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RETROSPECTIVE EVALUATION OF DIAGNOSTIC METHODS AND TREATMENT OPTIONS IN AMIODARONE-INDUCED THYROTOXICOSIS

AMİODARONA BAĞLI TİROTOKSİKOZDA TANI YÖNTEMLERİ VE TEDAVİ SEÇENEKLERİNİN RETROSPEKTİF DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: Amiodarone-induced thyrotoxicosis is an important cause of morbidity and mortality that is difficult for physicians to recognize and manage. We retrospectively analyzed the parameters used for diagnosis, classification, and treatment for amiodarone-induced thyrotoxicosis.

Material and Method: We included patients who had amiodarone-induced thyrotoxicosis (AIT). We recorded the demographics, the presence and characteristics of heart and thyroid diseases, the time and dosage of amiodarone exposure, thyroid function tests and thyroid auto-antibodies, and the diagnostic methods and management of thyroid disease.

Result: We included 25 patients (mean age: 64.1±15.3 years, 56% male) who were classified as type 1 (n:12; 48%), type 2 (n:7; 28%), and mixed-type amiodarone-induced thyrotoxicosis (AIT) (n:6; 24%). In the comparison of type 1 AIT to 2 AIT, free T3 and T4 concentrations were 5.1±1.6 pmol/L vs. 7.6±2.4 pmol/L, and 29.2±8.8 pmol/L vs. 34.9±11pmol/L, respectively. Iodine uptake measurements at the 2nd hour were positively correlated with the 24th-hour measurement (p=0.005). Antithyroid drug (n:20) was given for 24 months, glucocorticoid (n:7) and sodium perchlorate (n:5) were given for 7.4±1.7 and 3.5±2 months, respectively. The first treatment option was methimazole for type 1 AIT and methylprednisolone for type 2 AIT. The duration of remission was shorter in type 2 AIT (p=0.009). Five patients had radioactive iodine treatment, and one underwent thyroidectomy.

ÖZET

Amaç: Amiodarona bağlı tirotoksikoz (ABT) hekimler için tanıması ve yönetimi zor, morbidite ve mortalitesi yüksek bir durumdur. Bu çalışmada ABT tanısı, sınıflandırılması ve tedavi için kullanılan parametrelerin retrospektif olarak incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Amiodarona bağlı tirotoksikoz nedeniyle ayaktan tedavi gören hastalar dahil edildi. Demografik özellikler, kalp ve tiroid hastalıklarının varlığı ve özellikleri, amiodaron maruziyetinin zamanı ve dozu, tiroid fonksiyon testleri ve otoantikorları ve tiroid hastalığının tanı yöntemleri ve yönetimi kaydedildi.

Bulgular: Tip 1 (n:12; %48), tip 2 (n:7; %28) ve mikst tip (n:6; %24) ABT olarak sınıflandırılan 25 hasta (ortalama yaş: 64,1±15,3 yıl, %56'sı erkek) çalışmaya dahil edildi. Tip 1 ABT, tip 2 ABT ile karşılaştırıldığında, serbest T3 ve T4 konsantrasyonları sırasıyla 5,1±1,6 pmol/L'ye karşı 7,6±2,4 pmol/L ve 29,2±8,8 pmol/L'ye karşı 34,9±11 pmol/L idi. İkinci saat radyoaktif iyot tutulumu 24. saat radyoaktif iyot tutulumu ile pozitif korelasyon gösterdi (p=0.005). Tedavide sırasıyla, antitiroid ilaç (n=20) 24 ay, glukokortikoid (n=7) 7,4±1,7 ay ve sodyum perklorat (n=5) 3,5±2 ay kullanıldı. Tip 1 ABT için ilk tedavi seçeneği metimazol ve tip 2 ABT için metilprednizolon idi. Tip 2 ABT 'da remisyon süresi daha kısaydı (p=0,009). Beş hastaya radyoaktif iyot tedavisi, bir hastaya tiroidektomi uygulandı.

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Conclusion: The management of AITs is difficult. It should be kept in mind that these patients may need amiodarone again; therefore, ablative treatments should be planned if needed.

