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Identification of Optimal Fixed Radioactive Iodine Dose for Radioactive Iodine Treatment in the Patients with Benign Thyroid Disease Associated with Hyperthyroidism: Retrospective study

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Abstract
Aim: In this study, we aimed to examine the effectiveness of our approach to determining of the ambulatory low iodine-131 (I-131) dose performed in our clinic for the hyperthyroidism by retrospectively analyzing data of patients that received a low dose of I-131 in our institution for the treatment of hyperthyroidism.

Material and Methods: Medical records of 140 patients that received a ambulatory low dose of I-131 treatment in our institution were retrospectively reviewed. A total of 103 patients with available complete follow-up data were included: 15 patients with Graves' disease (GD), 36 patients with toxic adenoma (TA), and 52 patients with toxic multinodular goiter (TMNG). Age, sex, concomitant conditions other than thyroid disease, type and treatment duration of antithyroid medications, I-131 dose administered, and the presence and duration of response to RIT were recorded for each patient. Development of hypothyroidism or euthyroidism following RIT was considered as treatment response for patients with GD, whereas development of euthyroidism was an indication of treatment response for patients with toxic nodular goiter.

Results: Of 103 patients, 71 were female and 32 were male (mean age: 60 ± 12 years). The mean I-131 doses administered to patients with GD and toxic nodular goiter were 333 ± 74 MBq and 666 ± 148 MBq, respectively. Based on our treatment response criteria, our cure rates for GD, TA, and TMNG were 73.3%, 55.6%, and 65.4%, respectively. The mean duration of follow-up was 9 ± 6 months. Ninety patients received single dose and 13 patients received two doses of I-131. Hypothyroidism developed in

10 patients with GD and TA, and in 13 patients with TMNG. The mean time to hypothyroidism following a single dose was 3 ± 1 months for patients with GD and TA, and 4 ± 1 months for TMNG patients. Cumulative cure rates following the second doses were as follows: 93.3% for GD, 63.9% for TA, and 71.2% for TMNG.

Conclusion: The ambulatory I-131 doses used in our institution for the ambulatory treatment of benign thyroid diseases associated with hyperthyroidism were found to be effective.

Key words: Hyperthyroidism, Radioactive iodine, Therapy

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Benign Tiroit Hastalıklarında Gelişen Hipertiroidi Tablosunun Radyoaktif İyot ile Tedavisi için Optimum Sabit Radyoaktif İyot Dozunun Belirlenmesi: Retrospektif Çalışma

Özet

Amaç: Bu çalışmada kliniğimizde hipertiroidi nedeniyle ayaktan düşük doz İyot-131 (I-131) tedavisi alan hastalarının verilerini inceleyerek, hipertiroidi için kliniğimizde uyguladığımız radyoaktif iyot tedavi (RIT) dozunu belirleme yaklaşımımızın etkinliğini retrospektif olarak incelemeyi amaçladık.

Gereç ve Yöntem: Kliniğimizde sabit düşük doz I-131 tedavisi alan 140 hastanın verileri arşiv dosyalarından kohort olarak geriye dönük değerlendirildi. Takip sürecini tamamlamış 103 hasta çalışmaya alındı: 15'i Graves hastalığı (GH), 36'sı toksik adenom (TA) ve 52'si toksik multinodüler guatr (TMNG). Hastaların yaşı, cinsiyeti, eşlik eden tiroit dışı hastalıkları, kullandıkları antitiroit ilaç türü ve süresi, uygulanan I-131 dozu, RIT sonrası tedaviye cevap ve cevap süresi kaydedildi. Graves hastalarında RIT sonrası hipotiroidi veya ötiroidi gelişimi, toksik nodüler guatr hastalarında ötiroidi gelişimi tedaviye yanıt olarak kabul edildi.

Bulgular: Yüz üç hastanın 71'i kadın ve 32'si erkekti (yaş ortalaması ± SD: 60 ± 12 yıl). Graves hastalarına ortalama 333 ± 74 MBq, toksik nodüler guatr hastalarına ise 666 ± 148 MBq dozda I-131 tedavisi uygulanmıştı. Tedaviye yanıt kriterlerimize göre I-131 tedavisi sonrası kür oranlarımız GH için % 73.3, TA için % 55.6 ve TMNG için % 65.4'dür. Hastalar 6 ile 48 ay arasında ortalama 9 ± 6 ay takip edildi. Doksan hastaya tek doz, 13 hastaya iki doz I-131 uygulandı. Graves ve TA hastalarının 10'unda, TMNG'lı hastaların 13'ünde hipotiroidi tablosu izlendi. Tek doz uygulamasından sonra grupların hipotiroidiye giriş süreleri GH ve TA için 3 ± 1 ay, TMNG için 4 ± 1 aydı. İkinci doz uygulaması sonrası elde edilen toplam kür oranları GH için % 93.3, TA için % 63.9 ve TMNG için % 71.2'dir.

