

Radioiodine (I-131) Therapy and the Incidence of Hypothyroidism

S Tavintharan,**MBBS, MRCP (UK)*, F X Sundram,***FAMS, MSc (Nucl Med), DMRT*, L S Chew,****MBBS, FRACP*

Abstract

Radioiodine (I-131) is one of the accepted forms of treatment for thyrotoxicosis. The major drawback of this treatment is the definite incidence of hypothyroidism, which is either early or late, and is cumulative. We set out to analyse the local incidence of this outcome.

Patients with hyperthyroidism, treated with radioiodine from 1984 to end of 1989, and still on follow-up with the Department of Nuclear Medicine, Singapore General Hospital were analysed for the incidence of hypothyroidism.

Three hundred and eighty-two patients were analysed (305 females, 77 males). Their ages ranged from 14 to 85 years (mean 48.2, SD 11.1 years). The doses of radioiodine ranged from 4 to 18 mCi (mean 7.6 mCi, SD 1.8 mCi). Two hundred and sixty-two patients who received I-131 only required a single dose, while 87 needed one repeat dose of I-131, and 33 needed more than 2 doses. Of the 382 patients, 271 (70.9%) became clinically hypothyroid, 6 (1.6%) were subclinically hypothyroid, 100 (26.7%) were euthyroid and 3 (0.8%) remained hyperthyroid. One hundred and eighty-one patients (47.4%) were clinically hypothyroid at the end of 1 year, and an average rise of 4.8% per year was observed from the second to the fifth year. From the sixth year onwards, the average incidence of hypothyroidism was 1% per year.

I-131 is indeed an effective means of controlling thyrotoxicosis (99.2% were no longer hyperthyroid). The main problem with this treatment is hypothyroidism, and this is easily managed with L-thyroxine.

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Introduction

Hyperthyroidism is a common problem with a local prevalence of 1.28%, higher in females (1.58%) and 1.00% in males.* It is commonly treated with antithyroid drugs, especially thionamides, carbimazole and propylthiouracil. However, relapse with this form of treatment is not uncommon, with the local figure at 37.7% as shown in a study in 1990 by Tan et al.² Besides, in patients on antithyroid drugs, compliance often becomes an issue, especially with frequent relapses. Surgery is another effective choice, but risks both intraoperatively and postoperatively are well recognised.

Radioiodine (I-131) has been in use for almost 50 years to manage hyperthyroidism. It is not only safe and cheap, but is indeed effective. Although there have been fears with regards to the increased risks of leukaemia or thyroid carcinoma, several large trials have failed to find a statistically significant association.³⁻⁵ There is also no risks of infertility, and when avoided in pregnancy, there is no increase in congenital deformities either.^{6,7}

Hypothyroidism remains the only common long-term side effect of I-131 therapy. The incidence of hypothyroidism varies from centre to centre, dependent upon the dose of I-131 delivered.⁸ The incidence after the first year of treatment is about 6% after an average dose of only 2 mCi, and can be as high as 64% in trials which use 15 mCi. After the first year, the annual incidence of hypothyroidism is about 2% to 5%.⁸

We conducted a study to review the treatment of thyrotoxicosis with I-131. The aim was to study the efficacy of this form of therapy and also to find the incidence of subsequent hypothyroidism in these patients.

Patients And Method

Patients who received their first I-131 between January 1984 and end 1989, and attended follow-up with the Department of Nuclear Medicine, Singapore General Hospital for at least 4 years were included in the study. The study was done by a retrospective analysis of the casenotes of the patients included.

* Registrar

*** Senior Consultant and Head

Department of Medicine

Alexandra Hospital

** Senior Consultant and Head

Department of Nuclear Medicine

Singapore General Hospital

Address for Reprints: Dr S Tavintharan, Department of Medicine, Alexandra Hospital, Alexandra Road, Singapore 159964.

