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Radioiodine Therapy for Hyperthyroidism—Changing Pattern of Management over Three Decades at INMAS

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ABSTRACT

Iodine-131 therapy is a relatively simple, effective and economical method of treating hyperthyroidism. Even fifty years after the introduction of radioactive iodine, there is no concensus on the approach for selection of the dose for treatment of hyperthyroidism. Since the last three decades, the approach for radioiodine therapy at this Institute has been to treat with low, fractionated doses to produce partial destruction of the thyroid gland leaving the patient sufficient functioning gland for normal hormone production. New *in vitro* diagnostic techniques including free T_3, T_4 and sensitive TSH assay have been introduced over the past decade for the diagnosis of hyperthyroidism. Changes in the thyroid radioactive iodine uptake in the population due to introduction of iodized salt, and the high incidence of persistent hyperthyroidism after 'low dose radioiodine therapy, have prompted to go for a proportionate i&ease in the ^{131}I original dose schedules based on goitre grades. This has led to a nominal increase in the incidence of post therapy hypothyroidism. However, the basic principle of low, fractionated dose therapy is still being followed at this Institute, which appears suitable for our social and economic conditions.

1. INTRODUCTION

Thyroidectomy has been the mode of treatment of thyroid goitre since time immemorial. It was only in'the late nineteenth century that the distinction between toxic and non-toxic goitre was made, when the relation between thyroidectomy and relief of the toxic symptoms of hyperthyroidism was appreciated. Use of antithyroid

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drugs and radioiodine therapy for hyperthyroidism started almost simultaneously in the early 1940, and it was in 1942 that Hamilton and Hertz first put forward independent results on the use of radioiodine in hyperthyroidism[1,2]. The utility of radioiodine in the management of hyperthyroidism was considered a major breakthrough in the medical field ushering in a new era in the uses of radioactive substances in the management of medical disorders.,

The late Brig. SK. Mazumdar, who has been a pioneer of nuclear medicine in India, started a thyroid clinic at the Institute of Nuclear Medicine and Allied Sciences (INMAS) in 1961. He propagated the use of radioiodine in the management of hyperthyroidism almost from the very inception of this thyroid clinic, and the multiple low dose regime of radioiodine therapy in- hyperthyroidism as is being followed in this Institute has been his brainchild.

Over the years the thyroid research activities of the-Institute have been recognised all over the country, and the thyroid investigative techniques and tests have also diversified and multiplied., While radioactive iodine uptake (RAIU) and its related studies, protein bound iodine (PBI) and later T_3, T_4 and thyroid-stimulating (thyrotropic) hormone (TSH) estimation were the initial investigations carried out, a battery of tests including estimation of free T_3 and T_4, resin uptake studies, free T_3 and T_4 indices, serum thyroglobulin, thyroid autoantibodies, thyroid immunoglobulins, thyrotropin releasing hormone (TRH) stimulation test, thyroid scintiscanning including radioiodine and technetium pertechnetate scan, ultrasonography, thermography, fine needle aspiration cytology, computerised axial tomography (CT) and NMR scanning of the thyroid are at present being performed. Estimation of TSH by sensitive assay techniques has been the latest addition to the armementarium of investigative techniques being conducted at this Institute.

During the last 29 years over one lakh patients with thyroid ailments have been. treated at this Institute and at present more than ten thousand new patients come here annually for management of thyroid disorders. Of the one lakh cases, approximately ten thousand have come for the treatment of hyperthyroidism of which about three thousand have been treated with radioiodine at this Institute during some stage of thier treatment,

2. IODINE DEFICIENCY IN DELHI

Deficiency of iodine in an area is known to cause endemic goitre, Ramalingaswamy, et *al* in 1961, while discussing the aetiology of endemic goitre in the Himalayas had considered Delhi as a control area[3]. However in 1980, Pandav, et *al* in their studies found that Delhi itself had prevelance of endemic goitre[4]. Thus it can be surmised that over this period Delhi has turned from an iodine sufficient to an iodine deficient area. In an important research programme, 25,000 school children in the age group 5-18 years were' surveyed by an INMAS team of doctors, and of these 30 per cent were found to have goitre. Based on these and other studies, Delhi was declared endemic for goitre and the iodized salt programme was implemented by legislation in Delhi in the mid 1980s.

Introduction of iodized salt has direct implication on the diagnosis and management of hyperthyroidism as discussed below.