Sonuç: Hipertiroidi ile seyreden benign tiroit hastalıklarının I-131 ile ayaktan tedavisinde bölümümüzün uyguladığı sabit I-131 dozları hastaları etkin bir şekilde tedavi etmektedir.

Anahtar sözcükler: Hipertiroidizm, Radyoaktif iyot, Tedavi

Introduction

Radioactive iodine treatment (RIT) is performed with iodine-131 (I-131) which emits high energy beta radiation. Radioactive iodine is generally used for the treatment of hyperthyroidism in patients with Graves' disease (GD) and toxic nodular goiter (TNG) diagnoses [toxic adenoma (TA) and toxic multinodular goiter (TMNG)].[1] Activity of radioactive iodine treatment depends on the size of thyroid gland, radioactive iodine uptake (RAIU) level and I-131 metabolism in each individual.[2,3] There is no consensus on optimum I-131 dose or dose determination method for the treatment of hyperthyroidism.[4] Regardless of methods for determining doses or causes of hyperthyroidism, development of hyperthyroidism in patient within weeks, months, years following RIT is significant. Because uptake of

I-131 in thyroid gland is higher in GD than in toxic nodules, low doses should be preferred in consideration of relapse risk and severity of synchron cardiac and metabolic diseases. Higher I-131 doses are given to the patients with toxic nodular goiter because nodular tissue is not similar to the normal thyroid tissue anymore.[5] Despite the differences among those diseases, three approaches are available for the determination of I-131 dose and these are absorbed dose method, dose given for per thyroid gram and fixed dose approaches.

Patients with hyperthyroidism have been treated with low dose RIT for more than 20 years in our clinic and fixed low dose I-131 has been the dose level of choice. In this study, we aimed to assess I-131 dose determination method that we used for the treatment of thyperthyroidism. In order to achieve this aim, we analysed datas of outpatients receiving low dose I-131 treatment for hyperthyroidism, by regarding clinical factors [age, gender, antithyroid drug therapy (ATD) etc.] that may effect the treatments results.

Material and Method

Patients and Patient groups

Datas of 140 patients, who had been referred to our department with the diagnosis of GD and TNG and had received RIT, retrospectively evaluated with cohort analysis. Totally 103 patients who were followed until development of euthyroidism or hypothyroidism as a response to the radioactive iodine treatment or who could not recover despite the repeated RITs.

Patients with hyperthyroidism were seperated into 3 groups as their diagnoses; GD, TA and TMNG. The diagnose of GD was based on positive clinical symptoms and signs, diffuse goiter, high thyroid autoantibody, existance of ophthalmopathy, diffusely increased activity involvement in Tc-99m pertechnetate thyroid scintigraphy and laboratory results compatible with hyperthyroidism (high FT4 and FT3 / low TSH). The diagnose of TA and TMNG were based on detection of nodule(or nodules) by palpation of patients who had clinic and laboratory signs of hyperthyroidism, and based on detection of hyperactive nodule(or nodules) at Tc-99m pertechnetate scintigraphy.

Determination of Iodine-131 Dose

For GD patients; 185 MBq I-131 was applied if clinical and laboratory thyrotoxicosis signs could be controlled with low dose (50 - 100 mg in per 6 – 8 hours) ATD treatment and thyroid gland was in normal size. The 370 MBq I-131 was applied if clinical and laboratory and thyrotoxicosis signs could be controlled with high dose (100 - 200 mg in per 6 – 8 hours) ATD treatment and the size of thyroid gland was bigger than normal. The 444 - 555 MBq I-131 was applied if clinical and laboratory thyrotoxicosis signs could not be controlled with ATD treatment and thyroid gland was quite bigger than normal. In toxic nodular goiter (solitary or multinodulary), 444 - 555 MBq I-131 was applied if clinical and laboratory thyrotoxicosis signs were mild or moderate. If very severe, 740 - 925 MBq I-131 was applied.[6]

Treatment and Follow up Methods

According treatment and follow up protocol that our clinic follows, entire patients were informed verbally and in writing about the rules they were supposed to obey before and after RIT and about possible side effects they may suffer according to Radiation Safety Regulations[7] made by TAEA (Turkish Atomic energy Authority) and a guide published by Turkish Society of Nuclear Medicine Endocrin – Therapy Study Group[8] RIT. Entire patients signed a consent form to approve the treatment. Approval for retrospective analysis of clinical and laboratory information was obtained from the medical faculty ethical board.

