ORIGINAL ARTICLE

Randomized Controlled Trial on Comparison of the Course of Hyperthyroid Patients with and Without Antithyroid Drugs During the Immediate Post Radioactive Iodine Treatment Period

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This study was done to compare the clinical course of hyperthyroid patients with and without anti-thyroid drugs immediately post radioactive iodine treatment.

Materials and Methods: Patients with mild to moderate hyperthyroidism, aged 18 to 60 years, were divided into 2 groups, those who received RAI plus anti-thyroid (ATD) (propylthiouracil 100 mg q8H) (group A) and those who received RAI only (group B). Fixed doses of 8 mCi 131I were given and symptoms were scored daily for 3 weeks, using 3-severe, 2-moderate, 1-mild scores. Descriptive analysis using mean and standard deviation was used to determine the demographic profiles and Mann Whitney t-test for independent samples was utilized to compare the symptoms between the two groups. All statistical tests were pegged at .05 alpha level and p-values less than .05 were considered significant.

Results: There were 3 males and 5 females in group A (n=8, mean age: 38±12.82 yrs) and 2 males and 6 females in group B, (n=8, mean age: 41.37±15.14 yrs). TSH was suppressed in both groups and the mean FT4 for group A was 13.87±16.51 pmol/L, and for group B was 28.51±15.86 pmol/L. There was no significant difference in age, FT_4 and TSH. Mean scores were as follows: (Group A vs. Group B), week one: 1.36 vs. 1.55 (p=0.01); week two: 1.08 vs. 0.94 (p= 0.110), and week three: 0.71 vs. 0.92 (p= 0.006). A highly significant decrease in symptoms was noted in week three.

Conclusion: Analysis of our data showed that patients given ATD immediately post RAI experienced lesser symptoms of thyrotoxicosis during the first and third week after RAI treatment, favoring treatment with ATD.

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Introduction

Radioactive iodine (RAI) therapy is a well-established and effective treatment for hyperthyroidism. The effectiveness of RAI therapy stems from its ability to cause an intense radiation thyroiditis and subsequent fibrosis, thereby destroying the synthetic capacity of the thyroid.[1] A release of stored thyroid hormones into the circulation is presumably a result of follicular cell disruption.[2] This outpouring of thyroid hormones may lead to exacerbation of thyrotoxicosis, 10-14 days after radioactive iodine is given. Adverse clinical events like aggravation of patients with severe thyrotoxicosis,

congestive heart failure or even thyrotoxic crisis may occur[2,3] As a result many patients are given antithyroid drugs (ATD) before RAI administration in an attempt to prevent transient worsening of thyrotoxicosis. However, pretreatment with antithyroid drugs increase the risk of radioactive iodine failure.[4,5,6]

Limited data is available with regards to the use of antithyroid drugs post RAI treatment. In the few studies done on the effects of antithyroid drug administration post RAI treatment, patients receiving the drug, became euthyroid sooner than those who received no therapy. These studies however, were largely intended to address rates of normalization of thyroid function tests and long term cure, rates rather than acute exacerbations.[7]

Since antithyroid drugs may hasten the return to a euthyroid state, it is also possible that post RAI exacerbation of thyroid function as well as the incidence of thyroid storm might be prevented. With a more rapid normalization of thyroid function following antithyroid drug use post RAI, hyperthyroid patients will also have lesser thyrotoxic symptoms and a better sense of well-being.

The purpose of this study was to compare the clinical course of hyperthyroid patients with and without anti-thyroid drugs during the immediate post radioactive iodine treatment period.

Materials and Methods

This study is a prospective, randomized controlled trial conducted in an endocrine referral clinic at the University of Santo Tomas Hospital. Included in the study are patients 18 to 60 years old, diagnosed with mild to moderate hyperthyroidism, without previous treatment with ATD, or if previously treated, withdrawn at least two weeks prior to RAI treatment.

Excluded from the study were those severely hyperthyroid patients, over 60 years old and those with known cardiac or chronic pulmonary disease. Baseline thyroid function tests, were done and free T_4 (NV 11.5–23 Pmol/L) and TSH (NV 0.27–3.75 uIU/mL) were determined prior to RAI treatment; signs and symptoms of hyperthyroidism were likewise recorded. All patients received an arbitrary dose of 8 mCi of ^{131}I. Patients were randomized into two groups, those who received ATD after RAI treatment and those who were not given anti-thyroid drugs. ATD treatment for patients randomized to receive the drug was started three days after RAI. Propylthiouracil (PTU) 100 mg TID was given for a period of three weeks.