3. MANAGEMENT OF I-IYPERTIIYROIDISM

This can be considered broadly under two heads, namely, diagnosisand treatment.

3.1 Diagnosis

Diagnostic protocol at this Institute consists of four parts, viz. (a) clinical evaluation, (b) estimation of thyroid hormones T_3, T_4, TSH and thyroid autoantibodies, (c) ^{131}I thyroid uptake studies, and (d) in doubtful cases or where clinical picture does not match the above investigations, estimation of free T_3, T_4 and thyroxine index. TRH stimulation tests are also carried out.

3. I. 1 Clinical Evaluation

Clinical evaluation is not only to estabiish the diagnosis but also to determine the exact dose of radioiodine to be administered to the patient in case ^{131}I therapy is the choice of treatment.

Clinical factors in deciding radioiodine dose include

(i) Size of the gland-higher dose is administered for larger goitres.

(ii) Nodularity-patients with toxic nodular goitre are-given higher dose than those with toxic diffuse goitre.

(iii) Consistency-firm or hardgland will require more dose than soft glands.

(iv) Severity of toxicity-severely toxic patients required more dose than mildly toxic patients.

(v) Age-older age group patients require more dose than younger patients.

3.1.2 T_3, T_4, TSH and Autoantibodies Estimation

T_3, T_4 and TSH have been estimated by radioimmunoassay (RIA) at this institute since 1980. Estimation of TSH by RIA has its own diagnostic limitations and for the last two years it has been estimated by the sensitive immunoradiometric assay (IRMA). Sensitive TSH assay is extremely useful as a first line diagnostic test for evaluating thyroid function[5,6] and is routinely done by IRMA as a screening test of thyroid function.

Thyroglobulin and microsomal autoantibodies are known to rise in Grave's disease and autoimmune disorder of the thyroid'. These antibodies have been estimated in this Institute for a decade and in a retrospective study Shankar, et al have noted that negative autoantibody titres show prognostically significant results both in return of thyroid size to normal and of thyroid to euthyroid state in Grave's hyperthyroidism treated with radioiodines.

3. ^{131}I Thyroid Uptake Studies

^{131}I thyroid uptake studies have a great relevance in the diagnosis and management of thyrotoxicosis. In this test one capsule of ^{131}I (25-50 μCi) is administered to the patient after an overnight fast and three tests, viz. (a) thyroid uptake at 2, 4, 6, 24, 48 & 72 hours; (b) thyroid scan at 24 hours; and (c) PB ^{131}I, hepatic counts and thyroid discharge values at 48 hours are conducted.

In a study conducted in 1983 at this Institute, Prakash, et *al* reported a significant increase in the thyroid iodine uptake in comparison to iodine uptake levels in 1976 and attributed this increase to iodine deficiency in Delhi'.

In 1985, before the introduction of the iodized salt programme, the following values were considered of diagnostic importance in thyrotoxicosis[10]:

(i) Peak value of uptake in thyroid reaching within 6 hours.

(ii) Thyroid discharge more than 10 per cent at 48 hours.

(iii) More than three hundred hepatic counts per 50 μCi per minute.

(iv) PB ^{131}I more than 0.1 per cent per litre.

Increase in dietary iodine is known to decrease the iodine uptake in the thyroid[11,12]. Since the introduction of iodized salt in Delhi in 1986 the uptake levels have been decreasing and in 1988, Shankar, et *al* reported a marked change in the thyroid iodine uptake in hyperthyroid individuals in comparison to the studies conducted[13] in 1985. The thyroid uptake values are uniformly reduced and there was considerable delay in peak thyroid uptake time with reduction in the hepatic counts and thyroid discharge values. Based on these findings, the following parameters for diagnosis of hyperthyroidism based on ^{131}I uptake and related studies[14] have been formulated.

(i) More than 10 per cent RAIU at 2 hours.

(ii) More than 20 per cent RAIU at 4 hours.

(iii) More than 30 per cent RAIU at 6 hours.

(iv) More than 40 per cent RAJU at 24 hours.

(v) Peak RAIU within 24 hours.

(vi) More than 2 per cent discharge at 48 hours.

(vii) More than 150 hepatic counts per 50 μCi radioiodine per minute.

3.2 Treatment

Treatment of, hyperthyroidism can be broadly grouped under two heads, medical and surgical. Medical treatment can be further subdivided into antithyroid drug treatment and radioiodine therapy.