The patients were given a 2 weeks long low iodine diet before RIT.[9,10] Anti-thyroid drug therapy was stopped 3-5 days before the treatment; when necessary, ATD therapy was regulated again after the RIT application. The patients were asked not to eat at least 4 hours before receiving I-131 and 2 hours after receiving I-131. Under control of a nuclear medicine physician, the patients drank the determined dose of I-131. Two weeks after the treatment, patients were called for a follow up in terms of early hyperthyroidism symptoms and requirement of ATD. In early period of the treatment, patients presenting with hyperthyroidism symptoms were given beta blockers and/or ATD treatments. Later on, patients were followed up every month with physical examination and thyroid function tests (TFT). Patients developing euthyroidism monthly followed up for extra 3 months. If there was no drug intake, clinical and laboratory findings were compatible with euthyroidism and a low activity uptake in nodul and/or nodules of thyroid gland in Tc-99m pertechnetate thyroid scintigraphy was detected, then the patient was considered as ‘‘cured’’ and dropped from follow up. In monthly follow ups made up to 6 months, patients developing hyrothyroidism were given T4 replacement treatment by checking serum TSH values. These patients follow up additional 3 months per month in order to establish a definite hypothyroidism

diagnosis and to make sure TSH values were within the normal range thanks to replacement theratment. At the 6th month follow up, the patients, whose hyperthroidism symptoms and signs lessened, hormone profiles were seen to recover and who needed lower doses of drugs during ATD treatment, were followed up monthly until they became euthyroid. If severity of sign and symptoms of hyperthyroidism were the same and no changes could be seen in Tc-99m pertechnetate thyroid scintigraphy, second dose of RIT treatment was planned. Compared to the first dose which had been given to the patiens, second dose was increased approximately 25 %. Patents follow up after the second dose was the same of follow ups after the first dose.

Statistical Analysis

Calculable variables were shown as mean ± standard deviation. Chi-square and Kruskal Wallis Variance Analyses were used for incalculable variables and One-Way Analysis of variance was used for calculable variables. Bonferroni- corrected Mann Whitney U test was used when a difference was found as a result of Kruskal Wallis Variance Analysis, Multiple Comparison tests (Tukey) were used when a difference was found as a result of One-Way Analysis of variance. $P < 0.05$ was considered as statistically sifnificant.

Results

Clinical datas and demographic features of 103 patient (60 ± 12 years; range: 28 - 84 years) (out of 140) who completed their follow up process and whose clinical datas were scanned with a cohort study, were summarized in Table 1. The 71 of the patients were female (60 ± 12 years) and 32 of the patients were male (61 ± 11 years). Out of 103 patients, 15 had GD, 35 had TA and 52 had TMNG. Statistical analyses did not reveal a significant difference in terms of gender distribution of the patients between groups ($p > 0.05$). Mean age of patients were significantly different among groups ($p = 0.012$). Comparing to TMNG patients (63 ± 11 years; range: 39 - 84 years), GD patients (54 ± 14 years; range: 28 – 81years) were younger ($p = 0.016$).

Male patients responded less to the treatment compared with female patients ($p = 0.021$). Hyperthyroidism rate was found to be 25 % after the radioactive iodine treatment in male patients while it was found to be 9.9 % in female patients. In terms of treatment response, a significant difference was not detected when patient ages were regarded ($p > 0.05$).

Treatments datas belong to the patients who received radioactive iodine treatment and completed their follow up process were summarized in Table 2. Mean follow up time of the patients was 9 ± 6 months (range: 6 - 48 months). A single dose of I-131 was applied to 90 patients in our study group. Second dose of I-131 were given to 13 patients (out of 15 patients) whose hyperthyroidism symptoms sustained until the follow up of the 6^{th} month. Surgeries were performed on 2 patients (one GD, one TA). No patients received 3th dose of RIT. When entire patient groups are considered, average I-131 dose applied to the patients were 629 ± 185 MBq (range: 185 - 925 MBq). Mean dose of applied I-131 was 333 ± 74 MBq (range: 185 - 444 MBq) in GD patients and was 666 ± 148 MBq (range: 370 - 925 MBq) in TMNG patients. There was an apparent difference between I-131 doses applied to patient groups. 185 - 370 MBq dose of I-131 was applied to 93.3 % of GD patients and 740 - 925 MBq dose of I-131 was applied to 71.6 % of toxic nodular goiter patients ($p = 0.0001$).

