Successful Reduction in Thyroid and Nodule Volumes in Large Solitary and Multinodular Goiters with Serial ^{131}Iodine Therapy

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Abstract

Introduction: ^{131}Iodine therapy is effective in nodular non-toxic goiter with enhanced effects using recombinant thyroid stimulating hormone (rTSH). The eventual fibrosis of the thyroid tissue and blood vessels ligates the vascular supply of the nodule. The study aims to show the successful reduction of thyroid and nodule volumes in large solitary and multinodular goiters using serial low dose ^{131}iodine therapy (10mCi) at three to six months interval.

Methods: A retrospective analytical study was done from January 2010 to December 2012 and included twenty three patients with enlarged solitary and multinodular (nodule/s ≥2cm) non-toxic goiter (females: age range 35-65yrs) given serial ^{131}iodine therapy (eight to10mCi) at three to six-month interval. Before each course, serum thyroid stimulating hormone (TSH) was done to document hypothyroidism while thyroid gland and nodule sizes were monitored by ultrasonographic measurements serially with each ^{131}iodine therapy. Relief of compressive symptoms was monitored on follow-up at clinic.

Results: Thyroid size reduced by 38-40% from baseline after first radioactive iodine (RAI) and by 33-39% after the second RAI. Thyroid nodules reduced by 63-69% and 11-25% serially. Significant reduction was noted after the first RAI. One subject underwent third RAI with 80-85% overall reduction in nodule size. All patients developed post-RAI hypothyroidism and overall had greater than 50% increase in levothyroxine replacement dose after the last RAI. Significant relief of compressive symptoms was noted by 91% post-therapy. Four thyroid nodules disappeared which resulted in reduced total number of thyroid nodules from 29 to 25 nodules post serial RAI.

Conclusion: Serial ^{131}iodine therapy proved to have thyroid and nodule size reduction by more than 70% in this study. Among patients who do not consent or have contraindications to surgery, serial ^{131}iodine therapy may be considered a safe and effective non-surgical alternative.

Keywords: serial RAI, large multinodular goiter, solitary nodular goiter eduction

Introduction

Levothyroxine suppression therapy has been an initial practice for prevention or growth reduction of thyroid nodules. Studies have shown a moderate (50%-60%) reduction in goiter volume primarily within the first three months of treatment.[1] Surgery has still been widely considered the standard therapy for patients with very large compressive goiters.[2] However, it is not a favorable option among elderly people suffering from cardiovascular or other disabling disorders rendering them unsuitable for surgery. Several European studies have shown that radioactive iodine (RAI) resulted in significant goiter size reduction among patients with nontoxic multi-nodular goiter.[3,4] In a study by Sia-Atanacio and Mercado-Asis, ^{131}iodine therapy given at a mean dose of 14mCi on patients with nodular non-toxic goiter less than 2.0 cm showed complete disappearance of nodules in 20 patients and 38% and 29% size reduction on thyroid nodules and thyroid lobes respectively.[5] Being the only non-surgical alternative treatment for large multinodular goiter, RAI offers a mean thyroid volume reduction of approximately 40-50% one year after treatment.[4,6] In comparison to levothyroxine suppression therapy used for thyroid nodule size one centimeter or less, it did not offer benefit[6] and improvement in obstructive symptoms (dyspnea, dysphagia) in the majority of patients with large nodules.[7,8]

The intention to avoid dose dependent side effects done in an out-patient clinic among elderly patients favored the administration of low dose (8.0-10mCi) oral ^{131}iodine therapy in serial doses at three to six months interval. To date, there have been few reported studies done on low dose serial

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^{131}Iodine therapy for large non-toxic goiters. Current trends and studies are geared towards prior administration of recombinant human thyroid stimulating hormone TSH (rhTSH) with low doses of ^{131}Iodine therapy. In countries where rhTSH is not readily available and use of low iodine preparation is a common practice, serial low dose (eight to 10mCi) ^{131}Iodine therapy may prove to be effective in reduction of multinodular goiter even with nodules more than two centimeters.