Various dosage schedules of radioiodine have been advocated for the treatment of hyperthyroidism. No two clinics in the world would probably be following the same type of dosage schedule. These various regimes include administering of one large dose of radioiodine with the intention of ablating the thyroid, variable dosage method depending on the size of the gland and severity of thyrotoxicosis, and multiple small fractionated dose regimes[15-18].

In the large dose regimen about 160 microcurie/g of estimated thyroid weight is given to the patient leading to a hypothyroid state which is then followed by thyroxine replacement therapy. This mode of treatment, although inexpensive and offering a rapid cure to the patient, has the disadvantage of curing one disorder by knowingly inducing another.

In a developing country like India, it is economically not possible to maintain a patient on a life long replacement therapy. At this Institute, since its very inception, hyperthyroidism has been treated with small doses of radioiodine with the aim of minimising the risk of post-therapy hypothyroidism.

Though the aim has remained the same, the criteria and dosage amounts have varied over the years. This is because an analysis of patients treated till mid 1970s revealed that 15 per cent of patients remained persistently hyperthyroid even after two years radioiodine therapy and they required 3-5 years to become euthyroid.

Thus, as can be seen in Table 1, the dosage schedule was modified keeping the upper limit of radioiodine administered to a patient fixed at 5 mCi, but by increasing the dosage for various grades of goitre. The various criteria required for calculating dosage of radioiodine to be administered have already been mentioned.

Table 1. Radioiodine treatment schedule in two regimes

Gland size	Dose in mCi	
	1971-75	1975—88
Not palpable	1-1.5	1-2
Grade I	1.5-2	2-3
Grade II	2-3	3-4
Grade III	3-5	3.5-s
Grade IV	4-s	4-5

With the uptake of iodine markedly reducing after the introduction of iodized salt in the market, the dosage schedule was again modified in 1988. Classifying goitre by the WHO Stanbury Classification", grade IV goitre were now referred for surgery unlike in the two previous regimes, where they were treated with radio&line. Grade III goitres were treated with radioiodine only if the patient was unwilling for surgery or it was contraindicated. The dosage schedule which is currently being adopted since 1988 is given in Table 2.

Prior to therapy, severity of thyrotoxicosis is judged clinically and by T_3, T_4 and TSH estimation and thyroid uptake studies. All patients who have been treated with radioiodine were maintained on propranolol therapy, (unless contraindicated) after

Table 2. Radioiodine treatment schedule since 1988

Gland size	Dose in mCi
Grade OA	1.5-2.5
Grade OB	1.5-3.5
Grade I	2.5-4
Grade II	3—4.5
Grade III	4-5

the initial dose of radioiodine. Dose of propranolol varies from 40-120 mg per day in divided doses depending on the severity of the disease.

Prior to 1975, repeat doses of radioiodine used to be administered at 4-6 monthly intervals, the repeat dosage being half the first dose. This was repeated till the patient became euthyroid. From 1975 to 1988, between l-2 mCi radioiodine used to be given at 2-4 monthly intervals after the initial dose depending on the clinical condition of the patient, till euthyroid state was achieved. Since 1988, patients are being 're-evaluated and the same dosage of radioiodine as given in Table 2 is administered at 2–4 monthly intervals, till the patient is euthyroid. T_3 and T_4 estimation is done on each visit to confirm thyroid status.

In a comparative cumulative recovery rate study, it has been seen that in the initial two regimes, 66 per cent of the patients recovered in one year. In the latest regime since 1988, 85 per cent of the patients became euthyroid state in the same period. In the regime between 1961 and 1975, 15 per cent of the cases took 3-5 years to recover whereas 95 per cent of the cases in the 1975-1988 regime recovered within two years. Nodular goitres showed slow recovery while smaller glands recovered faster. Only two per cent of the patients treated till 1975 went into a state of permanent hypothyroidism while 10 per cent of patients in the regime treated till 1988 became permanently hypothyroid. Reducing the incidence of persistent hyperthyroidism by increasing the administered dose of radioiodine has its advantages, but is marginally offset by the nominal increase in the development of post-therapy hypothyroidism.

It can be concluded that although, due to environmental factors, the dosage schedule and management of hyperthyroidism with radioiodine has been modified and altered over the years, the basic structure as laid down by the late Brig. S.K. Mazumdar will continue to be the basis for management of hyperthyroidism.

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