Table 1. Demographic and clinical information of all study groups and subgroups.

	Graves disease **n = 15**	Toxic adenoma **n = 36**	**T**oxic multinodular goiter **n = 52**	**Total n = 103**
SEX				
Man (n)	5	7	20	32
Woman (n)	10	29	32	71
Mean Ages (Years)				
Man (min – max)	52 ± 7 (44 - 60)	58 ± 12 (39 -72)	64 ± 10 (45 - 82)	61 ± 11 (39 - 72)
Woman (min – max)	55 ± 17 (28 - 81)	59 ± 11 (34 - 81)	63 ± 11 (39 - 84)	60 ± 12 (28 - 84)
Operation				
Yes	1	3	2	6
No	14	33	50	97
Ophtalmopathy				
Yes	2	1	0	3
No	13	35	52	100
Cardiac complication				
Yes	0	1	14	15
No	15	35	38	88
Antithyroid medication				
Yes	15	27	39	81
No	0	9	13	22

Before radioactive iodine treatment, 81 patients (78.6%) received ATD treatment [Propylthiouracil (PTU) 71; Methimazole (MMI) 10]. Distribution according to I-131 treatment response of patients receiving ATD treatment before radioactive iodine treatment was shown in Table 3. A statistically significant difference was found between the treatment responses of 50 patients receiving ATD treatment for less than 6 months before the treatment and 31 patients using ATD for more than 6 months (p = 0.002). After RIT, rate of hyperthyroidism in patients receiving ATD treatment for more than 6 months was found to be 35.5%, while it was found to be 8% in patients receiving ATD treatment for less than 6 months.

After application of the first dose of I-131, hypothyroidism in 33 patients (32 %), euthyroidism in 55 patients (53.4%) and hyperthyroidism in 15 patients (14.6 %) were detected (Table 4). Hypothyroidism was detected in 5 patients, euthyroidism was detected in 6 patients and hyperthyroidism was detected in 2 patients out of 13 patients who had received the second dose. Two patients with persistant hyperthyroidism after second dose of I-131 application were referred for surgery. Total cure rates after the second RIT application were 93.3 % for GD, was 63.9 % for TA and 71.2 % for TMNG. Risk of hyperthyroidism development after the application of Iodine-131 was significantly higher in GD patients than in TA and TMNG patients (p = 0.002).

Table 2. Information of I-131 therapy of all study groups and subgroups

	GD	TA	TMNG	Total
I-131 dose number (n)	15	36	52	103
Single dose(n)	12	31	47	90
Two doses (n)	3	5	5	13
First I-131 dose				
740 - 925 MBq	0	27	36	63
444 - 555 MBq	1	5	9	15
185 - 370 MBq	14	4	7	25
Second I-131 dose				
740 - 925 MBq	0	2	4	6
444 - 555 MBq	3	3	1	7
Duration of euthyroid development in a single dose of I-131 (months)	2 ± 1	2 ± 1	3 ± 1	2 ± 1
Time for patients to enter hypothyroidism after I-131 treatment (months)				
Given a single dose	3 ± 1	3 ± 1	4 ± 1	3 ± 1
Time after the second dose	2 ± 1	2 ± 1	-	2 ± 1
Follow-up (months)	13 ± 7	9 ± 7	8 ± 3	9 ± 6
Given a single dose	10 ± 5	7 ± 2	7 ± 2	8 ± 3
Time after the second dose	15 ± 8	15 ± 14	9 ± 5	13 ± 10

GD:Graves disease; TA: toxic adenoma; TMNG: toxic multinodular goiter

Table 3. I-131 treatment response of patients according to receive antithyroid medication before I-131 treatment.

