Radioiodine therapy for hyperthyroidism

Review Article

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ABSTRACT

Radioiodine therapy is the safest, simplest, least expensive and most effective method for treatment of hyperthyroidism. The method employed in this research was a systematic bibliographic review, in which only valid studies or the clinically detailed enough open-labeled studies using validated scales were used. Iodine-131 (I-131) acts by the destructive effect of short-range beta radiation on thyroid cells. Indications for radioiodine therapy include toxic nodules (in which I-131 is the first choice of treatment), recurrent hyperthyroidism after antithyroid treatment or surgery, intolerance to antithyroid therapy due to side-effects and patient preference. Due to difficulties in previous methods for dose determination, fixed dose method of I-131 is now considered the best practical method for radioiodine therapy in primary hyperthyroidism. Absolute contraindications for radioiodine treatment are pregnancy and lactation. In pediatric patients, radioiodine therapy can be used, but is mainly considered in recurrent toxic goiter and when antithyroid medication is ineffective. There is no clear evidence indicative of carcinogenic or teratogenic effect of this agent.

Keywords: Radioiodine, Hyperthyroidism, Toxic goiter, Toxic nodule, I-131

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INTRODUCTION

Hyperthyroidism is a hypermetabolic condition due to overproduction of thyroid hormones (1-4) which is more common in women. Overt hyperthyroidism, is defined as subnormal serum thyrotropin concentrations with elevated free T4 or T3 concentrations (5, 6); however, in milder hyperthyroidism, serum T4 and free T4 estimates can be normal, only serum T3 may be elevated, and serum TSH will be <0.1 mU/L (or undetectable). These laboratory findings have been called "T3-toxicosis" and may represent the earliest stages of disease or secondary to autonomously functioning thyroid nodule. In general, when thyrotoxicosis is caused by hyperthyroidism, serum free T3 is more elevated than the free T4, though this value is rarely required for an accurate diagnosis. Subclinical hyperthyroidism is defined as a normal free T4 and normal total/free T3, with subnormal serum TSH concentration (2, 3, 7).Untreated hyperthyroidism may lead to cardiovascular disease, including atrial fibrillation, cardiomyopathy, and congestive heart failure (3). Increased bone turnover occurs with untreated hyperthyroidism, leading to osteoporosis and fracture (3, 5).

Thyrotoxicosis has multiple etiologies, manifestations, and potential therapies. Appropriate treatment requires an accurate diagnosis and is influenced by coexisting medical conditions and patient preference (3, 7). Radioiodine is the most popular therapy and is preferred by many patients (8, 9).

Treatment modalities include medical therapy by blockade of new hormone synthesis and release, and inhibition of the peripheral effects of thyroid hormone (thionamides, stable iodine, adrenergic blocking drugs), and ablation of thyroid tissue by radioactive iodine (RAI) or surgery. The selection among these therapeutic modalities involves clinical factors, the physician's preference, and the patient's choice (2). Radioiodine may be the treatment of choice for patients with toxic adenoma and toxic multinodular goiter despite disagreement regarding the amount or number of doses required to achieve a therapeutic response (1-3, 10, 11). I-131 is regarded as the treatment of choice for hyperthyroidism in patients older than 30 years and also in patients of any age in whom hyperthyroidism is accompanied by medical complications or other treatments choices has failed (12).

Diagnosis of hyperthyroidism

Ordinarily hypermetabolic and sympathomimetic symptoms are suggestive of hyperthyroidism. To confirm the diagnosis of thyrotoxicosis, suppressed TSH (<0.01 mU/L) and increased free T4 levels will suffice most of the time. Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected hyperthyroidism and should be used as an initial screening test (7). Free T4 index, which is derived by multiplying the total T4 and T3 uptake ratio, correlates well with actual FT4 but is lately replaced by the latter. In less than 5% of patients with thyrotoxicosis, the serum T3 assay may be needed to diagnose T3 toxicosis. Subclinical hyperthyroidism is diagnosed when the TSH level is subnormal and T4 and T3 levels are normal (2, 4). To exclude autoimmune based disorders, evaluation of antithyroid antibodies (TRAb, antiperoxidase, and antithyroglobulin antibodies) is needed (1, 13).

