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Analysis of Variable Dose i -131 Treatment in Management of Hyperthyroidism

KEYWORDS: Thyrotoxicosis, I 1131 therapy

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ABSTRACT *Radioiodine therapy is an established mode of treatment for thyrotoxicosis of large range of etiologies. Different therapeutic regimes have been attempted to institute appropriate dose of radio iodine in different clinical scenario. However the indications, patient selection criteria and dose regime choice remain highly controversial varying greatly from institution to institution.*

The objective of this study is to assess the efficacy of three different ranges of variable doses of 131 radio Iodine therapy in patients with hyperthyroidism and to evaluate the incidence of hypothyroidism following radio iodine therapy at different doses.

In this retrospective study, 127 patients treated with I-131 for hyperthyroidism between Jan 2006 - Jan 2007 was included who had regular follow up till one year.

The patients were categorized in three groups and treated with different dosage

This study shows that there is no definitive evidence of prolonging hypothyroidism in patients treated with small dose as compared to other two groups but often necessitating requirement of second dose of I 131.

Our study indicates that the optimal dose of 5mCi of radioiodine should be given for the complete cure of hyperthyroidism to minimize the necessity of multiple doses.

B) Introduction
Radioiodine therapy is an established mode of treatment for thyrotoxicosis of large range of etiologies. Different therapeutic regimes have been attempted to institute appropriate dose of radio iodine in different clinical scenario. However the indications, patient selection criteria and dose regime choice remain highly controversial varying greatly from institution to institution.

The chief goal of the radio iodine therapy is to achieve complete abolition of the hypersecretory endocrine state. However controversy arises whether hypothyroidism following therapy is a complication or an expected negative end point.

The objective of this study is to evaluate the effectiveness of the variable dose therapy and monitoring the incidence and occurrence of hypothyroidism.

A)Anatomy of thyroid
The thyroid is a brownish-red and highly vascular gland located anteriorly in the lower neck, extending from the level of the fifth cervical vertebra down to the first thoracic (1). Thyroid weight varies but averages 25-30 g in adults (Slightly heavier in women). The gland enlarges during menstruation and pregnancy (1).

B) Physiology of the gland:
The thyroid maintains the level of metabolism in the tissue that is optimal for their normal function. Thyroid hormones stimulate the O2 consumption of most of the cells in the body, help regulate lipid and carbohydrate metabolism and are necessary for normal growth and maturation. Thyroid function is controlled by the thyroid stimulating hormone (TSH, thyrotropin) of the anterior pituitary. The secretion of this gland is in turn regulated in part by thyrotropin releasing hormone (TRH) from hypothalamus and is subject to negative feedback mechanism by high circulating levels of thyroid hormones acting on the anterior pituitary and hypothalamus. The principle hormones secreted by the thyroid are thyroxin (T4) and triiodothyronin (T3). T3 is also formed in peripheral tissues by deiodenation of T4. Both hormones are iodine containing amino acids. T3 is more active than T4, whereas RT3 is inactive.

C) Hyperthyroidism
Thyrotoxicosis is the hypermetabolic condition associated with elevated levels of free thyroxine (FT4), free triiodothyronine (FT3), or both (2). Hyperthyroidism is a subset of thyrotoxicosis (excludes exogenous thyroid hormone intake and subacute thyroiditis) that is caused by excess synthesis and secretion of thyroid hormone by the thyroid (2) Excess thyroid hormone causes an increase in the metabolic rate that is associated with increased total body heat production and cardiovascular activity (increased heart contractility, heart rate, vasodilatation) (2).

The major symptoms of hyperthyroidism include palpitation, nervousness, sweating, hyperdefecation, and heat intolerance (2). Women often note a reduction in menstrual flow or oligomenorrhea (2). Common signs of hyperthyroidism include weight loss despite increased appetite, lid lag and stare, sinus tachycardia, atrial fibrillation or high output failure (in elderly individuals), fine tremor, and muscle weakness (2). Thyrotoxicosis leads to an apparent increase in sympathetic nervous system symptoms, including nervousness, stare, tremor, and tachycardia (2).

