD) TSH level was 0.14 ± 0.11 mIU/L.

Out of 95, follow up was possible for 60 (63%) patients and 35 (37 %) patients did not attend the center after their first follow up, probably they attended other centers for further follow up or became euthyroid. Thirty five (36.8 %) patients developed hypothyroidism following radioiodine therapy. Among the total of 95 patients,13 (13.6%) patients developed hypothyroidism within 3 months of radioiodine therapy; next 60 patients were considered for subsequent follow up and of them, 15 (25 %) patients developed hypothyroidism within 6 months, 5 (8.3 %) within 1 year, 2 (3.3 %) after 18 months. Thirty six (38 %) patients had markedly raised T_3 & T_4 and / or cardiovascular problem and they needed pretreatment with antithyroid drugs for 4 weeks prior to radioiodine therapy. Exophthalmos was present in 36 (38 %) patients and for one of them prednisolone was given, which was tapered gradually. Thyrotoxicosis was controlled (euthyroid or hypothyroid) in 85 (89 %) patients after receiving single dose of radioiodine therapy, 7 patients needed 2nd dose, 2 patients needed 3rd dose, and 4th dose was needed for 1 patient.

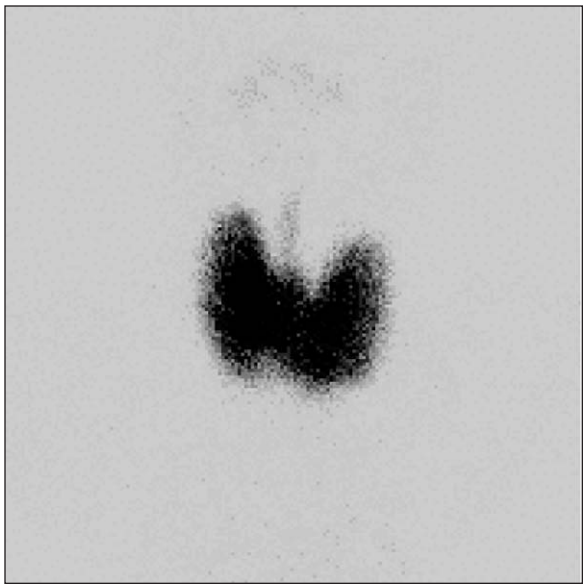

Fig.3: *Scan image of diffusely enlarged thyroid gland with intense and uniform radiotracer concentration allover.*

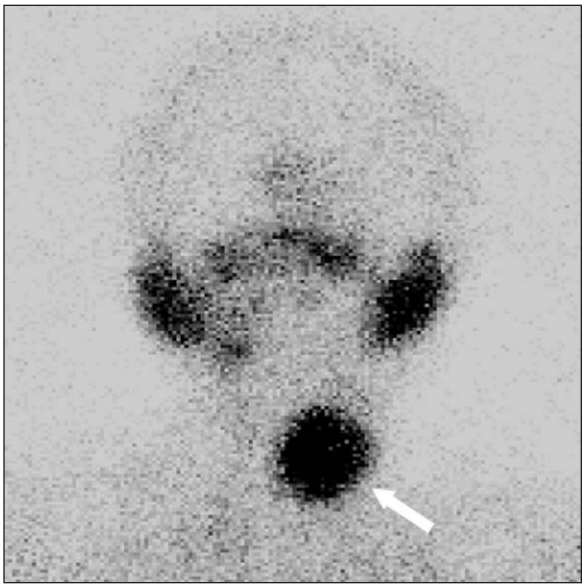

Fig.4: *Scan image of autonomously functioning toxic nodule in the left lobe*

Discussion:

Thyrotoxicosis may be managed by antithyroid drugs, surgery and radioiodine therapy.[4] Radioactive iodine is established as a simple, cheap and effective method of treating thyrotoxicosis, and in most of the cases represents the treatment of choice.[5] There is no evidence that thyroid carcinoma or leukaemia is induced by therapeutic dose of ^{131}I, or that its results in an increased frequency of congenital malformation among subsequent offspring.[6,7,8] Thyrotoxicosis may be divided into two major categories for which ^{131}I treatment may be indicated: (a) the nonautoimmune toxic nodule, including the autonomously functioning nodule and the toxic multinodular goiter; and (b) the autoimmune causes, notably Graves' disease (3).

Most patients with Graves' disease are treated with radioactive iodine ^{131}I, some early after diagnosis and others 6-12 months later. There is over 50 years of experience with use of therapeutic ^{131}I. Endocrinologists have become comfortable with treating patients, even children, with ^{131}I because of its high efficacy and low incidence of adverse affects. Symptomatic improvement is usually noted by 3 weeks after therapy. However, the full therapeutic effect takes 3-6 months because stored hormone must first be released and used. Some evidence suggests

that exacerbation of exophthalmos with ^{131}I therapy, so steroids are often administered.[9] In case of nodular goiter isotope is taken up selectively by the toxic nodules, which are then functionally destroyed and rest part of the gland is largely spared from the damaging effect. So the patient with toxic nodular goiter is likely to return to euthyroid state after ^{131}I therapy.[10] On the other hand in Graves' disease patient, there is relatively uniform global uptake of the ^{131}I, and ultimate progression of hypothyroidism is common.[4] Antithyroid drugs are generally ineffective for long term remission of hyperthyroidism. Harshman *et al* found that there is an early relapse or late recurrence of hyperthyroidism in about 50 % patients when treatment is stopped even after a prolonged period course of two years or more,[11] without surgical risk, still it is favored by many thyroidologists. Surgical management offers rapid resolution of hyperthyroidism, slower progression to permanent hypothyroidism, removal of large goiter causing compression and substernal extension. Indeed, isotope treatment of the nonimmune types of the hyperthyroidism would appear to be nearly ideal.[12]