Keywords: Amiodarone induced thyrotoxicosis, methimazole, methylprednisolone, perchlorate

Sonuç: Amiodaron ile indüklenen tirotoksikozların yönetimi zordur. Bu hastaların tekrar amiodarona ihtiyaç duyabileceği akılda tutulmalı, bu nedenle ihtiyaç halinde ablatif tedaviler planlanmalıdır.

Anahtar Kelimeler: Amiodaron tirotoksikozu, metimazol, metilprednizolon, perklorat

INTRODUCTION

Amiodarone is a potent antiarrhythmic drug with a structure similar to thyroxine (1, 2). Amiodarone affects thyroid functions in two ways: effects that occur with the intrinsic properties of the drug and effects that are dependent on its high iodine content. While amiodarone causes destructive thyroiditis with a direct cytotoxic effect on thyroid follicles, high iodine content causes inhibition of 5'-deiodinase activity (3-6). Depending on the degree of iodine exposure, some patients remain euthyroid, while others may develop amiodarone-induced thyrotoxicosis (AIT) or hypothyroidism. The incidence of AIT is 1-23% and it can occur early or years after treatment begins (7, 8). Two types of AIT are described: Type 1 AIT occurs due to increased thyroid hormone synthesis because of the iodine excess, type 2 AIT is caused by the destructive thyroiditis. However, mixed-type AIT may have characteristics of both conditions (9,10). Despite the useful findings, it can be difficult to distinguish between types of AIT. Moreover, identification of these types is critical for the management of treatment. Withdrawal of amiodarone may not be possible for type 1 AIT or cardiologists need to restart it. On the other hand, the effect of amiodarone may persist for months after discontinuation due to its long half-life. Antithyroid agents are used until euthyroidism is achieved. In selected patients, sodium perchlorate can be added (11-13). Radioactive iodine (RAI) or thyroidectomy can be radical solutions for type 1 AIT (14).

Glucocorticoids are the choice of therapy for the treatment of type 2 AIT. After the control of thyrotoxicosis, the dose of glucocorticoids should be gradually tapered and discontinued within 2-3 months (15). In cases with stable cardiac status and requiring rapid euthyroidism, discontinuation of amiodarone and resumption after achieving euthyroidism is an option; however, prophylactic thyroid ablation therapies such as RAI or thyroidectomy should be performed before restarting amiodarone. In cases where cardiac status is unstable and amiodarone treatment is necessary, amiodarone should not be discontinued, and salvage thyroidectomy should be considered, if necessary (16-18).

Combined treatment with methimazole and methylprednisolone is the most effective and rapid treatment for mixed-type AIT. Rapid response to treatment leads to diagnose type 2 AIT, while poor response leads to type 1 AIT. Amiodarone-induced thyrotoxicosis is an important cause of morbidity and mortality. There are difficulties in identifying the types of thyrotoxicosis, and management of patients can be challenging. In this study, we aimed retrospectively to evaluate the diagnostic methods and treatment options used in AITs.

MATERIAL and METHODS

In this cross-sectional study, we included patients over 18 who had AIT and were followed-up in our outpatient clinic between 2016 and 2017 for at least three months and who agreed to participate in the study.

We recorded age, gender, underlying heart disease and thyroid disease (if any), number of patients unable to discontinue amiodarone, duration of amiodarone treatment, daily and cumulative amiodarone dose, serum concentrations of free T3 (FT3), free T4 (FT4), thyroid-stimulating hormone (TSH) values at diagnosis, FT4/FT3 ratio, levels and positivity rates of anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg), thyrotropin receptor antibody (TRAb), initial urinary iodine excretion.

We documented thyroid volume, presence of nodules (if any), and vascularity with ultrasonography (USG). Thyroid volume was calculated with the Ellipsoid formula [Ellipsoid formula: Л/6 × lobe width (cm) × lobe depth (cm) × lobe length (cm)] and summed (19).