The selection of the best therapeutic option for a patient with multinodular goiter will depend on several factors, including size and location of the goiter, the presence and severity of compressive symptoms. Surgical complications such as injury to the recurrent laryngeal nerve, trachea, and parathyroid glands are more common in patients with large and substernal goiters.[9] Levothyroxine therapy treatment is particularly avoided in postmenopausal women with evidence of low bone mass, in the elderly and in those with cardiac disease, in whom the risk of this therapy generally outweighs its uncertain benefits.[1] ^{131}Iodine therapy when used to treat thyroid disease undergoes organification within the gland. It emits beta particles with a path length of only two to three millimeters destroys follicular cells by causing DNA damage and cellular necrosis. Routine monitoring for thyroid volume reduction includes ultrasound imaging, CT scan or magnetic resonance imaging (MRI). The achieved thyroid volume reduction ranges from 30-40% after the first year (with half of the effect appearing within the first three months) and from 50% to 60% after the third year.[10]

Methods

Study population and design

Patients with large solitary and multinodular goiter (≥2cm on either of the thyroid lobes) seen at the clinic from 2011 to 2013 who were biochemically and clinically euthyroid underwent serial low dose RAI therapy. These patients were unsuitable for surgery due to other medical problems. Included are those who did not consent for surgery. Seventeen subjects had large (≥2cm) solitary nodule while six had multinodular goiter. Subjects with a median age of 47 yrs (range 37-69yrs) completed two consecutive ^{131}Iodine therapies at eight to 10mCi at three to six months interval. Patients were monitored for the first two weeks post RAI then every two months thereafter. Close subjective correlation to relief of compressive symptoms were recorded in the clinic on follow-up visits.

^{131}Iodine therapy

^{131}Iodine was given as a single oral dose at the outpatient department isolation room in accordance to the official irradiation regulations. Since the side effects of ^{131}Iodine therapy are dose dependent, low dose (eight to 10mCi) was administered to avoid painful transient thyroiditis and swelling which may occur within the first few weeks after treatment. A second dose was given after three to six months.

Thyroid function

Thyroid stimulating hormone (TSH) was taken as an initial test and recorded at baseline, after first and second treatment. TSH was also done for the third time after ^{131}Iodine therapy for one patient who had three RAI dose treatment. Relative hypothyroidism developed after low doses of ^{131}Iodine were given serially. Levothyroxine replacement therapy was adjusted based on serial TSH results.

Thyroid imaging

Neck palpation was done on every patient and was correlated with ultrasound imaging findings. This was the only imaging modality used for baseline and serial measurements of both thyroid lobes and nodules. The same machine and reader was assigned to give measurements for all serial ultrasound imaging however the reader was blinded to the procedure done on all subjects. The baseline TSH on all subjects were not below the lower limit of the reference range, thyroid scintigraphy was not done in these subjects.

Compressive symptoms

Subjective complaints of compressive symptoms such as difficulty breathing, swallowing and choking sensation were all recorded prior to RAI as well as on subsequent follow-ups at the clinic. An endocrinologist evaluated for relief of compressive symptoms after serial RAI therapy and compared it from previous subjective findings.

Statistical analysis

Categorical data were summarized using frequency with percentage distribution, while numerical data were summarized using mean. In addition, percent change was computed. To determine significant change, paired t-test was used; and Pearson product-moment correlation coefficient was used to determine significant correlation. Data were processed using Microsoft Excel and analyzed using open sourced statistical software. An associated *p*-value less than 0.05 was considered significant.

Results

Baseline characteristics of study group

From 2011 to 2013, 23 subjects were gathered where 21 (82%) were females and two (18%) were males. The baseline characteristics are shown in Table I. The mean (±SD) age group was 43 (±15.5) years, and the range was 37-75 years. Six subjects had multinodular goiter with compressive

Table I. Demographic distribution and baseline clinical profile of subjects with large nodular and multinodular goiter

Baseline Characteristics	Baseline
Sex (M/F)	2/21
Age (years)	43 ± 15.5
Total number of subjects	23
Number of subjects with 1 nodule	17
Number of subjects with 2 nodules	6
Biggest thyroid lobe size (cc)	24.209
Biggest thyroid nodule size (cc)	6.990
Baseline TSH	1.30 ± 0.48
FNAB (all are negative)	(-)

symptoms while seventeen had large solitary nodules. Baseline TSH on subject population was at 1.30 uIU/L (± 0.48). All subjects were clinically and biochemically euthyroid with no history of previous thyroid surgeries and absence of malignant features at baseline ultrasonographic findings. All patients had benign histopathologic findings on fine-needle aspiration biopsy.

