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The Effect of Anti Thyroid Medications on the Therapeutic outcome of I-131 in Hyperthyroid Patients with Graves ' disease

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ABSTRACT

Objective: to detect the effect of anti-thyroid drugs (ATD) on the therapeutic outcome of I-131 in hyperthyroid Graves' patients. **Methods:** Retrospective study was done on 200 patients with Graves' disease treated with fixed dose of radioactive iodine (RAI) (12mCi). The patients were classified into three groups: Group I ($n = 70$) were treated by ATDs for more than 6 months and stopped it 5 days; group II ($n = 70$) were treated by ATDs for more than 6 months but stopped it only for two days or less, and group III ($n = 60$) had never been treated with ATD before RAI treatment (control group). **Results:** There was a statistical significant difference in the cure rate between group I and group II ($P < 0.001$), group II and group III ($P < 0.001$), but no significant

difference between group I and group III ($P = 0.453$) three months after RAI therapy. There was a statistical significant difference in the cure rate observed between group I and the group II ($P = 0.002$), group II and group III ($P < 0.001$), but no significant difference between group I and group III ($P = 0.060$) 6 months after RAI therapy. There was a statistical significant difference between the three groups 3 ($P < 0.001$), and 6 months ($P < 0.001$), after RAI therapy.

Conclusion: Administration of ATDs more than 6 month without discontinuation decreased response of RAI treatment in 3 and 6 months' follow-up. Discontinuation of ATDs for 5 days before RAI treatment is recommended.

Keywords: Graves' disease, Ant thyroid drug, radioactive iodine

INTRODUCTION:

Graves' disease (GD) is autoimmune disorders in which thyroid-stimulating hormone receptor antibodies can cause the thyroid gland synthesize large amounts of thyroid hormones. It is the most common cause of hyperthyroidism ^(1, 2). Treatment modalities of GD including anti-thyroid drugs (ATDs), radioactive iodine, and thyroidectomy. Radioactive iodine is increasingly used as the treatment of choice in most patients with Graves' hyperthyroidism because of its ease, low cost, and low rate of complications and relapse ^(1, 2). Treatment with anti-thyroid medications must be given for six months to one year to be effective. Even then, upon cessation of the drugs, the hyperthyroid state may recur. The risk of recurrence is approximately 40–50% and lifelong treatment with anti- thyroid drugs carries some side effects such as agranulocytosis and liver disease ⁽³⁾.

The three ATDs that are often used are Propylthiouracil (PTU), methimazole (MMI), and Carbimazole (CMZ). They are used either as a primary therapy for a certain period of time while awaiting remission of the disease, or as pretreatment prior to radioactive iodine treatment ^(4, 5). Pre-treatment with ATDs is indicated in older patients, in those with severe

hyperthyroidism and cardiovascular complications.

In such patients, it is common practice to achieve euthyroid state to reduce the risk of worsening of thyrotoxicosis due to radiation induced leakage of stored thyroid hormone, which can occur soon after RAI therapy ⁽⁶⁾. Worsening of the thyroid function has been described in approximately 10% of patients given RAI and 0.3% may experience a thyroid storm whether they are pre-treated or not. While there may be a transient rise in hormone levels in all patients, in pre-treated patients, this increase does not lead to an exacerbation due to lower baseline thyroid function ⁽⁷⁾.

Adjunctive anti-thyroid drugs reduce the biochemical exacerbation of hyperthyroidism directly after radioiodine treatment. The influence of ATDs on the response of radioactive iodine treatment is still controversial. Many studies have shown the correlation between ATD treatment and failure rate of radioactive iodine therapy, but others shown no correlation. The Society of Nuclear Medicine in procedure guideline for therapy of thyroid disease with ¹³¹Iodine suggested that ATDs should be discontinued for at least 3 days before the

Radioactive iodine therapy is given ^(5, 8, and 9). The reported recurrence rates after RAI treatment range from 10 to 40 percent of patients, with more severe cases of hyperthyroidism associated with higher rates of failure ^(10, 11). Absolute contraindications to RAI are few and include pregnancy, lactation, and inability to comply with radiation safety guidelines after treatment ^(12, 13).

PATIENTS and METHODS:

The study population included 200 cases of Graves' disease who had been treated with fixed dose (12mCi) of radioactive iodine (RAI-131) at Nuclear Medicine Unit (NEMROCK), Cairo University during the period of January 2006 till June 2016 after they were treated or untreated with ATDs for 6 months or more, all patients were followed for 6 months after RAI-131 therapy.