	Propylthiouracil	**Methimazole**	**Total**
	n = 71	**n = 10**	**n = 81**
GD (n)	**11**	**4**	**15**
Hypothyroid	8	2	10
Euthyroid	0	1	1
Hyperthyroid	3	1	4
TA (n)	**26**	**1**	**27**
Hypothyroid	7	0	7
Euthyroid	13	1	14
Hyperthyroid	6	0	6
TMNG (n)	**34**	**5**	**39**
Hypothyroid	7	1	8
Euthyroid	23	3	26
Hyperthyroid	4	1	5

GD:Graves disease; TA: toxic adenoma; TMNG: toxic multinodular goiter

Table 4. Evaluation of first dose I-131 application as sex

	GD, n = 15	**TA, n = 36**	**TMNG, n = 52**	**Total, n = 103**
Hypothyroid n (%)	**10 (66.7%)**	**10 (27.8%)**	**13 (25%)**	**33 (32%)**
Man	1	0	4	5
Woman	9	10	9	28
Euthyroid n (%)	**1 (6.7%)**	**20 (55.6%)**	**34 (65.4%)**	**55 (53.4%)**
Man	0	5	14	19
Woman	1	15	20	36
Hyperthyroid n (%)	**4 (26.7%)**	**6 (16.7%)**	**5 (9.6%)**	**15 (14.6%)**
Man	4	2	2	8
Woman	0	4	3	7

GD:Graves disease; TA: toxic adenoma; TMNG: toxic multinodular goiter

Discussion

Treatment of hyperthyroidism with radioactive iodine is a cheap and easy treatment method and it has minor side effects. During 60 years long history of I-131treatment, different methods had been developed in order to determine application dose, however a consensus still could not have been reached on the best method. This is because the different etiologies of diseases as well as age and gender of the patients, existance of factors that change radioresistance of thyroid gland (such as ATD), iodine dose that patients receive, size of thyroid gland, synchronous diseases, diffences in iodine uptake of thyroid tissue and different attitude of radioactive iodine for different doses.[11]

The Effect of Different Age and Gender

Graves' disease, TA and TMNG are more frequent in female patients. GD is generally seen in young patients while TMNG is seen in patients of advanced age.[1,6,12] Unsurprisingly, there were more female patients and GD patients were younger compared to TMNG patients in our study (p = 0.016).

In our study, after RIT, hyperthyroidism was detected in 25 % of male patients and in 9.9 % of male patients. Our rate of cure was 75 % in male patients and 90.1 % in female patients (Table 4). Many studies reported that cure rates are lower in males compared to females.[3,13,14] Allahabadia et al.[3] found the success of treatment after RIT as significantly worse in male hyperthyroidism patients compared to female patients with hyperthyroidism, especially GD. On the other hand, some studiesfound that rate of hyperthyroidism in male and female patients after I-131 treatment were quite similar.[11,21] However the reasons of differences[3,13,14] or similarities[11,21] of RIT response between genders could not be explained.

In our clinic, the rates of hyperthyroidism after RIT were seen in 15.6 % of male patients and in 39.4 % of female patients. In a study, Ahmad et al.[11] reported that after RIT, with the fixed I-131 dose of 400 MBq and 550 MBq, clinical manifestations of hyperthyroidism were seen in 80.4 % of male patients and in 60.9 % of female patients and that gender was a significant variable in terms of development of hyperthyroidism. But Allahabadi et al.[3] did not detect a significant difference in terms of the incidence of hypothyroidism between male (49.4 %) and female (50.5 %) patients after RIT. Boelaert et al.[13] reported the increased risk of hypothyroidism after the treatment of study group which consisted of 1.016 female and 262 male patients. The effect of estrogen hormone on immune system was suggested as a possible reason of higher GD incidence in female patients but why female patients responded better to RIT could not be explained.[13,14]

Use of Antithyroid Drugs Before Radioactive Iodine-131 Treatment

When assessing the efects of ATDs on RIT, one of the least assessed issue is whether duration of drug use has an effect on the results of RIT. In our study, failure of RIT in patients receiving ATD treatment for 6 months and less was 8% and was 35.5 % in patients receiving ATD treatment for more than 6 months.

According to the study of Alexander and Larsen [26], patings receiving ATD for less than 7 months responded better to the treatment compared to the patients receiving ATD treatment for more than 7 months.[26] Our cases with sustained hyperthyroidism after RIT were using ATDs (13 patients PTU, 2 patients MMI) therefore we can say that this effect was more prominent in patients using PTU. The reason for the development of radioprotective effect with the long term use of propylthiouracil is difficult to explain with only TSH stimulation or with inhibition of throid peroxidase.[27,32] We think that the effect of PTU use a long time on NIS should also be assessed. The effect of PTU withdrawal period on the treatment response before RIT is the most possible evidence for this.