Indications of I-131 therapy in thyrotoxicosis

Thyrotoxicosis due to overproduction of thyroid hormones is the main indication for radioiodine therapy. The most common causes include Graves' disease, toxic multinodular goiter, and toxic adenoma (1-5, 14):

Graves' disease: Graves' disease is the most common cause of hyperthyroidism, accounting for about 80% to 90% of all cases (1-3, 7, 15, 16). Graves' disease is an autoimmune disease in which the TSH receptor is stimulated by thyrotropin receptor antibodies (TRAbs), enhancing thyroid hormone production (1, 7, 17). Spontaneous remission occurs in approximately 30% of patient (5, 18). Although antithyroid drug is usually the first line of therapy, 50% to 80% of patients have a relapse and recurrent hyperthyroidism within 1 year after stopping of antithyroid medication for Graves' disease, radioiodine treatment is considered the preferred safe method for definite therapy in these patients (1).

Toxic nodular goiter (toxic adenoma or multinodular goiter): 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 (7, 19). Unlike Graves' disease in which up to 30% remission without treatment has been reported, toxic nodular goiter is progressive (18). For hyperfunctioning adenomas two definitive therapies are available: radioiodine and surgery (3). However many prefer isotope therapy as the first choice of treatment (1-7, 20). In toxic nodular goiter, radioiodine is selectively accumulated by the autonomous nodule while the uptake of radioactive iodine by the rest of the gland is suppressed because of greatly decreased pituitary TSH secretion (1-3, 21). Therefore, it destroys only nodular area and the remaining thyroid tissue is less affected. So, the effectiveness of radioiodine treatment in toxic nodules is very high and the risk of hypothyroidism is low (4). In view of the current increased awareness of adverse consequences associated with subclinical hyperthyroidism and the rarity of spontaneous resolution of hyperthyroidism in patients with autonomous functioning thyroid nodule (despite a propensity for spontaneous hemorrhage and degeneration), definitive therapy (surgery, radioiodine therapy) is recommended (1, 22).

Other indications: When TSH is persistently suppressed (<0.1 mU/L), treatment should be strongly considered in all individuals ≥65 years of age, and in postmenopausal women who are not on estrogens or bisphosphonates; patients with cardiac risk factors, heart disease or osteoporosis; and individuals with hyperthyroid symptoms (7).

A controversial indication for radioiodine therapy is asymptomatic benign non-toxic multinodular goiter. Conventional radioiodine I-131 therapy has been used for two decades as an effective and safe alternative to surgery in the treatment of these patients. This treatment is especially useful in patients who decline surgery or have contraindications due to co-morbidity especially in elderly in whom MNG is prevalent (23).

I-131 therapy is also the preferred method of therapy in the following situations: Females planning a pregnancy in the future (in more than 4–6 months following radioiodine therapy, provided thyroid hormone levels are normal), individuals with co-morbidities increasing surgical risk, and patients with previously operated or externally irradiated necks, or lack of access to a high-volume expert thyroid surgeon or in case of contraindications to antithyroid medication use (1-3, 7).

It is to be noted that I-131 is also used for treatment of some other causes of thyrotoxicosis namely struma ovarii which develops when ovarian teratomas contain enough thyroid tissue to cause true hyperthyroidism (1-3).

Treatment in children

The treatment of pediatric patients with Graves' disease varies considerably among institutions and practitioners. Because some

children will go into remission, antithyroid therapy for 1–2 years is still considered the first-line of treatment in most children. However, the majority of pediatric patients with Graves' disease will eventually require either radioactive iodine or surgery (1, 5, 7). Properly administered, radioactive iodine is an effective treatment for Graves' disease in the pediatric population (24, 25). I-131 is widely used in children, but still viewed as controversial by some practitioners owing primarily to concern over cancer risks (26, 27).

It is known that risk of thyroid cancer after external irradiation is highest in children <5 years of age, and declines with advancing age (28, 29). The clinical guidelines of the American Thyroid Association and the American Association of Clinical Endocrinologists do not include young age as a contraindication to I-131 therapy (7). However, I-131 therapy should be avoided in very young children (<5 years). I-131 therapy in patients between 5 and 10 years of age is acceptable if the calculated I-131 administered activity is <10 mCi. I-131 therapy in patients older than 10 years of age is acceptable. Thyroidectomy should be chosen when definitive therapy is required, the child is too young for I-131, surgery should be performed by an experienced thyroid surgeon (7).