The dose of I-131 given was empirical, based on size and nodularity of the thyroid gland, nodular. goitres receiving higher doses than diffuse goitres. Also, patients with thyrocardiac disease were given a higher dose. Post treatment, patients were followed up at 3 to 4 months interval for the first year, and 6 to 12 monthly thenceforth.

Thyroid status was assessed based on clinical symptoms and signs, thyroid stimulating hormone (TSH) and/or thyroxine levels. Patients were only labelled as "hypothyroid" if they had clinical features (symptoms $\pm$ signs), a raised TSH level, a low free or total thyroxine level, and required L-thyroxine treatment. Transient hypothyroidism was excluded if L-thyroxine could be successfully withdrawn within 6 months of I-131. Subclinical hypothyroidism was accepted as that with no clinical features, with normal thyroxine levels, but with the TSH levels greater than 5.0 mU/L and below 10.0 mU/L. Such cases were not included as "hypothyroid" but were followed up closely and were only included as "hypothyroid" if and when they required L-thyroxine replacement. Patients who defaulted follow-up after at least 4 years, and remained euthyroid at this point were included as "euthyroid".

Successful and effective therapy was defined as the permanent resolution of hyperthyroidism, regardless of whether the patients were euthyroid or hypothyroid.

For statistical analysis, t-test was used to compare means and Chi-square used to compare grouped data.

To avoid any confusion in terminology in the results and discussion that follows, the term "hypothyroidism" would be used to describe clinical hypothyroidism unless otherwise stated.

Results

A total of 382 patients were included in our study. There were 305 (79.8%) females and 77 (20.2%) males in the study. The mean age was 48.2 years (SD 11.1 years), with a range of between 14 and 85 years. The mean age for males was 47.8 years and that for females was 48.3 years. Patients received an average dose of 7.6 mCi (SD 1.8 mCi) with a range of between 4 and 18 mCi during each treatment. The modal dose was 7.0 mCi. A maximum follow-up of up to 10 years was achieved, with a mean follow-up period of 5.5 years (SD 1.75 years).

Administration of a single dose resulted in control of thyrotoxicosis in 262 (68.8%) of patients. Eighty-seven (22.8%) required 2 doses and a further 33 (8.6%) needed more than 2 doses of radioiodine.

There was no statistically significant difference between the first dose in those requiring 1 dose or those requiring repeat doses, the mean being 7.4 mCi in the first group and 7.7 mCi in the latter group ($P > 0.05$).

Two hundred and seventy-one (70.9%) of the 382 patients were hypothyroid on follow-up. Six patients (1.6%) had subclinical hypothyroidism, 100 (26.7%) were euthyroid and only 3 patients (0.8%) remained hyperthyroid and required treatment with antithyroid drugs.

At the end of the first year, 47.4% of the patients were hypothyroid. From the second to the fifth year, there was a 4.8% annual increase in incidence of hypothyroidism. From the sixth year onwards, the incidence of hypothyroidism was 1% per year (Fig. 1).

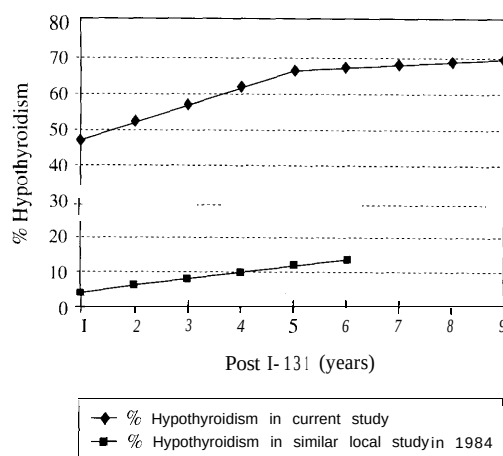


Fig. 1. Cumulative incidence of post-treatment hypothyroidism

There was no significant difference in the prevalence of hypothyroidism at the time of review in patients treated with a single dose and those requiring repeated treatment ($P > 0.5$). For the two hundred and sixty-two thyrotoxics who needed only one dose of radioiodine before control of their disease, 183 (69.8%) became hypothyroid on follow up. This prevalence was not significantly different from that of the group who required more than one dose of radioiodine, where 88 of the 120 patients (73.3%) developed hypothyroidism upon overall follow up.