ATD withdrawal period was suggested as a factor effecting treatment response before RIT. [21, 27- 29] Despite discontinuation of ATD treatment for 5 - 55 days before RIT, the use of PTU was not reported to reduce the success of the RIT.[27] However, it was suggested that stopping ATD before giving I-131 enhanced the effectivity of the treatment as 50 %.[29] In a study of Boelaert et al.[13] rate of successful treatments in patients using PTU and carbimazole (a MMI metabolite) before RIT are similar (77.2 % and 75.3%, respectively). Duration of ATD use was not evaluated in these 2 studies. [3, 29)] We found in our study that cutting ATD 3-5 days before RIT did not has an effect on RIT success for both ATDs. And this shows that our ATD stopping period was sufficient.

In our study, 81.7% of hyperthyroidism patients using PTU before RIT and 80.0% of hyperthyroidism patients using MMI before RIT were succesfully treated. Imeseis et al.[28] suggested that the use of PTU as a first treatment may reduce the efficacy of I-131 in the treatment of hyperthyroidism. On the other hand, they did not detect a significant difference between patients receiving MMI before RIT and patients who did not receive ATD treatment. Therefore, they recommeded MMI instead of PTU before RIT. [28] Korber et al.[27] found that ATD use during I-131 treatment did not have an effect on the success of

treatment in GD patients while it negatively effects the success of treatment in TNG patients. The possible reason for this effect is that TSH which is increased by ATD, stimulates the normal thyroid tissue and causes it to uptake more iodine, therefore toxic nodule uptakes lesser amount of I-131. This condition is described as "*steal phenomenon"*. In our group, 6 TA patients and 4 TMNG patients with ongoing hyperthyroidism after RIT were using PTU; so this supports the study of Korber et al.[27] ATD withdrawal time may be insufficient in these patients.

Other important subject to disscuss about is how ATD effects the risk of hypothyroidism after RIT. Boelaert et al.[13] reported in a study that there was no significant difference between hypothyroidism development risk of patients using PTU and carbimazole before RIT, without regarding the types of diseases. This is similar to the study findings of Alexander and Larsen.[26] Our findings correlate with the findings of these studies and support that ATD treatment before RIT does not have an effect on hypothyroidism development. After assessing the effect of ATD on efficacy of RIT in GD, we detected development of hypothyroidism in 66.7 % of GD patients using ATD. Because ATD is the first line therapy for GD patients, higher rates of ATD use is an expected outcome. If we assume that hypothyroidism is a desired outcome of RIT in GD patients, an interpretation like "hypothyroidism is frequent in GD patients who use ATD'' will not be realistic. We detected hypothyroidism development in 20.5 % of TMNG patients using ATD after RIT. Petersen - Bjegaard and Kirkegaard[30] reported in a study that hypothyroidism developed in 16.4% of TMNG patients and half of this patients were using PTU while the other half were using carbimazole. Even though our rates (Table 3) are different in patients using methimazole, our rates of hypothyroidism in TMNG patients can be said to be similar if we look at the issue from the aspect of ATD use. However, there is no sufficient data determining whether the type of ATD in TMNG patients play a role in terms of hypothyroidism developments. In addition to this, without regarding the drug type, datas determining whether ATD play a role in development of hypothyroidism are contradictory. Ahmad et al.[11] reported that rate of hyperthyroidism was significantly higher in patiens who did not use ATD after I-131 treatment. This situation was suggested to be caused by radioprotective effect of ATD treatment.[31] Walter et al.[32], who made the metaanalysis of 12 studies (1306 patients), reported that hypothyroidism development risk was higher in patients using ATD. Our results are different from both studies.[11, 32]

We found that hypothyroidism rates were similar in patients who used ATD (30.9%) and who did not use any ATDs (36.4%). In other words, use of ATDs did not effect the hypothyroidism development rate. We presume that sufficient discontinuing period of ATD of ATD before RIT thereby removal of radioprotective effect was the possible cause of this. Because the number of subjects in Ahmad[11] and Walter's studies[32] were more than our's, it is difficult to explain this difference for us.

