

Original article

Factors Predicting Treatment Failure in Patients Treated with Iodine-131 for Graves' Disease

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Abstract

Treatment of Graves' disease with iodine-131 (¹³¹I) is well-known; however, all patients do not respond to a single dose of ¹³¹I and may require higher and repeated doses. This study was carried out to identify the factors, which can predict treatment failure to a single dose of ¹³¹I treatment in these patients. Data of 150 patients with Graves' disease treated with 259-370 MBq of ¹³¹I followed-up for at least 1-year were retrospectively analyzed. Logistic regression analysis was used to predict factors which can predict treatment failure, such as age, sex, duration of disease, grade of goiter, duration of treatment with anti-thyroid drugs, mean dosage of anti-thyroid drugs used, ^{99m}Tc-pertechnetate (^{99m}TcO₄⁻) uptake at 20 min, dose of ¹³¹I administered, total triiodothyronine and thyroxine levels. Of the 150 patients, 25 patients required retreatment within 1 year of initial treatment with ¹³¹I. Logistic regression analysis revealed that male sex and ^{99m}TcO₄⁻ uptake were associated with treatment failure. On receiver operating characteristic (ROC) curve analysis, area under the curve (AUC) was significant for ^{99m}TcO₄⁻ uptake predicting treatment failure (AUC = 0.623; *P* = 0.039). Optimum cutoff for ^{99m}TcO₄⁻ uptake was 17.75 with a sensitivity of 68% and specificity of 66% to predict treatment failure. Patients with >17.75% ^{99m}TcO₄⁻ uptake had odds ratio of 3.14 (*P* = 0.014) for treatment failure and male patients had odds ratio of 1.783 for treatment failure. Our results suggest that male patients and patients with high pre-treatment ^{99m}TcO₄⁻ uptake are more likely to require repeated doses of ¹³¹I to achieve complete remission.

Keywords: Graves' disease, iodine-131 therapy, technetium-99m uptake, treatment failure

Introduction

Graves' disease is the most common cause of thyrotoxicosis.^[1] Treatment options for Graves' disease include anti-thyroid drugs, iodine-131 (¹³¹I) treatment and surgery.^[2] Though anti-thyroid drugs are the usual initial treatment of choice, durable complete remission is infrequently achieved with anti-thyroid drugs alone and relapse rates can be 50-90% in patients with nodular goiters.^[3-6] Radio-iodine ablation and surgery aim at reducing functioning thyroid volume, thereby reducing triiodothyronine (T3) and thyroxine (T4) secretion. ¹³¹I treatment is preferred over surgery as it is

simple, safe and easy to administer with good response rates. However, some patients do not achieve complete remission with standard doses of ¹³¹I and it is important to know the facts that induce treatment failure. In clinical practice ¹³¹I uptake determined by thyroid uptake probe and scintigraphy is used to calculate the dosage for ¹³¹I treatment.^[7,8] Conventional thinking is that that high ¹³¹I uptake at 24 h predicts favorable outcome to treatment with ¹³¹I. However, few studies have suggested that high ¹³¹I uptake can be associated with treatment failure with ¹³¹I.^[9,10] Thyroid uptake of ^{99m}TcO₄⁻ analogous to ¹³¹I uptake also measures functional activity of the thyroid gland, can be calculated by a gamma camera based method and is simple to apply. Significance of pre ¹³¹I treatment ^{99m}TcO₄⁻ uptake in the treatment of Graves' disease has not been widely evaluated. Zantut-Wittmann *et al.* in a study of 82 patients have reported that high pre ¹³¹I treatment ^{99m}TcO₄⁻ uptake and larger goiter are associated with a higher rate of treatment failure.^[11] Other workers reported a very good correlation between pre ¹³¹I treatment ^{99m}TcO₄⁻ uptake and the thyroid volume

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measured by ultrasonography (USG) suggesting a potential role of pre ^{131}I treatment $^{99\text{m}}\text{TcO}_4^-$ uptake in predicting the response to ^{131}I .^[12] The current study was aimed at finding out if pre ^{131}I treatment $^{99\text{m}}\text{TcO}_4^-$ uptake can predict treatment failure. The relevant factors such as age, sex, duration of disease, grade of goiter (according to WHO grading of goiter), duration of treatment with anti-thyroid drugs, dosage of anti-thyroid drugs, dose of ^{131}I administered, total T3 and T4 levels, which can be potentially associated with the treatment failure were also studied.