To find out if patients who received a higher cumulative dose of radioiodine were at a higher risk of becoming hypothyroid, we compared the prevalence of hypothyroidism according to the cumulative dose of radioiodine received. Table I illustrates the relationship between total dose of radioiodine administered and the prevalence of thyroid failure.

There was no statistically significant difference in the prevalence of hypothyroidism when compared according to the total dose of radioiodine received ($P > 0.1$).

The overall success rate of therapy, recognised as the permanent resolution of hyperthyroidism was 99.2%, with 91.6% achieving resolution in not more than 2 doses.

TABLE I: PREVALENCE OF HYPOTHYROIDISM ACCORDING TO CUMULATIVE DOSE OF I-131

Total dose (mCi)	Total number	Hypothyroid	%
4-5.9	19	16	84.2
6-7.9	131	89	67.9
8-10	110	75	68.2
>10	122	91	74.2

Discussion

Radioiodine therapy is a well accepted means of management of thyrotoxicosis. It has been used for around 50 years and is safe and easy to administer. It reduces production and secretion of thyroid hormone by causing necrosis of the follicular cells early, and leading to vascular and stromal fibrosis as a delayed action.⁸⁻¹⁰

There initially were fears of an increased risk of leukaemia and thyroid carcinoma, but these fears have been put to rest by some large studies.³⁻⁵ Infertility was also thought to be a possible complication, but it is now known that the gonadal irradiation in I-131 treatment is about the same as that experienced in intravenous pyelograms and barium enemas and this does not cause infertility.^{6,7} I-131 should be avoided in pregnancy, and pregnancy should be avoided for at least 4 months post therapy. As long as this precaution is adhered to, there is no significant risk of congenital abnormalities.^{7,11}

Hypothyroidism remains the only common problem with I-131 therapy. The incidence of hypothyroidism varies from centre to centre, dependent upon the dose of I-131 delivered.⁸ The ready availability specific diagnostic tests, and the cheap and predictable action of synthetic thyroxine makes the end result of hypothyroidism more acceptable.

Radioiodine is a definitive therapy for thyrotoxicosis. It comes in the form of capsules or as a liquid. The dosing is often based on the type of goitre, generally higher doses for multinodular goitres, and for thyrocardia.⁸⁻¹⁰ Radioiodine can be delivered either as a fixed standard dose, or as a calculated dose based on the weight and volume of the thyroid gland, and the fractional uptake of I-131 at 24 hours.⁸ The strategy of giving a calculated dose is aimed at reducing the incidence of post treatment hypothyroidism. However, with this regime, there is a compromise of an increased incidence of relapse of thyrotoxicosis. This is unacceptable to most, as hyperthyroidism is associated with morbidity which includes angina pectoris, arrhythmias, cardiac failure and an increase in the rate of bone loss.³ Many find the strategy to induce early hypothyroidism, then substituting with L-thyroxine at a time when the disease is under close control as the most appropriate option. This is easy to do as L-thyroxine is not only safe and cheap but also adequacy of dosage can be well monitored with sensitive TSH assays.¹²

In our study, we obtained a fairly large number of patients for analysis as they were still on follow-up with the Department of Nuclear Medicine. Careful record of the annual thyroid function tests, the presence of symptoms of hypothyroidism and details of treatment which included dates and doses of I-131 were invaluable for our analysis. These allowed the determination of the incidence and prevalence of hypothyroidism, and analysing the relationship between treatment and their overall outcomes. As analysis was made from a tertiary referral centre, we were not able to get details such as the nature of the goitre and thyroid antibody titres consistently for all our patients. As a result of this, we were unable to compare the outcomes of radioiodine treatment between Graves' disease and multinodular goitres.