Rates of Responce and Cure to Radioactive Iodine Treatment

Our rate of cure (hypothyroidism and euthyroidism) in GD patients is 73.3%. Response to treatment was accepted as euthyroidism for toxic nodulary goiter after RIT and cure rates were 55.6% in TA patients and 65.4% in TMNG patients in our study. Rate of cure in TA varies between 50% and 92% in literature (Table 5).[3,21,11,25] Generally smaller doses were used in studies which obtained lower cure rates than ours. Only Huymans et al.[25] found higher rate of euthyroidism (92%) than ours in TA patients with fixed application dose of 740 MBq I-131. The same study reported rate of hypothyroidism as 6 % and hyperthyroidism as 2 % after RIT. Huymans et al.[25] suggested there was not an association between hypothyroidism development and nodule size, on the contrary, it might be related to the high I-131 uptake in surrounding thyroid tissue of nodules. Therefore it appears like the only explanation of their very low rates of hyperthyroidism and hypothyroidism can be the total uptake of I-131 by nodule which in other words, means total supression. In our study Tc-99m pertechnetate thyroid scintigraphy performed before RIT showed that 29 out of 36 patients with TA diagnosis became autonomous (80.6 %) while 7 patients did not become autonomous (19.4 %). Hypothroidism continued after RIT in 2 out of 7 patients who had non autonomous nodules on scintigraphic examination while other 5 developed euthyroidism. The most possible reason of our different rates of hyperthyroidism, euthyroidism and hyperthyroidism after radioactive I-131 is that our study group involved some subjects with non autonomous nodules.

Rates of cases with ongoing hyperthyroidism after RIT were found in GD as 26.7 %, 16.7 % in TA and 9.6 % in. Our hyperthyroidism rates detected in GD patients resemble to the rates obtained with similar doses of I-131 in literature (Table 5). [3,21,23] However, rate of GD patients with hyperthyroidism after RIT was 9.7% was found in the study of Ahmad et al.[11] Nearly half of the patients were treated with 550 MBq I-131 and this was higher than any of I-131 doses which were applied in overall studies, included ours. Whereas cellular injury is parallel with radiation dose, lower incidence of hyperthyroidism is expected in higher doses.[4]

In published literature, reported the rates of hyperthyroidism for TA patients after RIT with the doses of 185 MBq and 555 MBq varies between 10 % and 26.1 % (Table 5).[11, 21, 33] Hyperthyroidism rate after RIT was 26.1% in a study of Erem et al.[21] When we compare the results with this study, our rate of hyperthyroidism is (16.7 %) lower for TA. Considering that Erem et al.[21] gave a fixed dose of 370 MBq I-131 treatment, this difference may be caused by the application of higher I-131 doses (740 - 925 MBq) for TA patients in our clinic. In a study, Ahmad et al.[11] reported hyperthyroidism in 10.7 % of TA patients after RIT. Sharma et al. [33] reported in a study that treatment failure rate was 10%. Similar doses (370 - 555 MBq) and similar rates were reported in both studies. We can not explain with the present data that why they obtained lower hyperthyroidism rates than ours with lower doses of I-131 in TA patients. As a results of our study, detected hyperthyroidism rates (9.6 %) in TMNG patients were lower compared to the ones in literature (16.7 % - 27.8 %) which were obtained with 185 - 555 MBq doses of I-131 (11,21). On the other hand, Abos et al.[34] determined the rate of hyperthyroidism as 9.2% in TMNG patients who received fixed dose of 555 MBq I-131. In this study, lower amount of I-131 doses than our RIT doses were used and similar rates of hypothyroidism were obtained. When we assess this datas and rates of hyperthyroidism in patients all together, we notice that Abos et al. [(34)] reported lower rates of hyperthyroidism compared to our rates (Table 5). Both these 3 literatures and our results show that treatment response in TMNG patients are related to the I-131 dose.

Hypothyroidism is another situation which may develop after RIT. Hypothyroidism was seen in 66.7 % of GD patients, in 27.8 % of TA patients and in 25 % of TMNG patients after the application of first fixed I-131 in our study. Hypothyroidism rates were reported as 46.2-77.4 % for GD, 8.7-39.3 % for TA and 8.9-33.3 % for TMNG in literature (Table 5).[11, 21, 23] The study of Erem et al.[21] gave the lowest rate; this might be caused by the application of 370 MBq I-131 dose in their study. Hypothyroidism rates reported in other studies were similar to our rates.