We noted the percentages of the 1st, 2nd, and 24th-hour radioactive iodine uptake (RAIU) in I-131 scintigraphy, treatment options [antithyroid drug/glucocorticoid/sodium perchlorate (NaCLO4)] with the dosage, duration, side effects, the type and the protocols of preparation for ablative treatment models, and the final thyroid function (euthyroidism/hypothyroidism/ hyperthyroidism) status with the treatment.

The research protocol was approved by the Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 26.05.2017, No: 10). The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (20).

Statistical analysis

All data were analyzed using SPSS software version 21.0 (SPSS Inc, Chicago, IL, license number: 9E5602E4D-B7A4975). Statistical analyses were conducted in accor-

dance with international statistical reporting standards (21). Variables were expressed as mean±standard deviation or median and minimum-maximum, where appropriate. The Chi-square test or Fisher's exact test was used to compare categorical variables. The Student's t-test and adjusted t-test were used to compare independent groups. Pearson's correlation analysis was used to determine whether there was a relationship between dependent and independent variables. One-way ANOVA test was used for the comparison of continuous variables between groups, while Tukey's honestly significant difference test was used for the post-hoc analysis at follow-up.

RESULTS

Of the patients (n=25), 56% (n=14) were male, and the mean age was 64.1±15.3 years. The indication to start amiodarone was atrial fibrillation (n=14; 56%), ventricular tachycardia (n=3; 12%), other tachyarrhythmias (n=3; 12%), and was unknown in 5 (20%) patients. Twenty-two (88%) patients had no known thyroid disease before starting amiodarone, while 1 (3%) had a history of hyperthyroidism, 1 (3%) multinodular goiter, and 1 (3%) hypothyroidism. The duration of amiodarone treatment was 21 months (range=3-156), the mean daily and cumulative dose were 197±56 mg and 106.450 mg (range=3.000-949.000), respectively.

Patients were classified as type 1 (n=12; 48%), type 2 (n=7; 28%), and mixed-type AIT (n=6; 24%). In the comparison of type 1 to 2 AIT, FT3, FT4, and TSH concentrations were 5.1±1.6 pmol/L vs. 7.6±2.4 pmol/L, 29.2±8.8 pmol/L vs. 34.9±11pmol/L, and 0.09±0.02 vs. 0.04±0.01 mIU/L, respectively.

The initial FT3 concentration was positively correlated with the FT4 concentration (r=0.709, p<0.002) and was negatively correlated with the iodine uptake measurement at the 2nd hour (r=-0.964, p<0.001), whereas no significant correlation was found among the cumulative amiodarone dose, initial TSH concentration, iodine uptake measurement at the 1st and 24th hours, thyroid volume, and methimazole dose used (p>0.05). A negative correlation between FT4 and TSH concentration (r=-0.860, p<0.001) and a positive correlation between FT4 concentration and methimazole dose (r=0.539, p=0.035) were found, while no significant correlation was found among TSH concentration, iodine uptake measurement at the 1st, 2nd, and 24th hours, and thyroid volume (p>0.05).

When the iodine uptake tests were compared, a positive correlation was found between the 2nd and 24th-hour iodine uptake (r=0.774, p=0.005).

The initial 24-hour urinary iodine excretion was 1142.3±340 µg/day in patients with type 1 AIT and 3329.5±1100 µg/day in patients with type 2 AIT; there was a statistically significant difference between the two groups (p=0.002) (Table 1).

Among the thyroid auto-antibodies, anti-TPO and anti-Tg were measured in 22 patients (88%) and TRAb in 11 (44%) patients. On USG (n=19) no nodule (n=9), solitary nodule (n=2), and multiple nodular goitre (n=3) were reported.

It was not possible to discontinue amiodarone treatment in six patients (24%) after the diagnosis of thyroid dysfunction. We found no significant difference for duration and cumulative dose of amiodarone, initial FT3, FT4, TSH levels, time to euthyroidism, and iodine uptakes at the 1st, 2nd, and 24th hours when we compared the patients who continued and discontinued amiodarone.