In children, radioiodine therapy should especially be considered in recurrent toxic goiter and when thyrostatic drugs are ineffective (4). Also this therapy may be indicated when a child has developed a reaction to antithyroid drugs, proper surgical expertise is not available, or the patient is not a suitable surgical candidate (7). If radioactive iodine is chosen as treatment for Graves' disease in children, it is recommended the patient be pretreated with methimazole and beta-adrenergic blockade until the patient is euthyroid. It is suggested sufficient I-131 should be administered in a single dose to render the patient hypothyroid (7, 30-32).

Contraindications for I-131 therapy

Absolute contraindications for radioiodine treatment are pregnancy, lactation, coexisting thyroid cancer, or suspicion of thyroid cancer, individuals unable to comply with radiation safety guidelines and females planning a pregnancy within 4–6 months (7). Because iodide readily crosses the placental barrier, radioiodine is absolutely contraindicated in pregnancy. As the fetal thyroid begins to accumulate iodine about 10^{th} week of pregnancy, I-131 could affect it if given after that time. It is also inappropriate earlier in pregnancy because of exposure of the fetus to unnecessary radiation from maternal I-131 as well as from I-131 crossing the placenta (1, 33).

Because a patient may be unaware that she is pregnant, a reliable pregnancy test (BHCG) before the administration of radioiodine to women in whom this possibility exists should be taken. Pregnancy should be postponed to approximately six months after isotope administration. By this time, the radioactivity of the isotope should be sufficiently decreased and the function of the thyroid gland should be normalized (1, 4, 5). Lactation should be discontinued. Discontinuance is based not only on the excessive time recommended for cessation of breast feeding but also on the high dose the breasts themselves would receive during the radiopharmaceutical breast transit. Hence therapy should be delayed until lactation ceases in order to minimize the radiation dose to the breast (at least 4-6 weeks). The patient may not resume breastfeeding for that child. Nursing may resume with the birth of another child (1, 2, 34-36). Radioiodine is considered safe for use in women of childbearing age and in older children (37). Patients who are allergic to iodinated contrast agents are usually not allergic to radioiodine (5). Moderately severe ophthalmopathy may be a contraindication to treatment with radioiodine, since radioiodine may exacerbate the condition (38-40).

Preparation/before radioiodine treatment

For the majority of patients with uncomplicated mild hyperthyroidism, preparation for I-131 therapy with antithyroid drugs is unnecessary (34, 41, 42). It is believed that there is insufficient evidence to show radioiodine worsening hyperthyroidism either clinically or biochemically, and it only delays treatment with radioactive iodine. In addition, there is evidence that pretreatment may reduce the efficacy of subsequent radioactive iodine therapy. In one study, failure was observed after the administration of propylthiouracil but not methimazole (43-45).

Pretreatment with methimazole and beta-adrenergic blockade prior to radioactive iodine therapy for Graves' disease should be considered in patients who are at increased risk for complications due to worsening of hyperthyroidism including severe hyperthyroidism, the elderly, and those with substantial co-morbidity that puts them at greater risk for complications or worsening hyperthyroidism (5, 7, 46-49). These co-morbidities include cardiovascular complications such as atrial fibrillation, heart failure, or pulmonary hypertension and those with renal failure, infection, trauma, poorly controlled diabetes mellitus, and cerebrovascular or pulmonary disease (7, 50-52).

To reduce the risk of treatment failure, antithyroid drugs should be stopped prior to radioiodine. The duration for this discontinuation is cited from 2-3 days (53) to one week before I-131 administration (7, 46). It can be restarted 3–7 days later, and generally tapered over 4–6 weeks as thyroid function normalizes (7). Although continuous antithyroid regimen will results in a stable thyroid function during I-131 therapy, but is hampered by the higher amounts of radioactivity required (47, 54).

It is also recommended that patients discontinue use of iodide-containing preparations, iodine supplements and other medications that could potentially affect the ability of thyroid tissue to accumulate iodide for a sufficient time before contemplated therapy (1, 7, 14, 36). Also possibility of pregnancy should be eliminated by a human chorionic gonadotropin (HCG) test, unless the patient is a premenarchal child, is in a certain postmenopausal state, or has had a documented hysterectomy or tubal ligation. Breastfeeding must be stopped and therapy must be delayed until lactation ceases in order to minimize the radiation dose to the breast (4-6 weeks) (1, 55). To maximize the absorption of I-131 the patient should be fast. Informed consent should be taken from all patients (1, 2).

