

Analysis of Lag Behind Thyrotropin State After Radioiodine Therapy in Hyperthyroid Patients

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ABSTRACT

Introduction: A good number of hyperthyroid patients may show delayed recovery of Thyroid Stimulating Hormone (TSH) level in clinically evident euthyroid condition after radioiodine therapy. This group of patients need to be addressed in therapeutic decision making. The purpose of the study was to evaluate the duration and pattern of lag in TSH recovery after I - 131 therapy and the relationship between clinical parameters with stable thyroid function status.

Materials and Methods: Total 192 hyperthyroid patients treated with I-131 were included in this study. These patients were followed up clinically and biochemically at three month, six month and one year after radioiodine therapy. Patients having suppressed TSH with normal Free Triiodothyronine (FT3) / Free Thyroxin (FT4) level and clinically euthyroid condition were followed-up for one year without giving antithyroid drug.

Results: At three months follow-up 42/192 (22%) had suppressed TSH with normal FT3/FT4 level. Duration of lagging behind state of TSH was three months for 42 patients (22 %), six months for 13 patients (7%) and One year in three patients (2 %). Twelve patients were lost from follow-up. Among 30 patients with lag behind TSH level, 16 (53%) became hypothyroid, 8 (27%) became euthyroid and 6 (20%) became hyperthyroid at one year follow-up. Lagging behind patient with high serum FT4 level at diagnosis and high Radio Active Iodine Uptake (RAIU) showed increased rate of relapse of hyperthyroidism.

Conclusion: Lagging state of TSH may be unexpectedly prolonged in some hyperthyroid patients treated with I-131. These patients should be followed up with both TSH and thyroid hormone levels. Most of them do not require further therapy with short period of time.

INTRODUCTION

Radioactive iodine (I-131) is currently the treatment of choice for Graves's disease (1). Radioiodine treatment is suggested as a safe, simple and cost effective method in benign thyroid diseases.

The aim of the therapy is to decrease the function and/or the volume of thyroid gland (2). After radioiodine therapy for hyperthyroidism, some patients may become hypothyroid or euthyroid which are considered as successful outcome of therapy, some remain hyperthyroid indicating treatment failure and need further radioiodine therapy or antithyroid drug. A group may also show suppressed Thyrotropin (TSH) level with normal or low FT3 and FT4 level. This group of patients is of great importance because most of them do not need further radioiodine therapy or antithyroid drug. This lag in the responsiveness of thyrotropin found after I-131 therapy was 60-90 days in some studies (3,4). In practice, some patients were found to have more prolonged period of delay in recovery of TSH. The purpose of the study was to evaluate the duration and pattern of lag in TSH in hyperthyroid patients following I-131 therapy and to help in proper management of such patients.

MATERIALS AND METHODS

This prospective observational study was carried out at National Institute of Nuclear Medicine and Allied Sciences (NINMAS) from January 2013 to December 2014. In this study, hyperthyroid patients referred to NINMAS (from January 2013 to December 2013) for radioiodine therapy were included. Hyperthyroid patients in conjunction with serious non-thyroidal illness, pregnancy, lactation and taking corticosteroids that influence pituitary-thyroid axis and patients with known pituitary dysfunction were excluded from the study.

Before giving radioiodine therapy, patients were evaluated by clinical history, physical examination, estimation of serum FT3, FT4 (measured by Radio immuno assay-RIA kit prepared by Institute of Atomic Energy (CIAE, Beijing), TSH (measured using a commercialized immuno radiometric assay kit prepared by CIAE, Beijing), anti Thyroglobulin antibody and anti peroxidase antibody (measured using RIA kits prepared by CIAE, Beijing), complete blood count, Ultrasonography of neck (using Siemens Acuson Antares with 5-10 MHZ transducer), radioiodine uptake (RAIU) at two hours and 24 hours (using a scintillation counter) and Technetium 99m (Tc-99m) scan. Informed consent was obtained from all patients prior to the administration I-131 and they have consented to participate in this study.

I-131 was administered with proper instruction to minimize radiation hazards. Activity of I-131 was given as moderately fixed dose. Later on some patients were lost from follow-up after receiving I-131 therapy. Finally, one hundred and ninety two patients were included in the study. These patients were followed-up clinically and with FT3 or FT4 and TSH level at three months, six months and one year following radioiodine therapy (1,5,6). Patients having suppressed TSH with normal or low FT3/FT4 level were followed up without adding any thyroid related drug. Their stable thyroid hormonal status were observed and treated accordingly.

The values were expressed as mean \pm SD. Statistical analysis were done using t test and χ^2 test for quantitative and qualitative variables respectively. P value <0.05 was considered significant. SPSS (version 22) was used for statistical analysis.