Materials and Methods

A total of 150 patients with diagnosis of Graves' disease treated with ^{131}I treatment (259–370 MBq) were included in the study. All the patients were diagnosed to have Graves' disease based on the clinical, biochemical and thyroid scan findings. All the patients underwent thyroid scan 20 min after intravenous injection of 148–185 MBq of $^{99\text{m}}\text{TcO}_4^-$ prior to ^{131}I therapy (within 30 days). Static planar image of head and neck was acquired for a period of 2 min. $^{99\text{m}}\text{TcO}_4^-$ uptake was calculated by camera based method using standard software. After treatment, all the patients were followed-up for a period of minimum 1 year with first follow-up being at 6–8 weeks followed by every 3 months. Follow-up included clinical examination, T3, T4, and thyroid-stimulating hormone estimation. Recurrence or treatment failure was diagnosed when thyrotoxic symptoms persisted or recurred within 6 months after administration of the first dose of ^{131}I . Binary logistic regression analysis was performed, including age, sex, duration of disease, Grade of goiter (according to WHO grading of goiter), duration of treatment with anti-thyroid drugs, dosage of anti-thyroid drugs, $^{99\text{m}}\text{TcO}_4^-$ uptake at 20 min, dose of ^{131}I administered (in mCi), total T3 and T4 levels. $P < 0.05$ was considered as significant.

Results

Of the 150 patients (111 female, 39 male; mean age 39 years; age range 16–71 years), 25 required retreatment with ^{131}I within 1 year. Duration of disease ranged from 1 to 12 years with a median of 5.7 years. Mean methimazole dose was 25 mg (range 10–60 mg) and mean duration of drug treatment was 6 months (range 1–30 months). Thirty-one patients had no goiter, 34 patients had grade I goiter, 85 patients had grade II goiter. None of the patients had heart failure or other significant co-morbidities. $^{99\text{m}}\text{TcO}_4^-$ uptake at 20 min ranged from 3.1% to 60% with a mean of 17.43. Mean T3 and T4 values were 2.65 ng/l (range 0.8–6.0), 12.88 $\mu\text{g}/\text{dl}$ (range 0.4–28), respectively. Binary logistic regression analysis revealed that male sex ($P = 0.029$) and $^{99\text{m}}\text{TcO}_4^-$ uptake

were associated with treatment failure ($P = 0.034$). On ROC curve analysis, area under the curve (AUC) was statistically significant for $^{99\text{m}}\text{TcO}_4^-$ uptake for predicting treatment failure (AUC = 0.623; $P = 0.039$). Optimum cut-off for $^{99\text{m}}\text{TcO}_4^-$ uptake was 17.75% with a sensitivity of 68% and specificity of 66% to predict treatment failure. Of 150 patients, 61 had $^{99\text{m}}\text{TcO}_4^-$ uptake $>17.75\%$, and treatment failure was observed in 17/61 (27.86%). Odds ratio was 3.14 ($P = 0.014$) for patients with $^{99\text{m}}\text{TcO}_4^-$ uptake $>17.75\%$ to predict treatment failure. Whereas, only 8 out of 89 patients (8.98%) with $^{99\text{m}}\text{TcO}_4^-$ uptake $<17.75\%$ were found to have treatment failure. Treatment failure was noted in 16/111 (14.44%) female patients and 9/39 (23%) patients leading to an odds ratio of 1.783 for male sex to predict treatment failure [Table 1]. Figure 1 shows thyroid scan of two patients (a) having very high pertechnetate uptake and (b) moderately increased pertechnetate uptake.