Pathophysiology of radioiodine treatment effect

Radioiodine (I-131) is increasingly used as the definitive treatment of choice in most patients with hyperthyroidism (14, 56). I-131 ablates thyroid tissue by selectively localizing in functioning thyroid tissue and emitting beta particles at 0.61 MeV (2, 57). Biological effects of I-131 include necrosis and impaired replication of nondestroyed follicular cells (58). This results in atrophy, fibrosis and a chronic inflammatory response, which may ultimately result in permanent thyroid failure (2, 56, 57). Changes in thyroid histology are associated with a reduction in thyroid volume which reflects thyroid damage (67% and 76% of pretreatment volume at 6 and 12 months, respectively) (31, 59). Radioiodine treatment for Graves' disease is also followed by changes in thyroid autoimmunity, which may result in a transient increase of TSH-receptor antibodies (TRAb) with thyroid stimulating antibody (TSAb) and in the de novo appearance of TRAb with TSH-blocking activity (TSHBAb) (60-63). After a single radioiodine administration, patients may become hypothyroid, euthyroid, or remain hyperthyroid (57). Hypothyroidism may develop within the first few months after I-131 therapy or in subsequent years, and largely depends on the dose of I-131 administered (1-4, 56, 64-67).

Dose strategies

The purpose of radioiodine treatment is to control hyperthyroidism by making the patient hypothyroid (7). This can be accomplished equally well by either administering a fixed activity or by calculating the activity based on the size of the thyroid and its ability to trap iodine (1, 68).

Fixed millicurie administration

The easiest and most practical method of radioiodine administration is to give an identical number of millicuries to all patients (1-3). The fixed dose amount varies depending patient's status from 3 to 7 mCi (111 to 259 MBq) (1) to 10–15 mCi (7) for Graves' disease. A high dose regimen of radioactive iodine treatment is more effective than the low dose one (69, 70). For radioiodine therapy of toxic multinodular goiters and solitary toxic autonomously functioning thyroid nodules, different principles of dose selection apply. The radioiodine is concentrated in the autonomously functioning nodules, and therefore the suppressed extranodular tissue receives far less radiation and can gain normal function when the TSH level normalizes after therapy. Therefore, the incidence of hypothyroidism after I-131therapy for toxic nodular goiter is less than that seen with therapy for Graves' hyperthyroidism. Larger doses of I-131 are required for management of toxic nodular goiters and the authors rarely give less than 20 mCi (740 MBq). In larger multinodular goiters, doses in the range of 30 to 75 mCi (1.1 to 2.77 GBq) may be required (2, 22, 71-73).

Delivered microcuries per gram

In this method the estimated thyroid gland size and the results of a 24-h RAIU test is needed to calculate the amount of I-131 to administer in order to achieve a desired concentration of I-131 in the thyroid gland. Delivered activity of 2.96–7.4 MBq (80–200 μCi) per gram of thyroid tissue is generally appropriate. The thyroid radiation dose depends on the RAIU as well as the biological and effective half-life of the radioiodine in the thyroid gland. This biological half-life can vary widely. Thyroid concentrations toward the upper end of the range (i.e., 7.4 MBq/gm [200μCi/gm]) are especially suitable for patients with nodular goiters, very large toxic diffuse goiters, and repeat therapies (1, 34, 55).

Patient's course

The typical of a patient's course after radioiodine administration is as follows: No clinical effect after 131 I for 3 to 4 weeks; Maximum effect usually seen in 3 to 4 months; Adjunctive drug administration may be used to obtain more rapid control; Re-treatment will usually not be considered for 4 to 6 months; and 90% to 95% of the patients no longer have hyperthyroidism after a single dose (2).

Post-treatment radiation protection considerations

The instructions of Nuclear Regulatory Commission regulations deal with the necessity to avoid close contact with infants, young children, and pregnant women for at least two days and to sleep alone for at least one night; consider bathroom practices; and to use separate eating utensils (2, 74).

Radioiodine treatment follow-up

Follow-up within the first 1–2 months after radioactive iodine therapy for Graves' disease should include an assessment of free T4 and total T3. For toxic adenoma and toxic multinodular goiter TSH should be checked too. If the patient remains thyrotoxic, biochemical monitoring should be continued at 4–6 week intervals (7). Afterwards the visit intervals can be determined by patient clinical status.