Calculating the dose, based on thyroid volume and iodine uptake, it is possible to reduce the incidence of early hypothyroidism. Combining the most sophisticated ultrasonogram techniques and dosimetry, one may expect better outcome with prompt (within 3-6months) control of hyperthyroidism and delayed onset of hypothyroidism. When treatment results in hypothyroidism, the commonly observed symptoms and signs of a slowed metabolism may be accompanied by headache and generalized muscle and joint discomfort. The headache is considered to be the result of pituitary swelling; both of these symptoms clear promptly with thyroid hormone replacement.[4]

^{131} I treatment causes significant reduction of thyroid volume in both toxic and nontoxic goiter.[13,14,15] The most obvious objective of radioiodine therapy is to render the patient euthyroid and off drug therapy. Routine use of antithyroid drugs prior to radioiodine therapy is not necessary. However in high risk patients with severe hyperthyroidism, associated with other complications particularly cardiovascular disease, and in old age group, it is reasonable and appropriate to bring these patients to euthyroid state with antithyroid drugs before radioiodine therapy.[16] In the present study, for 36 (38%) patients antithyroid drugs were given.

Exacerbation of symptoms may occur because of release of stored hormone from radiation thyroiditis and it may occur any time from 12 hours to 20 days after therapy, average 10-14 days. Since carbimazole blocks the organification of iodine within the thyroid, carbimazole therapy should be discontinued at least 48 hours before therapy is undertaken to ensure adequate residence of ^{131}I within the follicular cells.[17] Beta blockers which are also conventionally used for most of the patients to combat the symptoms do not affect radioiodine therapy.[18] Radioiodine therapy for hyperthyroidism has no significant complications but the major disadvantage is post treatment hypothyroidism. Chapman EM found no evidence of irradiation thyroiditis in patients administering less than 15 mCi of ^{131} I in a single dose.[19] Hypothyroidism is dose related; however, even with low doses, 76% patients have hypothyroidism by 11 years posttreatment. Range in first year varies between 5% and 70%. Average approximately 5.55 per month for first six months; 13% per month for second 6 months.[18] In the present study 13.6% developed hypothyroidism within 3 months of radioiodine therapy and 25 % within 6 months, which corresponds well with the previous study.

There are two ways of fixed dose administration: (a) Low dose- 3-5 mCi administered as a fixed dose. Since initial onset of hypothyroidism id dose related, has lower incidence of hypothyroidism. However, cure rate is lowered, as well. (b) High dose- 8-10mCi dose given to all patients, Success rate with one therapy using this dosage range >90%. Incidence of hypothyroidism within one or two years after treatment has a direct relationship with ^{131}I doses given to the patients [20] but delayed hypothyroidism develops at about the same rate regardless of the dose of ^{131}I used. [21,22]

All patients who have been treated with ^{131}I for hyperthyroidism must have long term follow up to detect the hypothyroidism, and motivation is very important in this respect. In the absence of any specific symptoms or signs, annual serum T_4

estimation is the best and easiest routine follow-up investigation for screening. If T_4 is below normal, hypothyroidism can be confirmed by measurement of serum TSH on the same sample. If recurrent hyperthyroidism is suspected clinically, serum T_3 should be estimated. The addition of sensitive TSH measurement to the follow up protocol improves the effectiveness of the assessment but increases the cost.[5]

Persistence of goiter along with hyperthyroidism at 3 months after treatment usually means treatment failure. However, it is still recommended to wait the additional 3 months under protection of a beta blocker and an antithyroid drug. Transient hypothyroidism may occur after several months. It is wise to delay T_4 replacement therapy until an additional 2-3 months have lapsed, allowing for the possibility that a rising TSH may raise T_4 and T_3 to normal levels. On the other hand, an enlarging goiter in a patient who is euthyroid or hypothyroid at 3 months after ^{131}I therapy may require T_4 replacement that will shrink the goiter and relieve the symptoms.[23]

In the present study 89 % patients were controlled (euthyroid/hypothyroid) receiving the single dose of radioiodine therapy which was close to that in other studies.[24,25] Recently one long term follow up study was carried out in the Institute of Nuclear Medicine and Ultrasound, Dhaka considering teenage hyperthyroidism and radioiodine therapy, which revealed that the mean administered dose of radioiodine was 10.69 ± 2.77 mCi and the mean age of the patients was 16-18 yrs. The effective control of hyperthyroidism after radioiodine treatment occurred in 60.72 % patients with a single dose, 35.71 % required a second dose and 3.57 % required more than two doses. Overall incidence rates of hypothyroidism after 1 year and 5 years of radioiodine therapy were 32.14 % and 75 % respectively and patients with Graves' disease showed a greater tendency in the evolution of early hypothyroidism.[26] Though the period of our study was not long enough to assess the outcome of radioiodine therapy for thyrotoxicosis, still follow up is continuining with the maintenance of their files.

Conclusion:

Radioiodine therapy for thyrotoxicosis is now becoming the treatment of choice due to its simplicity, relatively low cost and absence of significant complications. By measuring the exact thyroid volume and estimation of the proper dose, the incidence of hypothyroidism following therapy can be reduced. Motivation and good cooperation with the patients ensure regular follow up and ultimately better outcome of radioiodine therapy.

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