Antithyroid drugs (n=20) were given for 24 months (range=1-120), while sodium perchlorate (n=5) was administered for three months (range=1-6). Methylprednisolone or equivalent glucocorticoid was initiated in seven patients. The daily dose and the duration was 25.5 mg (range=15-40) and 7.4 months (range=2-12), respectively.

In terms of the side effects during AIT treatment, absolute agranulocytosis and thrombocytopenia developed in one of the 25 patients. One patient had multiple vertebral fractures due to the glucocorticoid-induced osteoporosis, while no side effects were detected in patients using sodium perchlorate.

Euthyroidism in 14 (56%), subclinical hypothyroidism in 5 (20%) patients were achieved after medical treatment. However in six of them (24%) hyperthyroidism could not controlled with medical treatment. The time to euthyroidism was seven months (range=1-36), and the duration of remission was significantly shorter in type 2 AIT compared to type 1 AIT (5.6±1.4 vs. 13.3±3.8 months, p=0.009) (Table 1).

Five patients had RAI treatment, and one patient underwent thyroidectomy as a radical treatment. The mean RAI dose was 30±8 mCi. Repeated doses were needed in two patients because of persistant hyperthyroidism. The comparison of patients with type 1 and 2 AIT data was given in Table 1.

Of the patients who we could not classify as type 1 or 2 AIT and thus were defined as mixed-type AIT, 50% were female, and the mean age was 63±20 years. Only one patient in this group continued amiodarone after the diagnosis of AIT. The median duration of amiodarone treatment was 18 months (range=4-36), and the median daily dose was 200 mg (range=50-400). Free T3, FT4, and TSH levels were 9.6 pmol/L (range=5.3-14.8), 46.5 pmol/L (range=12-100), and 0.01 mIU/L (range=0-23), respectively. The anti-TPO, anti-Tg, and TRab values were 11 IU/mL (range=5.6-21), 186.5 IU/mL (range=10.8-480), and 1.5 IU/L

Table 1: The comparison of patients with type 1 and 2 amiodarone-induced thyrotoxicosis

Variables	Type 1 AIT (n=12)	Type 2 AIT (n=7)	p
Age (years)	64.2±11.6	64.7±18.9	0.773
Gender (F/M)	5/7	3/4	0.090
Number of patients unable to discontinue amiodarone	4	1	0.510
Duration of amiodarone used (months)	36 (4-156)	20.5 (3-108)	0.884
Dose of amiodarone (mg/day)	190.9±30.1	200	0.090
Free T3 at diagnosis (pmol/L)	5.1±1.6	7.6±2.4	0.140
Free T4 at diagnosis (pmol/L)	29.2±8.8	34.9±11	0.211
Free T4/Free T3 ratio	5.2 (3.7-52.7)	4.7 (3-6.6)	0.710
TSH at diagnosis (mIU/L)	0.09±0.02	0.04±0.01	0.482
Anti-TPO (IU/mL)	11±3.3	10.9±3.1	0.958
Anti-Tg (IU/mL)	183.6±59	209±67	0.860
TRAb (IU/L)	0.7 (0.01-4.4)	2.3 (0.01-4.7)	0.980
Anti-TPO positivity (n, %)	10 (40)	6 (24)	0.632
Anti-Tg positivity (n, %)	10 (40)	6 (24)	0.436
TRAb positivity (n)	2	1	0.944
Time to euthyroidism (months)	13.3±3.8	5.6±1.4	**0.009***
Thyroid volume (cm^3)	39 (18-72)	12 (10-30)	0.229
Increased vascularity in Doppler USG (n)	4	2	0.260
Presence of nodules (n)	8	1	0.235
RAIU 1. hour (%)	1.6±0.5	1.5±0.4	0.200
RAIU 2. hour (%)	1.9±0.6	1.4±0.1	**0.020***
RAIU 24. hour (%)	1.7±0.5	1.2±0.3	0.920
Initial 24-hour urinary iodine excretion (µg/day)	1142.3±340	3329.5±1100	**0.002***
Number of patients using methimazole	9	4	0.260
Dose of methimazole (mg/day)	10 (5-15)	22.5 (15-30)	0.513
Number of patients using propylthiouracil	3	0	N/A
Number of patients using methylprednisolone	1	3	0.305
Dose of methylprednisolone (mg/day)	18±2.8	28±7.3	0.490
Duration of methylprednisolone used (months)	6.5±2.1	7.5±2.3	0.870