D)Treatment of hyperthyroidism
Antithyroid drugs have been one of the standard modalities of therapy for hyperthyroidism, either as first choice therapy or as pretreatment before radioactive iodine in selected patients3.

Beta-blockers (e.g. Propranolol, Nadolol) can be given in the early stages to control the symptoms of hyperthyroidism. They have no effect on the thyroid gland and do not treat the cause of the problem.

Volume : 4 | Issue : 3 | Mar 2014 | ISSN - 2249-555X

Radioactive iodine therapy is the most common treatment of hyperthyroidism in adults in the United States. Although the effect is less rapid than antithyroid medication or thyroidectomy, it is effective, safe, and does not require hospitalization.

Dose determination: (33)
a) Standard dose method:
When a 3 to 4 mCi of dose of I131 is administered orally to patients with toxicgoiter , two of the three patients become well 4 months latter. A rare patient becomes hypothyroid and most of the rest experience some degree of relief of hyper thyroidism. In those not in remission, improvement is usually sufficient to permit further treatment with the isotope.

About 85% of the patients enter remission or become hypothyroid after a second dose of 3 to 4 mCi and a third dose of 3 to 4 mCi increases the rate of remission plus hypothyroidismapproximately to 90%.

b) Variable dose method:
Because of the biological variability in resistance to radiation effect; and in order to limit the radiation dose to the thyroid in an effort to minimize early and late onset of hypothyroidism , the wide range of doses of I 131 used . The millicurie is retained as the dosage unit instead of probable radiation dose to the thyroid from such a dose because greater inaccuracies in the assumption required to estimate the radiation dose.

Remission can be induced in 90% of patients after one or more treatments and early hypothyroidism develops in 7% of patients. Between 1 to 5 mCi dose is given with reduced dose schedule .the average dose is 3 mCi. The patients with mild hypothyroidism and very small gland receives least amount , and severly toxic patient with a very large and nodular gland the most.

If remission is not induced in the first dose, the second dose is given according to the same criteria, but generally not before 6 months after the first dose.

A bigger dose is administered depending upon the gland size and degree of hyperthyroidism.

c) Multiple small doses method:
The desired total quantity of I 131 can be given in 500 uCi doses instead of single large dose. Six or more doses are administered at weekly intervals. The method, introduced to avoid hypothyroidism ,induced the highest incidence of late hypothyroidism at mean 10 yrs.

d) Radiation dose method:
3500 to 4000 rads are provided to the gland. A major source of error is in the appraisal of the gland size by palpation and another source of error is in the difficulty of determining the effective half life of the isotope.

Readministration of I-131 is just as practical, safe and convenient as initial treatment. It is common to administer second dose (20%) or even third and fourth dose (5%), but not retreated earlier than 6 months unless the patient is overtly clinically and biochemically thyrotoxic.(3,9)

Toxic multinodular goiter should be treated with higher dose, as the tissue is relatively radioresistant due to inhomogeneity; RAI turnover is higher with lower retained dose.(8,10,11)

Hypothyroidism is definite complication after destructive therapy hence life long L-T4 supplementation and follow up is required.(3,8,12)

Methods and Materials:
127 patients were selected who had regular follow up till one year. The patients were referred to our department from Dept of Endocrinology and Department of Internal Medicine. This was a retrospective study, the patients treated with I-131 for hyperthyroidism were included. The diagnosis of hyperthyroidism was made clinically by history and physical examination, and confirmed by laboratory study (T4 or Free T4 and TSH). Tc 99n Tco4 scanning was done to see avidity of TcO4 uptake.

The dose given to the patients was determined by the size of goiter, clinical problems, avidity of TcO4 on uptake scan and history of any prior antithyroid medication.

At our center patients were divided into three groups.

Group I:
patients with grade I goiter and mild clinical symptoms patients who received pretreatment with antithyroid drugs and with controlled status of hyperthyroidism. They were treated with < 3 or 3 mCi of I131.

Group II:
Included patients with first time clinical presentation, patients with Grave's disease with Grade II or grade III goiter along with high uptake of Tc99m pertechnetate. This group was treated with 5 mCi of I131.