To monitor the thyrotoxic symptoms post RAI, a checklist lifted from the University of Santo Tomas (UST) Formulated Clinical Index Scoring was made.[8] Scores were as follows: 3 if severe, 2 if moderate and 1 if mild. The patients were requested to monitor their symptoms daily after RAI treatment and were requested to mail or submit their checklists, three weeks after the therapy. To compare the demographic profiles of patients, mean and standard deviation were used and Mann Whitney U test was utilized for independent samples to compare the symptoms between the two groups. All statistical tests were pegged at .05 alpha level and p-values less than .05 as significant.

Results

Clinical Profile

A total of sixteen patients were included in the study. They were randomly assigned to 2 treatment groups: those who received ATD after RAI therapy (Group A, n=8) and those who were given RAI per se (Group B, n=8). There were 3 males and 5 females in Group A and 2 males and 6 females in Group B. The ages of the study population were as follows: Group A, 21 to 57 years old, mean age 38±12.82 years and Group B, 20 to 60, o significant difference in the ages (p value of mean age 41.37±15.14 years. There was no 0.65) of the two groups).

Table 1. Clinical and Hormonal Profile of the Study Population

Subjects	Mean±SD	p value
1) Age (years)		
Group A (21-57)	38±12.82	0.65
Group B (20-60)	41.37±15.14	
2) Free T_4 Level (pmol/L)		
Group A	13.87±16.51	0.15
Group B	28.51±15.86	
3) TSH Level (μIU/ml)		
Group A	0.53±0.62	0.09
Group B	0.81±0.81	

Hormonal Profile

The mean fT4 (NV=11.5–23 pmol/L) of each treatment arm were, Group A 13.87±16.5 and Group B 28.51±15.8 pmol/L. Although Group B had higher free T4 levels, there was no significant difference in the fT4 values between the two groups. The TSH levels for both groups were suppressed (Table 1).

Clinical Course and Symptomatology

Evaluation of symptoms based on the UST Formulated Clinical Index Scoring, revealed the following to be predominant among subjects in Group A, with the corresponding mean scores: Increased appetite (Week 1:1.82; Week 2:1.43, Week 3:1.14), increased sweating (week 1: 1.70, week 2: 1.57, week 3: 1.30) and heat intolerance (week 1: 1.54; week 2: 1.39; week 3: 1.27) (Fig. 1).

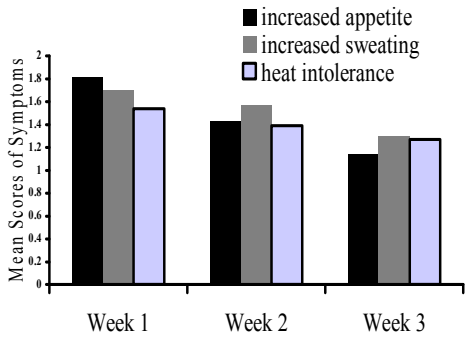

Fig.1. Symptoms among patients (Group A) with ATD after RAI treatment

Among subjects in Group B, the predominant symptoms were as follows: Increased appetite (week 1: 1.88, week 2: 1.14, week 3: 0.79), palpitations (week 1: 1.75, week 2: 1.02, week 3: 0.55), and heat intolerance (week 1: 1.73, week 2: 0.93, week 3: 0.79) (Fig. 2). Other symptoms, also and easy fatigability with mean scores of predominant during week 2, were irritability 1.07 and 1.04, respectively.

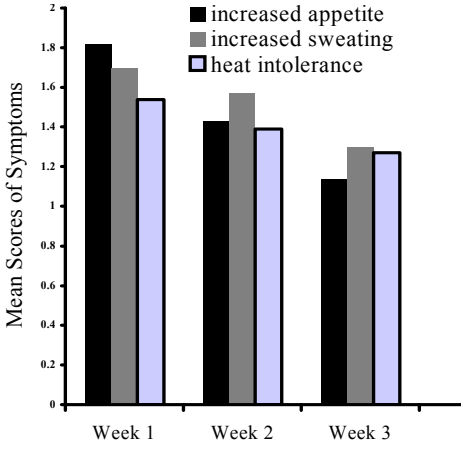

Fig.2. Symptoms among patients (Group B) without ATD after RAI treatment

When the following mean scores were compared (Group A vs. Group B): Week 1 (1.36 vs 1.55), week 2 (1.08 vs 0.94) and week 3 (0.71 vs. 0.92), there was significant difference during the first (p value 0.001) and third weeks (p value 0.006) after RAI treatment (Table 2). However, there was no

significant difference during the second week (p value 0.110). Patients given ATD had lesser degree of symptoms compared to those without ATD.