Thyroid and nodule size reduction

After the first RAI, there was a decrease in thyroid size by 38-40% from the baseline and further by 33-39% decrease after the second RAI (Figure 1). The average thyroid volume at baseline measurement was 7.79-9.03 cc with significant

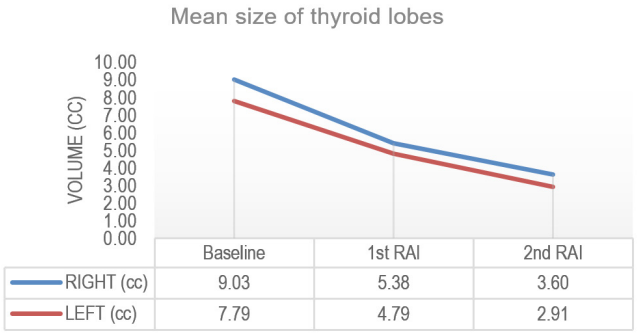

Figure 1. Reduction of Thyroid Lobes after Serial Low Dose ^{131}Iodine Therapy

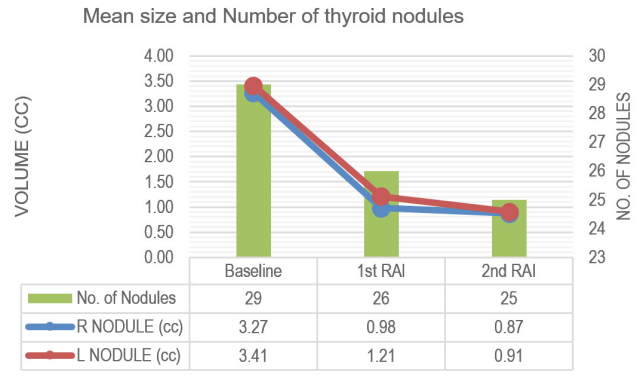

Figure. 2 Reduction of Number of Thyroid Nodules and Size after Serial Low Dose ^{131}Iodine Therapy

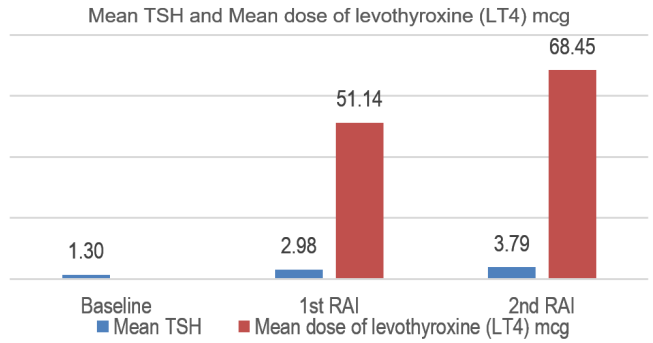

Figure. 3 Thyroid function status (TSH) and hormone replacement after serial low dose ^{131}iodine therapy

reduction in size to 4.79-5.38 cc after the first RAI and subsequently to 2.91-3.60 cc after the second RAI (10mCi) at three to six-month interval. At baseline, 29 nodules were noted with an average volume at 3.27-3.41 cc. The figures below showed the decreased volume of the nodules from baseline, then at 0.98-1.21 cc after first RAI, then at 0.87 0.91 cc after the second RAI. The highest response of thyroid nodule volume is observed after the first course of treatment. Moreover, a reduction in total number of nodules was observed with disappearance of three nodules after the first RAI and subsequently one nodule after the second RAI was observed (Figure 2).

Thyroid function

Baseline TSH prior to serial ^{131}iodine therapy was at 1.30uIU/L (Table I). Subsequent increase in TSH levels to 2.98 after first RAI and 3.79 after second RAI (Figure 3). Maintenance levothyroxine was at a mean dose of 65-70 mcg per day (Figure 3). Treatment of post-RAI hypothyroidism with Levothyroxine therapy ensures better quality of life along with relief of compressive symptoms. On the account of high possibility of developing hypothyroidism, levothyroxine therapy was started even after the first RAI treatment and maintained with continued titration guided by serial TSH monitoring until subsequent follow-ups.