RESULTS

Total 192 hyperthyroid patients treated with radioiodine therapy were included in the study. Among them 58 were male and 134 were female (male: female; 1:2.3). Among them, 160 (83%) were Diffuse Toxic Goiter (TG), 25 (13%) were Toxic Toxic Multi Nodular Goiter (TMNG) and seven (4%) were Solitary Toxic Nodular Goiter (STNG). Biochemical status of these patients at three months, six months and one year follow-up after I-131 therapy are shown in Table-1.

Table1: Biochemical status of I-131 treated hyperthyroid patients at 3 months, 6 months and 1 year follow-up

Biochemical Status	At 3 month F/U	At 6 month F/U	At 1 year F/U
Hypothyroid state	75 (39%)	99 (51%)	106 (55%)
Euthyroid state	49 (26%)	34 (18%)	21 (11%)
Hyperthyroid state	26 (13%)	28 (15%)	32 (17%)
Lagging behind TSH	42 (22%)	13 (7%)	3 (2%)
Lost	0	18 (9%)	30 (15%)
Total	192 (100%)	192 (100%)	192 (100%)

Lagging behind TSH that is suppressed TSH below 0.3mIU/L (normal range-0.3-5 mIU/L) with normal FT3 (2.8 to 9.5 pmol/L) or FT4 (9.5 to 25.5 pmol/L) level were found in 22%, 7% and 2% at three months, six months and one year respectively after radioiodine therapy. These patients were the focus of interest.

Patients showing lag behind TSH at first follow-up (three months after I-131 therapy) were 42 in number. These patients were followed up for minimum one year without adding any anti thyroid drug. During subsequent follow-up 12 patients were lost from follow-up. At last, total 30 patients of lagging behind TSH group were followed-up for minimum one year. Stable thyroid function status one year after I-131 therapy of patients with lag behind TSH are given in Table 2.

Table - 2: Stable Thyroid function status one year after 1st I-131 therapy in patients with suppressed TSH found at 3 months (n=30).

Group	Frequency (N)	Percentage
Hypothyroid state	16	(53%)
Euthyroid state	8	(27%)
Hyperthyroid state	6	(20%)
Total	30	(100%)

One year after radioiodine therapy, 16 patients became hypothyroid and eight patients became euthyroid. These 24 patients (80%) did not need any antithyroid drug or further radioiodine therapy. These 24 patients with remission of hyperthyroidism were grouped as Group-A. Rest six patients (20%) with recurrence of hyperthyroidism needed further radioiodine therapy and were grouped as Group-B (shown in Table-3).

Table - 3: Requirement of further I-131 therapy one year after 1st I-131 therapy in patients with suppressed TSH found at three months (n=30).

Group	Frequency (N)	Percentage
Group-A (further treatment not required)	24	(80%)
Group-B (further treatment required)	6	(20%)
Total	30	(100%)

Group-wise (Group A & B) characteristics at diagnosis and initial I-131 doses of patients with lag behind TSH found at first follow-up with their statistical p values are shown in Table-4.

Table-4: Group-wise comparison of characteristics at diagnosis and initial I-131 dose of patients with lagging TSH found at 1st follow-up.

	Total patient (n=30)	Group-A (n=24)	Group-B (n=6)	P value
Age (years)	42.7±13.2	41.87±12.45	46.0±16.96	0.51 •
Sex (Female: Male)	2.7:1	1:1	3.8:1	0.15 •
Cause				
Toxic Goiter	25(83.3%)	20 (83.3%)	5(83.3%)	0.39 •
Toxic Solitary Nodular Goiter	2(6.7%)	1(4.2%)	1(16.7%)	
Toxic Multi Nodular Goiter	3(10.0%)	3(12.5%)	0(0%)	
RAIU (%)				
2 hrs	21.0±10.1	29.0±10.75	19.00±9.09	0.02 •
24 hrs	31.2±14.9	44.17±7.83	27.92±14.53	0.01 •
FT4 at Diagnosis (Pmol/L)	43.7±16.2	40.77±14.29	55.30±19.37	0.04 •
TSH at Diagnosis (mIU/L)	0.20±0.24	0.20±0.26	0.19±0.21	0.96 •
I 131 dose (mCi)	11.9±1.5	11.88±1.48	11.83±1.83	0.96 •

P value <0.05 was considered significant.

- Unpaired Student's t test was done to see level of significance
- χ^2 test was done to see level of significance.

Age, RAIU, FT4 level, TSH level and I-131 dose are given as mean ± SD. Other parameters are given as number and percentage of patients.

