Effect of Single Dose of Radioiodine Therapy on Volume Reduction of Thyroid Gland in Hyperthyroidism

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ABSTRACT

Introduction: **Radioactive iodine therapy (RAIT) in patients with hyperthyroidism (HT) causes apoptosis of thyrocytes to bring about restoration of thyroid function. The aim of the study was to find the short term extent of reduction of thyroid gland volume (TGV) by non-invasive quantitative assessment using ultrasound imaging (USG).**

Patients and Methods: **This prospective study was conducted on a group of patients who had received RAIT due to primary hyperthyroidism at National Institute of Nuclear Medicine & Allied Sciences (NINMAS). Pre-therapy work up included hormone assay and baseline measurement of TGV by US before administration of appropriate fixed dose RAIT. Short term follow-up with hormone assay and serial measurements of TGV on two occasions were done at three and six months following the RAIT. Observed temporal changes of parameters were analyzed using appropriate statistics.**

Results: **Total 117 patients with primary hyperthyroidism had received RAIT with diagnosis of diffuse toxic goiter in 86 patients, toxic multinodular goiter in 21 cases and single toxic nodular goiter in 10 cases. There was a decline of mean TGV from the baseline level of 24 ml to 14 ml at three months followed by a further decline to 9.1 ml at six months. Thus the volume reduction of thyroid gland was calculated to be 42% at three months and 62% at six months. The volume reduction was observed to be in a correlative trend with the normalization of hormone levels. The proportion of patients who showed persistent hyperthyroidism till the study end point was 23%.**

Conclusion: **Single dose of radioactive iodine therapy resulted in reduction of TGV up to 62% till six months after RAIT while 23% patients showed persistent hyperthyroidism. The correlative trend of volume reduction with normalization of hormone levels indicates potentiality of TGV to emerge as an adjunct to conventional assessment of treatment efficacy following RAIT.**

Key words: **Radioiodine therapy, Thyroid gland volume, Hyperthyroidism, High resolution ultrasound.**

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INTRODUCTION

Radioactive iodine therapy (RAIT) for management of hyperthyroidism (HT) has been practiced in Bangladesh for four decades (1) with reports of satisfactory short-term outcome (2, 3). Incidence of HT was found to be 0.86% in a community based cross sectional study on 925 individuals (4). The common clinical manifestations include diffuse toxic goiter or Graves' disease (GD), single toxic nodular goiter (STG) and toxic multinodular goiter (TMNG) (5). Management with RAIT in all cases of HT is feasible irrespective of age including the pre-pubertal (6) and is considered safe since studies on large number of patients administered with RAIT, followed up for considerably long durations have never demonstrated increased risk of mutagenesis or carcinoma (7, 8). RAIT has long been a recommended management strategy for HT with a higher preference over anti-thyroid drug (ATD) and surgery (9). RAIT lacks recurrence as in case with ATD (10) as well as it lacks morbidities and poor cosmetic outcome unlike surgical intervention (11).

RAIT is selectively taken by sodium iodine symporter of thyroid epithelial cell and causes cell death by beta emission that ensue reduction in size of thyroid gland (12, 13). Nygaard et al. observed a decrease of thyroid gland size after RAIT in both toxic and nontoxic goiters (14). Assessment of change of thyroid gland size by non-invasive measurement of thyroid gland volume (TGV) is thus believed to be an important

adjunct to clinical assessment of efficacy after treatment with RAIT.

HRUS is validated as gold standard for assessment of TGV (15, 16) and a recommended diagnostic method for assessment of goiter by World Health Organization (WHO) and International Council for the Control of Iodine Deficiency Disorders (ICCIDD) because high resolution ultrasound (HRUS) facilitates precise delineation of gland with adequate characterization of glandular parenchyma (17).

Thus, this study aimed to observe volume change of thyroid gland after radioiodine therapy by HRUS as an advantageous non-invasive modality.

PATIENTS AND METHODS

This prospective study was conducted on a group of patients that included all primary hyperthyroid patients who had undergone RAIT after being referred to thyroid division of National Institute of Nuclear Medicine & Allied Sciences (NINMAS), BAEC. Measurement of TGV with high resolution of ultrasound imaging (HRUS) was done in each patient on three occasions. The baseline measurements were taken before administering RAIT when each patient also had to undergo a pre-defined structured clinical assessment that including symptoms, physical examination and recording of vital signs, assessment of blood levels of free thyroxine (FT4), thyrotrophine (TSH), planar thyroid scan with 99mTc pertechnetate and radioactive iodine uptake (RAIU). All patients then underwent RAIT with modified fixed dose protocol according to institutional standard of practice. Post RAIT assessment of TGV by HRUS then done on two occasions while all the patients were undergoing a routine protocol-wise three monthly follow up till six months after RAIT. Assay for FT4, TSH were done during each follow-up. Reduction of TGV was calculated by subtracting the post RAIT measurement from that of the pre RAIT measurement in each patient. HRUS of neck with a 7.5 MHz linear transducer with appropriate gain setting was used in real time equipment (Toshiba Core Vision Pro, Tokyo, Japan). During imaging patient was positioned supine with hyper-extended neck by a pillow under the shoulders. The thyroid gland was identified and visual assessment was done for outline delineation and parenchymal echo-characterization. Each lobe was scanned in both transverse and longitudinal plane in order to estimate its length, width and thickness. Volume of each lobe was calculated done by ellipsoid method using appropriate formula. The volumes of both lobes were then added to calculate the total TGV. Isthmus and pyramidal lobe (if present) were ignored.