The patients were classified into three groups: Group I (n = 70) were treated by ATDs for more than 6 months and stopped it 5 days; group II (n = 70) were treated by ATDs for more than 6 months but stopped it only for two days or less, and group III (n = 60) had never been treated with ATD before RAI treatment (control group).

The study included 130 females and 70 male patients with Graves' disease with different age groups above 18 Years with no history of previous thyroidectomy. Their data were collected including age, sex, symptoms, duration of symptoms, thyroid hormonal profile, type, duration and response to previous medical treatment. Clinical examination for gland size, consistency, nodularity, & other neck swellings, eye signs examination was done and patients with active eye disease were excluded from the study.

Pre-RAI-131 medical treatment was given to 140/200 (70%) patients (Group I&II) in the form of Carbimazole, at a median dose of 30 mg/day for a median period of 6 months, 60 patients (30%) (Group III) had never been treated with ATDs before radioactive iodine treatment. Laboratory investigations including FT3, FT4, TSH levels and antibodies (measured by radioimmunoassay), with normal reference ranges as follow: TSH: 0.5- 5 mIU/L, T3: 60- 181 ng/mL, T4: 5.5- 12.3 ng/ml. Neck ultrasound to detect size of the gland, presence of any nodules& other neck swellings. Thyroid scan with technetium-99m pertechnetate (Tc 99m): was done for all patients with calculation of thyroid uptake.

The patients were imaged in a supine position with neck extension on anterior view using gamma camera fitted with low energy high resolution parallel-hole collimator, with the window at $\pm 15\%$ centered on 140 Kev in a 128x128 matrix for 500,000 counts per view, to evaluate gland size, and nodules.

Quantitative evaluation of thyroid uptake based on images of the gland and syringe counts before and after tracer injection. Thyroid uptake with Tc 99m was estimated for all cases with normal reference range = (0.5-4) %. Fixed dose of RAI-131 therapy (Fixed dose method) (12mCi) were given to all patients, with 6 months follow up guided by FT3, FT4, and TSH levels 3, 6 months after treatment. Successful treatment was considered when the patient turned euthyroid or hypothyroid. Euthyroid state was defined as T3, FT4, and TSHs serum levels within the normal range.

Hypothyroidism was defined as low thyroid hormone and increased TSHs. Cured rates were observed 3 and 6 months after radioactive iodine. Fifty (25%) patients received another dose of RAI-131 post 6 months due to persistent symptoms of thyrotoxicosis and high FT3, FT4, and low TSH levels).

Statistical Evaluation: Data analysis of 200 cases with **Graves' disease** including: Age group, sex of patients, most predominant symptoms, thyroid hormone levels, Tc 99m thyroid scan & uptake, Thyroid ultrasonography, type and duration of ATDs in group I&II patients and Duration of cessation of ATDs before RAI-131 therapy.

Differences of cure rate between the three groups at 3 months and 6 months were compared with the Chi-square test. Statistical analysis was done using the Statistical Package of Social Sciences (SPSS) advanced statistics version 22. 2013 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. A P-value < 0.05 was considered significant.

RESULTS:

This study included 200 patients, that were clinically & radio-laboratory diagnosed as GD. They were divided into three groups according to either they were received pre-RAI-131 medical treatment or not, and when they stopped it before RAI-131 treatment.

Medical treatment was given to 140/200 (70%) patients (Group I&II) in the form of Carbimazole, at a median dose of 30 mg/day for a median period of 6 months, 60 patients (30%) (Group 3) had never been treated with ATDs before radioactive iodine treatment. All groups' show no statistically significant difference as regard the age, where means age was 33± 9.72 years in group 1, 32± 11.71 in group 2, while it was 33± 11.76 years in group 3. GD was more common among females (65%). Concerning symptoms of toxicity, palpitation, tachycardia, loss of weight, tremors, nervousness, heat intolerance, exophthalmos & neck swelling were common among all groups.

As regard to the gland size, all of patients had mildly enlarged gland as detected by thyroid scan and thyroid ultrasonography, patients with moderately or markedly enlarged gland were excluded from the study. Concerning thyroid uptake value detected from Tc 99m thyroid scan, all patients had thyroid uptake ranges from 5 to 13%, patients with very high uptake values were excluded from the study. (Very high thyroid uptake may leads to rapid iodine turnover and this can reduce

the effect of therapeutic dose of radioiodine) With respect to severity of Thyrotoxicosis, and by using normal reference range for serum TSH from 0.5 to 5 mIU/L, 66.4% of GD patients in G1&II were localized in first stage (0.01-0.05) "Severely suppressed TSH", while only 43.3% in GIII localized in the same stage (P<0.05).