Table 2. Comparison of symptoms of the study population

Period of Observation	Group A (n=8) (W/ATD)	Group B (n=8) (W/O ATD)	p value
Week 1	1.36	1.55	0.001*
Week 2	1.08	0.94	0.110
Week 3	0.71	0.92	0.006*

* $p<0.05$, Mann Whitney U Test

Discussion

Radioactive iodine treatment has been used to treat hyperthyroidism for over 6 decades because it is clinically effective, safe and cost-effective in comparison with other therapeutic alternatives.[9] It accounts for seventy-nine percent of referrals for definitive treatment of adults with this condition.[10] There are three general approaches in giving ^{131}I therapy; prescribe a fixed dose for all patients, prescribe a dose corrected for the size of the thyroid and its ability to accumulate iodine or prescribe a quantity of ^{131}I calculated to deliver a specific radiation dose to the thyroid.[9]

The optimal outcomes after ^{131}I therapy are euthyroidism using multiple doses (fractionated therapy) or using a single dose, and hypothyroidism which is easily controlled by giving long term replacement therapy with thyroid hormone.[10] It is known however, that there is no single RAI dose or treatment method that can reliably accomplish these treatment goals due to a number of variables affecting the outcome including characteristics of the patient (age, gender and gland size), severity and duration of the underlying autoimmune thyroid stimulus, radiation delivered to the gland (^{131}I fractional uptake, homogeneity of distribution and effective half-life) and preceding antithyroid therapy.[9]

Quantitative principles have been applied to ensure reproducible and consistent responses to therapy and it appears that optimal doses of 131I could be determined with sophisticated dosimetry based on four facts; the absorbed thyroid radiation dose required, mass of the thyroid gland, effective half-life of ^{131}I and distribution of RAI within the gland by scintigraphy. These data permit calculation of the precise quantity of ^{131}I required to deliver a specific absorbed radiation dose to the thyroid. The reported absorbed dose ranges from 60 Gy to 300 Gy.

In older studies, worsening of thyroid function has been documented to occur one to two weeks after treatment and is likely related to radiation-induced thyroiditis. It is an acute condition occurring within two weeks after exposure of the thyroid to radioiodines characterized by symptoms of inflammation and eventual necrosis of some or all cells in the thyroid gland. The symptoms are usually mild and are related to local pain and tenderness over the thyroid gland. Acute radiation thyroiditis was reported to be found in four to five percent of patients with thyrotoxicosis.[10] Mc Dermont et al found sixteen cases of thyroid storm occurring after RAI treatment This problem developed an average of six days after RAI therapy and carried a twenty-five percent mortality.[2]

Antithyroid drug therapy given after ablative therapy may hasten the return to a euthyroid state and may possibly prevent postradiodine exacerbations of thyroid function.

Two randomized studies examined the effects of post treatment antithyroid drug administration. Patients receiving Methimazole administered in a block-replace regimen became euthyroid sooner than those who received no therapy. In another prospective study, where patients received PTU or potassium iodide therapy, there was no difference in thyroid function after six weeks suggesting no benefit from the treatment. In neither of these two prospective studies were clinically significant exacerbations reported in any of the treatment arms.[11]

In our study, patients who received antithyroid treatment after RAI reported having lesser thyrotoxic symptoms compared to patients who received RAI per se and this observation was significantly noted on the first and third week of ATD treatment. Subjects treated with ATD reported improvement of thyrotoxic symptoms and a better sense of well-being.

This study however, has some limitations. The number of subjects in each arm is small hence may not reflect a significant difference between the two groups. Although PTU was given only for 3 weeks, a period which may not be enough to cause euthyroidism in some patients, this study only aimed to compare the clinical course of patients with and without ATD post RAI treatment.

To conclude, analysis of our data showed that patients with ATD post RAI experienced lesser symptoms of thyrotoxicosis in the first and third week, favoring treatment with ATD.

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