Group III:
Included patients with long standing goiter, multinodular goiter and autonomous thyroid nodule. This group was treated with >5 mCi of I131.

All the patients were followed up at 6 weeks (clinically), 3 months (clinically and biochemically) and then 6 monthly (clinically and biochemically).

Clinical parameters like weight gain, reduction in goiter size, symptomatic improvement and biochemical normalization of thyroid hormone levels were evaluated in the followup.

Total 127 patients' records were analyzed, which included 32 males and 95 females. Successful therapy was defined as euthyroidism or permanent hypothyroidism based on T4 and TSH measurements obtained. Period of occurrence of hypothyroidism following radioiodine therapy was assessed during follow up period of one year. Patients with hypothyroidism were classified on the basis of occurrence of hypothyroidism within 6 months and after 6 months of treatment of I131. Number of patients requiring second dose of I131 treatment were also analyzed. Statistical analysis was done with fisher's test.

Results:

Table No1.

Age groups	Males	Females
<20	1	4
21-30	7	29
31-40	11	36
41-50	6	19
51-60	6	5
>60	1	2
Total	32	95

The ratio of female to male patients was 3:1. The average age of patients was 36.34. Number of patients treated in Group I was20 group II was 87 and group III was 20.

Volume : 4 | Issue : 3 | Mar 2014 | ISSN - 2249-555X

Table no .2

Parameter	Statistics	≤ 3 (n=20) Group I	>3 and ≤ 5 (n=87) Group II	>5 (n=20) Group III
Gender (M/F)	n (%) / n (%)	3(15) / 17(85)	22(25.3) / 65(74.7)	7(35) / 13(65)
Age (yrs)	n	20 (100)	87 (100)	20 (100)
	Mean± SD	35± 11.3	35.8± 10.7	43.9± 10
	Median	35	35	45
	95% CI for Mean	(29.7, 40.2)	(33.5, 38.1)	(39.2, 48.6)
	Range (min, max)	(17, 54)	(12, 65)	(25, 60)

Requirement of second dose of I 131

Treatment group	Number of patients in Treatment group	Number of patients requiring second dose
Group I	20	14 (70%)
Group II	87	20(22%)
Group III	20	6 (30%)

The requirement of second dose therapy was 70% patients from Group I, 22% patients from group II and 30% patients from group III.

Relative risk of patients of group I for requiring second dose was 3 and 2.73 as compared to group II and group III respectively which was statistically significant.

There was no e/o of prolonging occurrence of hypothyroidism in group I. No e/o any significantly increased relative risk of hypothyroidism noted in any of the treatment group.

1. Statistical analysis of different therapy groups requiring second dose Test applied - non parametric Fisher's exact test

Group	Second dose required (%)	Second dose not required (%)	Total (%)
I	14 (13)	6(6)	20 (19)
II	20 (19)	67 (63)	87 (81)
Total	34 (32)	73 (68)	107 (100)

P value= 0.0001
Relative risk – 3

b. Comparison between Group I and Group III

b. Comparison between Group I and Group III

Group	Second dose required (%)	Second dose not required (%)	Total (%)
I	14 (35)	6(15)	20 (50)
III	6 (15)	14 (35)	20 (50)
Total	20 (50)	20 (50)	40 (100)

P value= 0.02 Relative risk – 2.73

C) Comparison between Group II and Group III

Group	Second dose required (%)	No Second dose required (%)	Total (%)
II	20 (19)	67(63)	87 (81)
III	6 (6)	14 (13)	20 (19)
Total	26 (50)	81 (76)	107 (100)

P value= 0.57 Relative risk – 0.76

The relative risk of requirement of second dose was statistically significant in group I when compared with group II and group III.

Discussion:

The most common cause of thyrotoxicosis is Graves' disease (50-60%). Toxic multinodular goiter (Plummer's disease) occurs in 15-20% of patients with hyperthyroidism. It occurs most commonly in elderly individuals, especially in patients with a long-standing goiter. Toxic thyroid adenomas comprise approximately 3-5% of patients who are hyperthyroid. 15- 20% of the thyrotoxic cases are contributed by thyroiditis.