In general hypothyroidism occurs 6-12 months after treatment, but may be observed at any time. Hence, follow-up with thyroid function tests is required at least once a year even for patients who are euthyroid. The treatment of choice after developing hypothyroidism is levothyroxine sodium which is used as replacement therapy. To check for efficacy of this therapy Free T4 and TSH levels should be within normal limits. After the patient is on an established dose of levothyroxine, annual follow-up with TSH is adequate (14).

Success rate

The global success rate of first dose of radioiodine treatment for hyperthyroidism is recorded at least 70% (4, 75-78).

Retreatment with radioactive iodine

If hyperthyroidism persists beyond 6 months following I-131 therapy, retreatment with radioactive iodine is suggested. For Graves' disease if there is only minimal response 3 months after therapy, retreatment with I-131 is suggested (7). Following radioiodine therapy, the residual thyroid tissue usually shows a more rapid thyroid radioiodine turn over than previously. So, a larger amount of I-131 must be given in a way 20 to 30% more radioiodine be deposited in the thyroid (1). For Graves' disease, remission is unlikely if antibodies against the TSH-receptor remain above 10mU/l after 6 months of antithyroidal treatment and radioiodine or thyroidectomy can be recommended (46).

Post-therapy hypothyroidism

It is assumed that radioiodine treatment leads to hypothyroidism in most patients. However, it cannot be considered as a side-effect of such therapy (75). On the other hand induction of hypothyroidism is considered the goal of therapy (7, 79).Various studies have shown that 20% to 64% of patients became hypothyroid 1 year after treatment and that the subsequent incidence of hypothyroidism is approximately 3% to 5% each year (2, 69, 75, 80-82).It has been suggested that the linear relationship between radiation dose and hypothyroidism accounts for the early incidence of hypothyroidism. Late hypothyroidism which occurs at a relatively fixed rate appears independent of dose and may be more related to the natural history of the disease (83).

As the global incidence of hypothyroidism is regardless of dose, it has been suggested that large amounts of I-131 should be given routinely to produce earlier and more certain control. With such a strategy, permanent supplementation with thyroid hormone is started at the earliest possible moment (1, 5, 84, 85).

Complication of radioiodine therapy for thyrotoxicosis

Early complications

Exacerbation of Hyperthyroidism: There have been a number of case reports of exacerbation of hyperthyroidism following radioiodine therapy. This is due to post-radiation thyrocyte destruction and thyroid hormones release (4). So the patients with existing cardiac disease and at risk of such complications should receive careful management of their heart disease, as well as antithyroid drugs to deplete thyroidal hormone content before receiving I-131therapy (1).

Radioiodine and ophthalmopathy

Most, but not all studies of patients with Graves' disease suggest that radioiodine therapy is associated with the appearance or exacerbation of ophthalmopathy more often than antithyroid drug therapy or surgery (5, 86-89). The changes are often mild and transient, at least in patients who have mild

or no ophthalmopathy before therapy. However, thyroid-associated orbitopathy cannot be considered as a contraindication for isotope therapy (4). Radioiodine treatment may increase the inflammatory process and exacerbate the ophthalmological symptoms. This is due to radiation thyroiditis, which releases thyroid antigens and stimulates antithyroid antibody production (90). Patients without clinically detectable orbitopathy are apparently unlikely to develop significant eye disease after radioiodine treatment, although patients who do have significant eye involvement before treatment have an increased risk of an exacerbation of eye disease after radioiodine. Smoking, high levels of pretreatment serum triiodothyronine, and post-radioiodine hypothyroidism are associated with increased risk of Graves' orbitopathy (91). Pretreatment with antithyroidal drugs to restore euthyroidism, which also frequently leads to improvement of orbitopathy and cessation of smoking is recommended (92). The use of oral prednisone doses of 0.3 to 0.4 mg/kg/day started at the time of radioiodine has been reported to prevent worsening of orbitopathy after treatment (1, 5, 40, 92, 93). Radioiodine may also be associated with the onset or worsening of infiltrative dermopathy (pretibial myxedema) (94).

Late complications

There is no clear evidence of increased rate of malignancy or genetic consequences in patients treated with radioiodine (95-97).

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