Continuous data was expressed as mean and standard deviation (SD), median and value ranges. Categorical data was presented as frequency and percentage. Analysis of variance (ANOVA) of with post-hoq comparison through Hochberg test was done for comparison of TGV reduction among various clinical groups of hyperthyroidism. Two-sided p value <0.05 was considered as statistically significant.

RESULTS

Total 117 patients with mean age of 42.7 ± 12.6 years (median 42 years and range 15 – 77 years) had undergone RAIT. Among them 42 were male and 75 were female. Table 1 shows distribution of age and sex among the study population. The clinical diagnoses among patients undergoing RAIT were diffuse toxic goiter (GD) in 86(73.5%), single toxic nodular goiter (STG) 10 (8.5%) and toxic multiple nodular goiter (MNG) in 21(17.9%).

Table 1: Distribution of age and sex of the study population (n=117)

Age	Frequency	Percent
Below 30 years	22	18.8
30 – 39 years	21	17.9
40 – 49 years	37	31.7
50 – 59 years	22	18.8
60 years or above	15	12.8
Total	117	100
Sex		
Male	42	35.9
Female	75	64.1
Total	117	100

All patients after receiving RAIT in standard dose were under regular institutional protocol of follow up with serial hormone assay after three and six months. At first follow-up 41% (48) were euthyroid, 28.2% (33) were hypothyroid and 30.8% (36) were found hyperthyroid. At 2nd follow-up 53.8% (63) were found euthyroid, 23.1% (27) were hypothyroid and another 23.1% (27) were found hyperthyroid. RAIT response among three categories of hyperthyroidism is provided in Table 2.

Table 2: Comparison of thyroid status in three types of hyperthyroidism.

	At 3 months		At 6 months	
	Frequency	Percent	Frequency	Percent
Diffuse Toxic Goiter				
Euthyroid	38	44.2	45	52.3
Hypothyroid	28	32.6	17	19.8
Hyperthyroid	20	23.3	24	27.9
Total	86	100.0	86	100.0
Toxic Multinodular goiter				
Euthyroid	8	38.1	12	57.1
Hypothyroid	4	19.0	7	33.3
Hyperthyroid	9	42.9	2	9.5
Total	21	100.0	21	100.0
Single Toxic Nodular Goiter				
Euthyroid	2	20.0	6	60.0
Hypothyroid	1	10.0	3	30.0
Hyperthyroid	7	70.0	1	10.0
Total	10	100.0	10	100.0

The cumulative data revealed that, during the 1st follow up there was an increase of mean TSH level with a concomitant reduction of mean TGV in comparison to the baseline. During the 2nd follow up there was however a decrease of mean TSH level with a further concomitant reduction of TGV in comparison to the 1st follow up. For the entire group of study patients the mean TSH at baseline was 0.2 ± 0.34 m IU/L, increasing to mean of 13.6 ± 0.26 m IU/Lat 1st follow-up and then a decline to 7.1± 1.7 m IU/L at 2nd follow-up. The laboratory normal range for TSH assay was 0.3 to 5 m IU/L. For the entire group of study patients the mean TGV at baseline was 24.0 ±22.9 ml, reduced to 14.0 ± 12.5 ml at 1st follow up and then further reduced to 9.1 ± 10.0 ml at second follow up. Thus volume reduction of thyroid gland was 42% at three months and 63% at six months.

Table 3: Comparison of thyroid volume in three types of Thyrotoxicosis

Thyroid disease	Thyroid gland volume in ml		
	Base line	1st follow-up	2nd follow-up
GD (n=86)	18.6 ± 10.6	10.3 ± 6.5	5.9 = 4.1
Toxic MNG (n=21)	41.5 ± 41.3	24.2 ± 16.0	17.7 ± 14.4
STG (n=10)	25.0 ± 18.0	19.6 ± 21.8	13.5 ± 16.6

GD-Diffuse Toxic Goiter or Grave's disease, TMNG- Toxic multiple nodular goiter, STG Single Toxic Nodular goiter

Table 4: Multiple Comparisons following ANOVA showing TGV reduction.