AIT: Amiodarone-induced thyrotoxicosis, anti-Tg: Anti-thyroglobulin, anti-TPO: Anti-thyroid peroxidase, F: Female, M: Male, RAIU: Radioactive iodine uptake, TRAb: Thyrothyropine receptor antibody, TSH: Thyroid stimulating hormone, USG: Ultrasonography, *: p <0.05

(range:0-4), respectively. The median time to euthyroidism was nine months (range=5-12), the median thyroid volume was 13 cm^3 (range=7-20), and the initial 24-hour urinary iodine excretion was 1042 µg/day. The percentages of the 1st, 2nd, and 24th-hour RAIU were 2.5% (range=1.3-16), 2.4% (range=1.4-19), and 3% (range=1.2-28), respectively. Of the patients, 50% used methylprednisolone with a median dose of 32 mg (range=16-40) and with a median duration of 11 months (range=2-12), while 66.7% used methimazole with a median dose of 20 mg (range=20-25) and with a duration of 12.5 months (range:2-36).

DISCUSSION

Amiodarone is one of the most commonly used drugs for severe arrhythmias; however, it can cause amiodarone-induced thyroid dysfunction which affects morbidity and mortality rates.

In iodine-deficient regions, AIT was more frequent compared to hypothyroidism (22). The incidence of AIT was found to be high in Cape Town despite normal iodine exposure (23). It may be associated with different factors

other than iodine exposure (24). Although our country is a moderate to severe iodine-deficient region, we have no data about the prevalence of AIT.

Amiodarone-induced thyrotoxicosis is classified into type 1, where iodine uptake is increased/normal, and type 2, where iodine uptake is absent/very low (<2%); however, this distinction is not easy. Furthermore, due to the critical condition of the patient, it may not be possible to apply all diagnostic methods in the classification of AIT types. Also, during the follow-up period, it can be understood that the AIT classification made in the initial evaluation is incorrect. Amiodarone induced thyrotoxicosis is a difficult subject for many endocrinologists, and they may not have enough experience about its management. Raghavan RP et al. conducted an e-mail survey in the United Kingdom among endocrinologists on the management of AIT (25). The mean number of the cases examined in the last year by the physicians who completed the survey was 2.5. It was observed that 80% of the physicians used Anti-TPO, and 83% used the presence of goiter to differentiate between the type 1 and 2 AIT. The frequencies of the diagnostic methods used were 35% for RAIU, 35% for technetium scintigraphy, 34% for colored Doppler USG, 3.7% for serum interleukin-6, and 1.5% for urinary iodine excretion.

The number of patients in our study was 25 in two years, the main diagnostic test to differentiate the type of AIT was Anti-TPO (88%). Doppler USG was used in 52%, TRab in 44%, RAIU in 44%, thyroid USG in 36%, and urinary iodine excretion in 36%. We did not use interleukin-6 concentration. Detecting the presence of thyroid antibodies is an easy and a quick way, but mostly it is not enough to diferentiate the types of AITs.

For the initial treatment of type 1 AIT, 74% of the patients used thionamides alone, while 5.7% used thionamidesin combination with glucocorticoids in the study of Raghavan RP et al. These rates were lower than the ones in the European Thyroid Association (ETA) study. The "wait and see" approach, which was determined as 1% in the ETA study, was 6% in this study, and the difference between the rates of potassium perchlorate and thionamides combination (1.9% vs. 31%) was noteworthy (26). In the treatment of type 2 AIT, 30.8% of the patients used only glucocorticoids, and 35.6% used glucocorticoids combined with thionamides. Interestingly, 25% reported that they would use thionamides alone. However, it is known that the response to glucocorticoid treatment is better, and the symptoms improve faster in type 2 AIT (25). It can be said that the annual number of AIT cases examined by the physicians participating the study conducted in the United Kingdom was low, and the frequencies of potassium perchlorate use in type 1 AIT and glucocorticoid use in type 2 AIT were less than expected. In our study which represents a single-center approach to the management of AITs, 48% of the patients had type 1 AIT and 28% had type 2 AIT. The remaining 6 cases (24%) were classified as mixed-type AIT. In a study involving 20 patients reported from our country, 12 patients were reported to have type 1 AIT (60%), and six patients (40%) had type 2 AIT (27). Although these results are similar to these of our study, mixed-type cases also had an important place in our series.