Table 5: A comparative evaluation of I-131 treatment results in patients with Graves' disease, toxic adenoma and toxic multinodular goiter with literature

		Graves' disease				**Toxic adenoma**				**Toxic multinodular goiter**			
	Dose MBq	Euthyroid	Hypothyroid	Cure #	Hyperthyroid	Euthyroid	Hypothyroid	Cure #	Hyperthyroid	Euthyroid	Hypothyroid	Cure #	Hyperthyroid
Current study	*	6.7%	66.7%	73.3%	26.7%	55.6%	27.8%	83.3%	16.7%	65.4%	25.0%	90.4%	9.6%
Erem et al.[21]	370	23.0%	46.2%	69.2%	30.8%	65.2%	8.7%	73.9%	26.1%	63.3%	8.9%	72.2%	27.8%
Ahmad et al. [11]	400-550	12.9%	77.4%	90.3%	9.7%	50.0%	39.3%	89.3%	10.7%	50.0%	33.3%	83.3%	16.7%
Allahabadi et al.[3]	185 - 370	15.0%	54.5%	69.5%	30.5%	39.7%	31.7%	71.4%	28.6%	39.7%	31.7%	71.4%	28.6%
Sharma et al.[33]	370							90.0%	10.0%				
Huysmans et al.[25]	740					92.0%	6.0%	98.0%	2.0%				
Abos et al.[34]	555									78.1%	8.4%	72.2%	9.2%
Leslie et al.[23]	235	0%	73.0%		27.0%								
	350	9.0%	65.0%		26.0%								

*: In our dose scheme, doses of I-131 administered to more than 80% of patients , 185 - 370 MBq for GD, 740 - 925 for toxic multinodular goiter MBq .
: Hypothyroidism and euthyroidism are together.

Treatment Response Period after Radioactive Iodine Treatment

Euthyroidism development time after application of a single dose was determined as 2 ± 1 months for GD patients, 2 ± 1 months for TA patients and 3 ± 1 months for TMNG patients (Table 2). Erem et al.[21], determined euthyroidism development period as 5.9 ± 5.6 months after application of fixed I-131 dose. This time was given for all patients groups and it was longer than the euthyroidism development times that we detected in our patients. Their RIT dose was quite lower than the average I-131 dose we applied (629 ± 185 MBq). This situation indicates that euthyroidism development time for patients is related to I-131 dose.

Hypothyroidism development period after application of a single dose was 3 ± 1 months in GD patients, 3 ± 1 months in TA patients and 4 ± 1 months in TMNG patients (Table 2). Catargi et al.[35] reported hypothyroidism development within 4-6 months with 74 - 111 MBq dose of I-131. Hypothyroidism developed in our GD patients earlier (2-5 months), possibly because we had applied higher doses of I-131 (185 - 370 MBq). In a study, Erem et al.[21] determined hypothyroidism development period as 6.4 ± 5.8 months in all patients. Compared to patients of Erem et al.[21], our hypothyroidism development period in GD, TA and TMNG patients were earlier, because we applied higher doses of I-131 in GD, TA and TMNG patients.

Success of the treatment in GD, TA and TMNG patients is compatible with literature. If cure criteria for TMNG are based on euthyroidism and hypothyroidism rather than euthyroidism, as in many studies present in literature (Table 4), higher cure rates are found. When we analyse rates of hypothyroidism development after RIT for each 3 groups, we notices that ones which used similar doses of I-131 obtained similar rates with us. Recurrence rates of hyperthyroidism after RIT are at acceptable values for each disease (GD, TA, TMNG). Actually, 185 - 370 MBq for GD patients and 740 - 925 MBq for TA and TMNG patients appear to be adequate doses for the efficient treatment of hyperthyroidism. Cure rates of benign thyroid diseases with I-131 are lower in male patients than in female patients. However, hypothyroidism develops more often in females than in males. RIT success rates are found lower in patients who use ATD for more than 6 months before starting RIT, compared to the patients who use ATD treatments for 6 months or less than 6 months. Because sufficient time to discontinue the ATD treatment (3-5 days) before RIT, RIT responses of the ATD using and non user patients are same. Without regarding type of disease, ATD use before RIT does not effect the rate of hypothyroidism after RIT.

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During this study, any drug company that has a direct link to the subject of the research, a company that supplies and / or produces medical instruments, equipment and materials, or any commercial firm, may have a material impact on the decision to be made during the evaluation of the study and / or no spiritual support.

Conflict of Interest

Regarding this study, authors and / or family members have no scientific or medical committee membership or relationship with members, counseling, expertise, employment status in any company, shareholding and similar situations

Author Contributions

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