There was no significant difference among group I&II in duration of disease (P = 0.218), however the duration of the disease in group III was much shorter (4 ± 2.68 months).

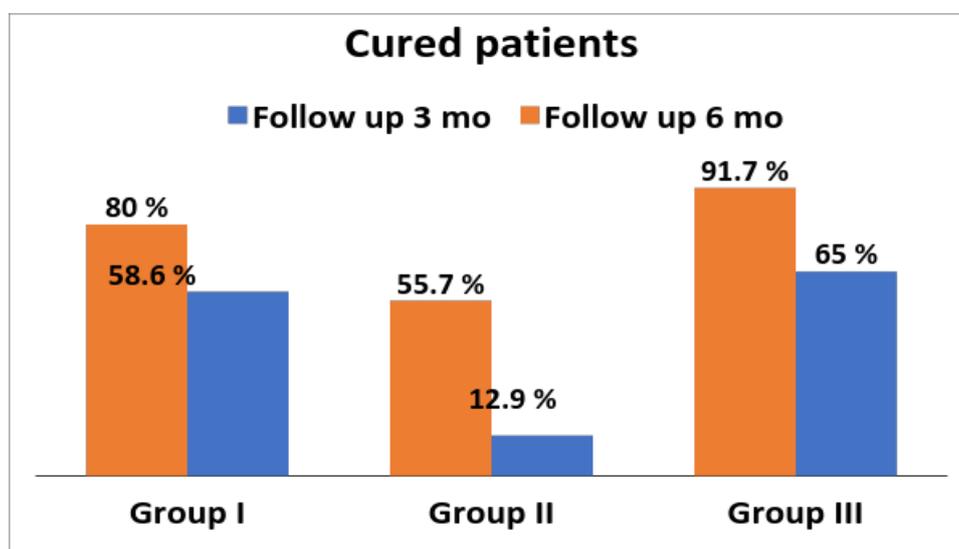
All patients received fixed dose of RAI-131 of 12 m Ci, follow up 3&6 months post RAI therapy was done. Three months after radioactive iodine therapy, 41 patients (58.6%) of group I, 9 patients (12.9%) of group II, and 39 subjects (65%) of group III showed a good response as detected by serum TSH level, while, rest of patients Showed less response. In Six months follow up after treatment, 56 patients (80%) of group I, 39 patients (55.7%) of group II, and 55 subjects (91.7%) of group III showed a good response. (*Table 1 & Fig 1*).

(Table 1). Cure rates 3 and 6 months after radioactive iodine therapy in all groups.

group	Follow up 3 months	Follow up 6 months	Treated with 2 nd dose	total
	Cured patients	Cured patients		
I	41/70 (58.6%)	56/70 (80%)	14/70 (20%)	70
II	9/70 (12.9%)	39 /70 (55.7%)	31/70 (44.3%)	70
III	39/60 (65%)	55/60 (91.7%)	5/60 (8.3%)	60

Only 14 subjects (20%) of group I, 31 subjects (44.3%) of group II, and 5 subjects (8.3%) of group III received another dose of radioactive iodine therapy [total number 50/200(25%)] (**Table 2**). There was a statistical significant difference in cure rate between the group I and the group II ($P < 0.001$), group II and group III ($P < 0.001$), but no statistical significant difference between group I and group III ($P = 0.453$) three months after radioactive iodine therapy.

There was a statistical significant difference in the cure rate between group I and the group II ($P = 0.002$), group II and group III ($P < 0.001$), but no statistical significant difference between group I and group III ($P = 0.060$) at 6 months after radioactive iodine therapy. However, there was a statistical significant difference between the three groups 3 months ($P < 0.001$), and 6 months ($P < 0.001$), after radioactive iodine therapy (**Table 3**).



(Fig 1). Cure rates 3 and 6 months after radioactive iodine therapy in all groups.

Table 2. Patients who needed 2nd dose of RAI-131 in all groups.

			Group			Total
			Group I	group II	Group III	
treatment with 2 nd _dose	Patients who did not receive 2 nd dose	number	56	39	55	150
		% within Group	80.0%	55.7%	91.7%	75.0%
	Patients who received 2 nd dose	number	14	31	5	50
		% within Group	20.0%	44.3%	8.3%	25.0%
Total		number	70	70	60	200
		% within Group	100.0%	100.0%	100.0%	100.0%

(Table 3). Comparison of cure rates 3 and 6 months after radioactive iodine therapy between the studied groups.