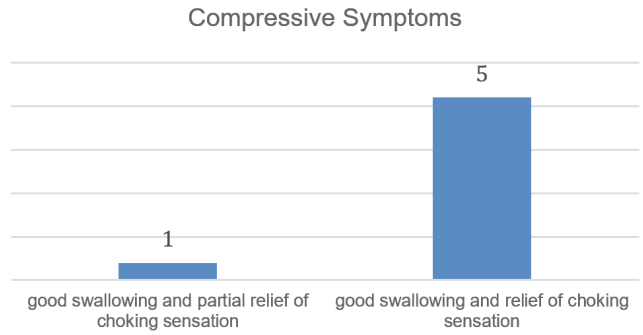

Figure. 4 Improvement of compressive symptoms after serial low dose ^{131}Iodine therapy

Compressive symptoms

Six subjects with multinodular goiter had significant improvement of compressive symptoms noted by disappearance of choking sensation immediately after the first RAI. Relief of compressive symptoms was noted immediately after the first RAI with disappearance of choking sensation. Subsequent relief of dysphagia and dyspnea was fully noted after the second RAI (Figure 4). One patient reported with partial relief of symptoms eventually had complete relief six months after second dose of RAI.

Discussion

The recent use of recombinant TSH (rTSH) as enhancers pronounced the effectiveness of RAI by enhancing radioactive iodine uptake (RAIU). Dietary iodine restriction is still widely used as pre-treatment thyroid enhancer. In correlation to decreased iodine pool, it is still widespread that many areas in the Philippines are still considered to be iodine deficient. We have proven the effectiveness of ^{131}iodine therapy in solitary and multinodular non-toxic goiter without rTSH on the premise that thyroid function must be normal among population with relative iodine deficiency. Radioiodine causes direct injury to the thyroid follicles and eventually diffuses fibrosis of the thyroid tissue and blood vessels eventually resulting in ligated blood supply to the thyroid nodules. Overall, outcome will be a reduction of total thyroid volume and shrinkage or disappearance of nodules.

This is a retrospective descriptive study done on 23 patients with enlarged solitary and multinodular goiters (nodules ≥2.0cm) with a median age of 43 years old (range 35-65 years) who were clinically & biochemically euthyroid. All patients had normal TSH and fT4 ensuring an intact iodine trapping mechanism. All had benign ultrasonographic features and negative fine-needle aspiration biopsy (FNAB). Subjects completed two consecutive ^{131}iodine therapy at 8-10mCi at interval of three to six months. An overall reduction in size by 60% on thyroid gland and 73% reduction on thyroid nodules. There was significant of compressive symptoms has been emphasized in this study. The disappearance of four thyroid nodules after the second RAI remarkably depicts the ongoing process of fibrosis of thyroid tissues and blood vessels causing shrinkage and eventually dissolution of nodules within six-month period. The important distinction here is that low dose serial ^{131}iodine therapy was found to have significant reduction both on the enlarged goiter and nodule size. Knowing the dose-dependent side effects of radioactive iodine, administration at low doses abates even minor symptoms making this procedure comfortable for the patient. For patients who are inoperable due to cardiovascular or other disorders, serial low dose ^{131}iodine therapy is a good alternative for relief of symptomatic patients.

Thyroid scintigraphy was not performed in this study. These nodules could appear cold or warm on thyroid scan. In some cases it could even be a hot nodule but with an unsuppressed TSH. This is possible in the background of iodine deficiency more often seen in many iodine deficient/ insufficient areas including the Philippines. In this study, patients were considered to have normal and intact iodide trapping mechanism along with a normal TSH. However, TSH may remain normal or unsuppressed even with an autonomous functioning nodule in the background of iodine deficiency because of the low proliferation rate of thyroid epithelial cells and the low synthesis rate of thyroid hormones by iodine-depleted thyroid glands.[11] Thus, it remains to be one of the limitations in this study that thyroid scintigraphy was not part of the initial thyroid assessment in the aspect of function and detection of areas of possible autonomously functioning thyroid nodules (AFTN) despite non-suppressed TSH. Anti-thyroperoxidase (TPO) antibodies are usually taken in support of high clinical suspicion for thyroiditis through history but because of its cost and limited availability it was not done on these set of patients. Instead, an fine needle aspiration biopsy (FNAB) was done on all subjects which in case of thyroiditis would show lymphocytic infiltrates in an enlarged gland confirming autoimmune thyroiditis.

Conclusion

Serial ^{131}iodine therapy proved to have successful goiter and nodular size reduction by more than 50% even among patients with enlarged nodular non-toxic goiter. Among patients who did not consent or have contraindications to surgery, serial ^{131}iodine therapy may be considered a safe and effective nonsurgical alternative.

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