	1st follow up				2nd follow up			
Comparison	Mean Difference	Std. Error	95% CI	p value	Mean Difference	Std. Error	95% CI	p-value
GD vs. Toxic MNG	8.8	3.4	5.0-17.2	0.034*	14.8	3.8	5.3, 24.3	.002*
GD vs. STG	1.6	4.8	-9.7-13.0	0.983	7.1	4.0	-3.7, 17.7	.227
Toxic MNG vs. STG	-7.3	5.4	-20.3-5.8	0.446	-7.8	5.3	-20.8, 5.3	.321

GD Diffuse Toxic Goiter or Grave's disease, MNG Multiple nodular goiter. STG Single Toxic Nodular goiter
The mean difference is significant at the 0.05 level.ANOVA: F = 3.3 P = .040

While the mean TGV was found to decrease continually in each follow up in comparison to baseline, the mean FT4, though had an initial decline in 1st follow up , was seen to remain nearly unchanged during 2nd follow up, remaining in plateau. For the entire group of study patients the mean FT4 levels during baseline, 1st follow up and 2nd follow up were 35.3 ± 16.6 pmol/L, 19.3 ± 11.5 p mol/L and to 20.3 ± 8.1pmol/L. The laboratory normal range for FT4 assay was 9.5 to 25.5 p mol/L.

Since study patients were from three common clinical entities, GD, STG and toxic MNG, the comparison of TGV change among these three groups of patients were advantageously done. Table 3 shows the mean TGV among these three groups in each of three time points of TGV assessment by HRUS. Alike the cumulative trend the mean TGV was found to decrease continually in each follow up in comparison to baseline in each group of patients.

ANOVA of volume reduction with post-hoq comparison through Hochberg test revealed statistically significant difference in thyroid volume reduction during 1st and 2nd follow-up between GD and toxic MNG while no statistically significant difference was observed among other pairs (Table 4).

DISCUSSION

The current study used an ellipsoid method for assessment of TGV using HRUS. This ellipsoid algorithm reported with the use of two orthogonal images, longitudinal and transverse scans, of each lobe (18, 19). The maximal length of a lobe in its three dimensions, namely cranio-caudal (c c), latero-medial (LM) and antero-posterior (AP) are measured followed by estimation of volume of that lobe using a cubic formula where: volume of lobe V = c x C C x LM x AP was described (18). The constant 'c' in formula have reported values of 0.479 and 0.523 (or $\pi/6$) (20, 21) with reports of higher accuracy using a value of 0.52 (22). Isthmus and pyramidal lobe (if present) were ignored in the current study following a report from Kuwait (23).

The current study restates the already proven role of RAIT to bring about a restoration of blood levels of FT4 and TSH hormones towards euthyroid picture with a concomitant alleviation of clinical manifestations of hyperthyroidism. The mean level of TSH was markedly increased during first follow-up and returned to near normal value during second follow-up due to replacement levothyroxine therapy. This was reflected by rise of baseline level of mean FT4 during 1st follow-up and then staying in a plateau during 2nd follow-up.

The current study has found a decrement of TGV while performing serial measurements of TGV before RAIT followed by three and six months after RAIT in patients with hyperthyroidism. This finding is consistent with a previous report showing reduction of TGV up to 72% of initial volume within the first three months in 64 patients followed by continual size reduction till two years after RAIT (24). The objective and quantitative assessment of TGV by HRUS has gained acceptance as a standard routine procedure rather than assessment of thyroid enlargement by palpation during clinical visit (25). The current study attempted to explore further role of HRUS to determine reduction of TGV through serial measurement and comparison. Results of the current study indicate a correlative trend of TGV regression with normalization of FT4 and TSH blood levels. However, within the duration of study 23% patients retained hyperthyroid state and were scheduled for further RAIT. This indicates a need of further investigations to determine a cut-off value of TGV for response assessment with a potential implication in selection of patients for further RAIT. Thus, practice of HRUS measurement of TGV following RAIT is considered to have potential to be accepted as an adjunct to hormone assay for assessment of therapy response.

The current study comprised patients having GD, STG and toxic MNG with observation of regressive decrement of TGV in each sub-groups; being more decrement in GD than the other two entities. This finding is consistent with a report of pronounced TGV reduction in diffuse toxic goiter or GD patients by a mean of 76% after three years of treatment (26).

This phenomenon has been explained with the hypothesis that RAIT impart high dose of radiation to all thyroid cells in case of GD. In contrast toxic nodule of nodular goiter takes up most of the radio-active iodine causing its self destruction and concomitant protection of para-nodular normal tissue that receives small doses of radiation (27).

However, for selection of the small proportion of patient who shall remain unresponsive to single dose of RAIT and shall require further dose, determination of a cut off for TGV through further research, will be to be useful.

CONCLUSION

Single dose of RAIT was found to cause reduction of TGV in a larger proportion of patients. This re-discovers the capability of RAIT for non-invasive alleviation of clinical manifestations of hyperthyroidism avoiding the morbidity and poor cosmetic outcome of surgery as well as avoiding the risk of recurrence associated with ATD. In addition, the apparent correlative trend of TGV reduction with normalization of hormone levels indicates potentiality

of HRUS to appear in an extended role of assessment of therapy response following RAIT beyond its conventional role in pre-therapy work-up.

DISCLOSURE

No competing financial interests exist

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