In the present study, thionamides were used in all patients with type 1 AIT and in 57.1% of patients with type 2 AIT, while glucocorticoids were used in 28% of the patients overall. Erdoğan MF et al. evaluated the place of the stepwise approach in the treatment of AIT. Twenty patients were initially given 30-50 mg/day methimazole and 1000 mg/day potassium perchlorate for one month, and 12 patients (7-type 1 and 5-type 2) showed a significant decrease in thyroid hormones or euthyroidism. In the patients with inadequate response, 40-48 mg/day prednisolone was added in the second step, and euthyroidism was achieved in all of them. In that study, it was reported that initial classification may lead to unnecessary glucocorticoid administration, and stepwise treatment may be a good option. Also, they suggested that methimazole, potassium perchlorate, and prednisolone could be started together in severe cases (27).

In our study, one patient had a known history of multinodular goiter, and 10 patients had a nodular goiter on ultrasonographic evaluation. Increased frequency of nodules may be associated with iodine deficiency.

Radioactive iodine uptake at the 1st, 2nd, and 24th hour were measured in 11 (44%) of the patients. The 2nd hour measurement was compatible with the 24th hour measurement, and it was also a guide for AIT classification. In this context, our findings indicated that the 2nd hour RAIU measurement may be sufficient to determine a rapid treatment plan especially in severe patients.

Initial urinary iodine levels were evaluated in 17 (68%) patients. Eight of these patients had type 1 AIT, five had type 2 AIT, and four had mixed-type AIT. In our study, although initial urinary iodine level was lower in the patients with type 1 AIT than in the ones with type 2 AIT, the daily iodine excretion of both groups was >500 µg/L, indicating severe iodine exposure.

Generally, methylprednisolone 30 mg/day (or equivalent glucocorticoid) as initial therapy, and dose reduction with clinical improvement is recommended (28). In our study group, 28±7.3 mg/day prednisolone was used in type 2 AIT patients for 7.5±2.3 months. Because of the limiting effect of thyroid follicle cells destruction, recovery period of thyrotoxicosis was shorter in the patients with type 2 AIT. These findings were compatible with the literature (28).

Prophylactic thionamide to prevent the recurrence of type 1 AIT and the preparation for emergent thyroidectomy has rarely been reported in the literature. There is insufficient data to prove its efficacy and safety (29), and this method was not used in our study group.

Sodium perchlorate (NaCLO4) is a hard-to-reach treatment modality and has significant side effects, such as bone marrow suppression. Perchlorate was used in six patients at a dose of 300 mg thrice a day for 3 (1-6) months. Although it is not recommended to be used for longer than six weeks due to the risk of agranulocytosis, we needed to use perchlorate for a longer period in two patients because of the severity of thyrotoxicosis with blood cell counts checked every two weeks, and no adverse effect was noted. Seven patients received glucocorticoids and one patient developed severe osteoporosis resulting in vertebral fracture. Methimazole treatment was discontinued in a patient due to the absolute neutropenia (0/μL), and granulocyte colony-stimulating factor (G-CSF) was administered 30 mIU/day for four days. The neutropenia resolved on day five. One patient developed thrombocytopenia. The patients who experienced haematological adverse events did not receive any perchlorate treatment.

Radioactive iodine ablation therapy was administered as a radical treatment in three patients who developed complications related to the treatments, and levothyroxine replacement therapy was started after hypothyroidism was achieved.