Selection of dose: 5 approaches have been employed (7)

1. Small doses repeated as necessary. (Empirical)
2. A large ablative dose.
3. A sliding scale based on thyroid size.
4. A standard formula based on estimated thyroid size: (7,8)

Required dose in mCi = gland weight in gm x uCi desired/gm

% Uptake at 24 hours

5. Precise dosimetry for the administered dose.

Empirical dosimetry i.e. 5-10 mCi, 90-95 % cure rate has been seen with single dose .(8,9) In our study we divided patients in three treatment groups and patients were treated with variable doses.

The purpose of our study was to determine the relationship between the cure of hyperthyroidism and the amount of I131 administered. Clarifying this relationship makes it easier to choose a dose appropriate for the needs of individual patient when permanent cure of hyperthyroidism is the desired outcome.

It has been shown that hypothyroidism follows sooner or later in nearly all patients. Its occurrence within one or two years after treatment is related to dose, but delayed hypothyroidism develops at about the same rate regardless of the amount of I131given.(B) Elimination of hyperthyroidism then becomes the central issue, and the pendulum swings towards larger doses, although most thyroidologists still support treatment to achieve the euthyroid state. In our study, thyroiditis cases were not included as there is no indication for radioiodine in the treatment of thyroiditis. Total 127 patients were divided in three treatment groups based upon the clinical presentation and therapeutic option. In our study, 31.5% cases required a second dose and 1.67% cases required more than two therapies. It is common to administer second dose of radioiodine (20%) or even third or forth dose (5%) to achieve euthyroidism or hypothyroidism (3).

Our study showed that required therapeutic response with a single dose is achieved in 77% of the patients in group II (>3 mci upto 5mci) . Most of the cases which constituted the multiple doses in this group were females with MNG and were given ~5 mCi of I-131 in the first therapy, which would have been inadequate to deliver desired dose to the gland. 70% of the patients who were treated with group I regimen (<3 mCi – 3 mCi) required second dose which clearly showed inadequate dose delivery to eliminate hyperthyroid state. The study done by Smith et al (A) also showed that by reducing the dose to half of the conventional dose, multiple doses were mandated .

Hypothyroidism is considered by some experts to be the expected goal of radioactive iodine therapy Higher doses of I-131 sometimes are used to intentionally induce hypothyroidism, allowing the patient to be managed for hypothyroidism alone.(5,6)

In our study there was no significant difference in the time of occurrence of hypothyroidism in different treatment groups because the dose range was only 3 to 7 mCi as against >10 mCi which would result in significant increase in occurrence of hypothyroidism.

There was no e/o prolonging occurrence of hypothyroidism

Volume : 4 | Issue : 3 | Mar 2014 | ISSN - 2249-555X

by treating patients with lower dose of I131 i.e. group I , on contrary the requirement of second treatment was increased in this group..

Our study showed that If physician treats patients with lesser doses because of concern about increased likelihood of hypothyroidism from the initial dose, it means accepting a 70% likelihood of additional treatment requirement as compared to 22% likelihood if higher dose is selected. The study by Robert Et al (B**) also** shows that accepting a 30% likelihood of additional treatment compared to 13% likelihood if higher dose is selected.

The patient's direct cost, time from work, and morbidity increase markedly if the initial dose fails to cure.

Conclusion:

In this study the male to female ratio for hyperthyroidism was found to be 3:1. The most common type of hyperthyroidism was found to be diffuse toxic goiter. Complete cure was established in most of the patients in grup 2 ie 5 mci dose with a single dose .However, for patients with toxic multinodular and large goiters needed second dose.

Patients treated with group I treatment regimen, i.e. small dose 3 mCi or <3mCi required multiple doses suggesting ineffective radiation dose delivered to hyperfunctioning gland to suppress its function.

As expected , because of the high dose given (7mCi) in gr III patients, requirement of second dose was less in comparison with group I.

This study shows that there is no definitive evidence of prolonging hypothyroidism in Group I patients as compared to other two groups.

Our study indicates that the optimal dose of >5mCi of radioiodine should be given for the complete cure of hyperthyroidism to avoid the necessity of multiple doses.

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