	Group I (70)	Group II (70)	Group III (60)		χ^2	P value
	Cured patients n(%)					
Follow up 3 months	41/70 (58.6%)	9/70 (12.9%)	39/60 (65%)	I,II	31.858	< 0.001**
				II,III	37.716	< 0.001**
				I,III	0.564	0.453
				All groups	44.201	< 0.001**
Follow up 6 months	56/70 (80%)	39/70 (55.7%)	55/60 (91.7%)	I,II	9.464	0.002**
				II,III	20.855	< 0.001**
				I,III	3.524	0.060
				All groups	23.708	< 0.001**

P<0.01** is highly significant

DISCUSSION:

Graves' disease (GD) is the most common cause of hyperthyroidism, which is responsible for approximately 50-60% of the cases ⁽¹⁴⁾. Carbimazole (CMZ), Methimazole (MTZ) and propylthiouracil (PTU) are used for the primary treatment of thyrotoxicosis due to GD or as a means of preparing the patient for definitive therapy with surgery or RAI (15). Pre-treatment of selected patients is indicated in older patients, in those with severe hyperthyroidism and cardiovascular complications.

In such patients, it is common practice to achieve euthyroid state to reduce the risk of worsening of thyrotoxicosis due to radiation induced leakage of stored thyroid hormone, which can occur soon after RAI therapy ^(6,16).

CMZ does not reduce efficacy of RAI therapy ^(6, 17) as long as the treatment is stopped from 3–5 days prior to therapy ⁽¹⁸⁾. Another meta-analysis suggests that all anti thyroid medication should be withheld for at least a week prior to therapy to improve the outcome ^(7,19).

The effect of oral ATDs on radioactive iodine therapy had been studied for a long time, but it is still controversial. The results of this study showed that

radioactive iodine therapy provided excellent results in patients who had not received ATDs prior to radioactive iodine therapy or in those who had stopped ATDs for 5 days before radioactive iodine therapy. This result are matched with Kubota, *et al.* and **Sabri, *et al.***, they indicated that the effectiveness of radioactive iodine therapy in hyperthyroid patients taking ATDs for more than 1 year can be improved by discontinuation of these drugs more than 3 days ^(20,21).

Some studies suggested that the ATDs may have a protective effect, which leads to lowering the effective half-life and uptake of radioactive iodine in the thyroid gland.

Thus, the target organ (thyroid) dose will decrease, resulting in a decrease of the effectiveness of radioactive iodine therapy. **Moka *et al.*** stated that discontinuation of ATDs before radioactive iodine is needed. This study is supported by Hancock *et al.*, Andrade *et al.* and Walter *et al.*, which recommended termination of ATDs one week before radioactive iodine therapy ^(22, 23, 19, and 7).

In this study, 12 mCi of radioactive iodine based on our empirical experience for fixed dose was used, as all patients in this

Study had mildly enlarged gland as detected by thyroid scan and thyroid ultrasound.

There was a statistical significant difference in the cure rate between the group I and the group II ($P < 0.001$), group II and group III ($P < 0.001$), but no statistical significant difference between group I and group III ($P = 0.453$) three months after radioactive iodine therapy.

There was also a statistical significant difference in the cure rate between group I and the group II ($P = 0.002$), group II and group III ($P < 0.001$), but no statistical significant difference between group I and group III ($P = 0.060$) at 6 months after radioactive iodine therapy.

However, there was a statistical significant difference between the three groups 3 months ($P < 0.001$), and 6 months ($P < 0.001$), after radioactive iodine therapy.

Imseis *et al.* Also, evaluated the effect of MMI to therapeutic efficacy of ^{131}I in hyperthyroid patients who were pretreated with ATDs. The study concluded that premedication with MMI did not interfere the response to ^{131}I therapy ⁽²⁴⁾. Similar results were reported by Andrade *et al.*, they showed that there was no difference after radioactive iodine treatment with or without MMI pretreatment ⁽¹⁹⁾. However, **Shivaprasad *et al.*** . Concluded that patients pretreated with CMZ have lower efficacy with ^{131}I therapy compared to non-pretreated patients ⁽²⁵⁾.

CONCLUSIONS:

The administration of oral ATDs more than 6 months without withdrawal for 5 days decreased response of radioactive iodine therapy in the 3 and 6 months' follow-up in GD patients. Discontinuation of ATDs for 5 days before RAI treatment is recommended.

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