There is no clear consensus on the discontinuation of amiodarone therapy. Arrhythmias can lead to serious complications in patients with AIT. Amiodarone is a potent antiarrhythmic, and the potential to worsen heart failure due to the negative inotropic side effects of other antiarrhythmics makes discontinuation difficult (30). On the other hand, some protective effects of amiodarone, such as its inhibitory effect on beta-adrenergic receptors, the inhibition of T4 deiodination and the blocking effects of T3 binding to thyroid receptors disappear with the discontinuation of the drug. However, it has been reported that early discontinuation would not be beneficial due to its long half-life (31). The decision to continue amiodarone should be based on cardiac findings, independent of thyroid hormone levels. In our study, amiodarone was continued in 6 (24%) patients. However, there was no information about the increase of arrhythmias in patients who discontinued the drug in the early period.

In our case group, RAI was preferred in 5 (20%) patients, and thyroidectomy was preferred in 1(4%) as radical solutions. Radioactive iodine treatment is not possible in the early period due to iodine contamination and low RAIU. If amiodarone can be discontinued, RAI treatment should be administered approximately 6-12 months later when the urinary iodine level normalizes and the RAIU reaches a sufficient level.

The new ETA guideline does not recommend the use of recombinant TSH (rhTSH) as it may increase the risk of exaggerated T4 increase and thus arrhythmia risk (28). However, our cases were managed before the publication of this guideline. Thus, with a single dose of rhTSH 0.9 mg/mL intramuscularly, FT4 concentration was increased 49 pmol/L to 100 pmol/L. The patient did not experience any cardiac deterioration or life-threatening arrhythmia during this period, and developed hypothyroidism in the 4th month of the treatment. It should also be kept in mind that some patients with low/absent RAIU values in the initial evaluations may have increased iodine intake during the follow-up and may have become eligible for RAI treatment.

According to the ETA guideline, thyroidectomy is currently the best option for rapid restoration of euthyroidism (28). However, in our series, only one patient underwent thyroidectomy, and we were inferior to the literature. Thyroidectomy is recommended without delay in AIT patients with impaired cardiac function or severe underlying cardiac disease and in patients whose thyrotoxicosis does not respond to medical therapies. It may be considered especially in type 1 AIT patients who have to continue amiodarone, have an autonomous thyroid gland, and in type 2 AIT patients with a high probability of relapse; however, preparation with glucocorticoids, β-blockers or plasmapheresis should be performed immediately before the surgery. We did not perform salvage thyroidectomy. Preferring RAI treatment more than thyroidectomy is probably associated with our conservative approach.

The present study had several limitations. We used retrospective records, which are not considered to be the best data sources. The sample size was not large enough. Due to the cross-sectional nature of the study, we could not establish causality by design, but could only describe relationships. Another limitation was that the results could not be generalized to the whole country, given the differences between regions and iodine replacement/depletion characteristics. Furthermore, it was clinically difficult to distinguish between the AIT types; for example, a pre-existing inflammatory process in the thyroid tissue makes typing increasingly difficult and is misinterpreted as mixed thyrotoxicosis. On the other hand, there were a limited number of studies on AIT in our country (27, 32). The numbers of patients in these studies were 20 and 4. In this regard, we consider that our study will contribute to filling the gaps in the literature. Furthermore, the comprehensive assessment performed in the present study was noteworthy. Our study was conducted in the largest metropolis in the country, and therefore, we believe that our study will elucidate the gaps about the management of AITs.

CONCLUSION

The management of AITs is difficult. Amiodarone-induced thyroid dysfunctions require the cooperation of endocrinologists and cardiologists. It is a fact that studies evaluating the awareness of cardiologists are also needed. An awareness questionnaire could be planned for patients using amiodarone to ask whether thyroid functions and thyroid antibodies are evaluated before starting treatment, how often thyroid functions are checked under treatment, and whether they refer to an endocrinologist when a problem is detected. Multicenter studies are needed in our country to determine the diagnostic tools, treatment approaches. It should be kept in mind that these patients may need amiodarone again; therefore, ablative treatments should be planned if needed.

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