The prevalence of hypothyroidism in our study was 70.9%, after a follow-up of up to 10 years. The patients received a mean dose of 7.6 mCi and 99.2% achieved permanent resolution of hyperthyroidism, 91.6% needing either 2 doses or less. Our incidence of hypothyroidism was similar to the Chicago group of Sridama et al¹³ who had a cumulative incidence of hypothyroidism of up to 76.1% at the end of the 11th year. In the above study, the mean dose of I-131 used was 4.9 ± 3.0 mCi compared to our mean dose of 7.6 mCi. The authors in the Chicago group noted that although the incidence of early hypothyroidism was lower due to the lower dose received (11.7% at the end of the first year, as compared to 47.4% in our study), the long-term cumulative incidence was similar.

In another study done in The Royal Victoria Infirmary in Newcastle-upon-Tyne by Kendall-Taylor and colleagues,¹⁴ a standard ablative dose of 15 mCi of I-131 was used to eradicate hyperthyroidism and in this study, a significantly larger proportion, 64% of the patients were already hypothyroid at the end of the first year.

Besides the incidence of hypothyroidism, the other interesting feature is that of the proportion of patients who needed repeat doses of radioiodine. In our study, 31.4% of patients required repeat treatment with radioiodine. This result is similar to the 33.7% noted in the Chicago group,¹³ who used a dose of radioiodine which was calculated based on thyroid size. However, when we look at the data from The Royal Victoria Infirmary in Newcastle-upon-Tyne by Kendall-Taylor and colleagues,¹⁴ only 4.4% of their patients required repeat treatment, after receiving a fixed ablative dose of 15 mCi. These data support the fact that when we use the strategy of giving a calculated dose of radioiodine to reduce the incidence of post treatment hypothyroidism, we may have to settle for a compromise of an increased incidence of relapse or uncontrolled thyrotoxicosis.

We also compared our results with that of a similar retrospective study done locally in 1984 by Sundram.¹⁵

It was based on patients who received radioiodine in the years 1973, 1974 and 1975 and followed up to 1980. In this study, the mean dose of radioiodine used was 6.7 mCi, and a six-year follow-up was achieved. The incidence of hypothyroidism was 4% in the first year, and an average rise of 2.2% per year in the remaining 5 years of follow-up. The incidence of hypothyroidism was much lower than our present study (cumulative incidence in the sixth year is 12.9% in this study compared to 67.6% in our study). This can be due to a few causes. Firstly, the doses used in our study was higher than that in the previous study (mean of 7.6 mCi as compared to 6.7 mCi). The difference in dosing is much more evident when we note that in the previous study only 112 of the 417 patients (26.9%) received a cumulative dose of greater than or equal to 8 mCi, as compared to 232 of 382 (60.7%) in our study. The second important reason for the difference in incidence in hypothyroidism between the 2 studies could be the use of sensitive TSH assays in our study. TSH assays were locally only available routinely from 1981, and as such not used in the previous study. As TSH assays are a highly sensitive and specific means of diagnosing hypothyroidism, this could, to a certain extent, account for the higher incidence of hypothyroidism in our study as compared to the previous paper.

In conclusion, when we embark into the treatment of thyrotoxicosis, we should always define our goals clearly. Our aim should be to achieve prompt, predictable control of the overactive thyroid gland, both of which are satisfied by radioiodine. With radioiodine, we should aim to achieve this with a single dose of I-131. Controversy always arises whether hypothyroidism is a satisfactory end point for success of therapy. The morbidity associated with hypothyroidism is well known, but as discussed earlier, the convenience of thyroxine replacement, and the advances in TSH assays certainly contributes to its acceptability as an end point. The choice of dosage of I-131 remains another issue of debate, and there still remains uncertainty as to which regime is superior, the standard fixed dose, calculated dose or the ablative regime. In deciding the dose, we should not only take into account the volume of the gland and the I-131 uptake at 24 hours. Patients attitudes and opin-

ions, their reliability and compliance, the overall health care costs, and finally any inconveniences involved in re-treatment must also be borne in mind when making this important decision which has potential lifelong implications.

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