There were no statistically significant differences between two groups regarding age, sex, causes, and serum TSH level at diagnosis and Initial I-131 doses. Significant difference between two groups were noted in serum FT4 level at diagnosis and two hours and 24 hours radioiodine uptake indicating that hyperthyroid relapsed cases were highly toxic at diagnosis.

DISCUSSION

Radioiodine therapy is the treatment of choice for hyperthyroidism. In USA 70-90% of Grave's hyperthyroidism is treated with radioiodine as first line therapy, whereas in Germany the conservative antithyroid drug therapy for 1-1.5 years is recommended for 90% (7). After radioiodine therapy for hyperthyroidism, a group of patients show suppressed TSH with normal or low FT3 and/or FT4 level. This period of lag in TSH is not predictive of eventual treatment outcome. Moreover, decision upon further therapy depends on clinical status and serum levels of TSH and thyroid hormones. So evaluation of the duration of this lag behind state is important. Only few studies with small sample size regarding suppressed TSH level after radioiodine therapy were found. The present study was done prospectively with comparatively large number of hyperthyroid patients (192) followed-up for minimum 12 months.

Albert et al (2000) studied retrospectively 49 hyperthyroid patients treated with radioactive iodine and found nine patients (16%) lag in their TSH responsiveness. Among them, TSH remains low in five (55%) for three months, three (33%) for nine months and one (11%) for 12 months (3). Similar to earlier study, the present study also showed delayed recovery period of thyrotropin than expected duration of 60 to 90 days and the number of patients of lag behind TSH group decreased in subsequent follow-up. Whereas, another study showed 90% patients with Grave's hyperthyroidism had suppressed TSH despite a low or normal FT3 or FT4 level following radioiodine therapy (4). This dissimilarity may be due to inclusion of all kinds of hyperthyroid patients in current study instead of only Grave's disease.

The exact cause of continued suppression of serum TSH level is not clear. This may be due to blunted TSH response to thyroid releasing hormone (TRH) during this period and suppression occurs primarily at the level of the pituitary thyrotrophs (4). A number of studies proposed different causes of transient suppressed serum TSH level during antithyroid drug therapy. Prummel et al (2000) reported that TSH receptor was expressed in the folliculo-stellate (FS) cells of the human anterior pituitary gland, and TSH secretion might be down regulated through TSH receptor via a paracrine feedback loop (8). Delayed recovery of pituitary-thyroid axis may be also from long standing thyroid hormone excess (9).

Present study showed that after one year of I-131 therapy majority (80%) of patients with suppressed TSH had remission from hyperthyroidism and did not need further antithyroid drug or radioiodine therapy. On the contrary, only 20% patient had recurrence of hyperthyroidism after one year of radioiodine therapy and needed further I-131 therapy. Hyperthyroid recurrence (Group-B) had high FT4 value at diagnosis and high RAIU at two hours and 24 hours than remission group A (p values are 0.04, 0.02 and 0.01 respectively.). These findings are supported by Chung et al. (2006). According to them, continued suppression of serum TSH level may be attributed to TSH receptor antibody (TRAb) activity as well as pretreatment severity of thyrotoxicosis and the time to recovery of thyroid hormone with Grave's disease during antithyroid drug therapy (10). In contrast, Brokken et al. reported that TRAb suppressed serum TSH levels independently of circulating thyroid hormone levels in a rat model, suggesting a functioning pituitary TSH receptor most likely by binding to the pituitary TSH receptor (11,12). However, patient's age, sex, type of hyperthyroidism, serum TSH level at diagnosis and 1st dose of I-131 didn't seem to be a factor for recurrence of hyperthyroidism in TSH lagging behind patients in the current study.

Different authors found prolonged period of delay in recovery of TSH after radioiodine therapy in hyperthyroid patients though the expected duration is 60 to 90 days. They recommend to follow-up these

patients with both serum thyroid hormone and TSH level. According to American Association of Clinical Endocrinologists (AACE) thyroid guidelines, patients with unstable thyroid states such as those recently treated for hyperthyroidism, measurement of serum T4 level more accurately indicates thyroid status than dose serum TSH (1).

Drop out of patients during follow-up period, was a factor for smaller sample size of this study. Further similar type of study with bigger sample size is recommended.

CONCLUSION

Lagging behind state of TSH despite normal thyroid hormone level may be unexpectedly prolonged in some hyperthyroid patients treated with radioactive iodine. Prolonged suppression of serum TSH levels are found to be related to the pretreatment severity of thyrotoxicosis. These patients should be followed up with both Serum TSH and thyroid hormone levels. Most of them do not require further therapy within observed period of time.

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