Discussion

Anti-thyroid drugs, surgery and ^{131}I are the options for treatment of Grave's disease.^[1] Anti-thyroid drugs though the first line of treatment do not cure the disease and

Table 1: $^{99\text{m}}\text{TcO}_4^-$ uptake values and gender in predicting treatment failure to ^{131}I therapy

Total number of patients (n=150)	Treatment failure (n=25) (%)	No treatment failure (n=125) (%)	Odds ratio
TcO_4^- uptake $\geq 17.75\%$ (n=61)	17/61 (28)	44/61 (72)	3.14 for high TcO_4^- uptake
TcO_4^- uptake $< 17.75\%$ (n=89)	8/89 (9)	81/89 (91)	
Males (n=39)	9 (23.0)	30 (77)	1.783 for male sex
Females (n=111)	16 (14.4)	95 (85.6)	

¹³¹I: Iodine-131; ^{99m}TcO₄⁻: ^{99m}Tc-pertechnetate

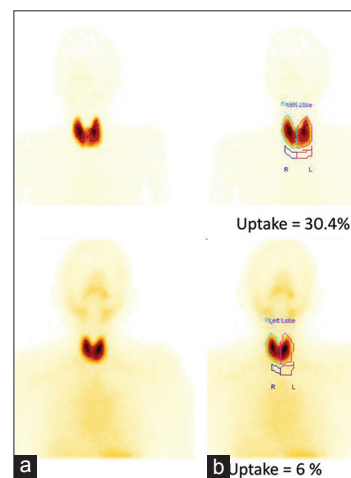


Figure 1: $^{99\text{m}}\text{Tc}$ -pertechnetate thyroid scan of two patients (a) showing very high uptake of 30% and had to be retreated within 1-year of iodine-131 (^{131}I) therapy, (b) showing moderately high uptake of 6% and was euthyroid during 1-year follow-up, after a single dose of ^{131}I therapy

relapse occurs in about 50% of the patients.^[2,3] Surgery and ¹³¹I therapy offer permanent cure. ¹³¹I is considered as treatment of choice in preference to surgery for treatment of Grave's disease. Surgery is usually reserved for patients with radio-iodine resistant disease or patients with large goiters with pressure symptoms or with cosmetic concerns. Advantages of ¹³¹I therapy are that it is simple, safe and easy to administer and can be carried out as an outpatient procedure. However, a fraction of patients do not respond to a single dose of ¹³¹I and repeated doses might be required to achieve complete remission. Most common cause implicated for treatment failure is inadequate dose delivered to thyroid gland. Two broad methodologies to calculate dosage of ¹³¹I which are empirical and dosimetry based methods. Dosimetry based method aims at achieving high rates of cure and euthyroidism, but these methods cause higher utilization of resources.^[13] Empirical method is simple and includes administration of a fixed dose of ¹³¹I. However, empirical dose, which needs to be administered to achieve high cure rates, has remained a constant matter of debate. Many studies addressing this topic have shown that empirical therapy is not inferior to dosimetry based therapy and higher dose (370 MBq) is associated with higher cure rates than lower doses (185 MBq).^[14-16] Moreover, aim of treatment of Grave's disease is to achieve either euthyroidism or hypothyroidism and so treatment with higher doses remains a logical choice with acceptable higher risk of hypothyroidism.^[17] However, even with higher doses of up to 370 MBq dose a fraction of patients do not respond to a single dose of therapy.^[9] Our study was aimed to identify the factors associated with treatment failure with higher dose of ¹³¹I and thus lead to further studies aimed at increasing dose still higher to increase cure rates. In this study, all the patients received a higher dose of 259–370 MBq (mean dose of 305 MBq). Twenty-five (16.6%) patients had to be retreated within a year and complete remission was achieved in 125 patients, and cure rate was (83.4%). This is higher than complete remission rates achieved with a lower dose (around 185 MBq) and consistent with studies reporting higher success rates with higher dose of ¹³¹I.^[9,14] In our study, male sex was associated with increased failure rates and is in concordance with previous studies.^[9] Few earlier studies have reported that patients with large goiters have poor response rates,^[18] however in our study, large goiter was not predictor of treatment failure. This might be due to the fact that in our study goiter was graded visually according to new WHO classification^[19] and also no quantification of the volume was done. Quantification of thyroid volume by USG or other modalities would have probably revealed the significance of thyroid volume in predicting the treatment failure. Other parameters considered like age, duration of disease, mean dose or duration of methimazole used did not predict treatment failure in our study. Importantly intake of anti-thyroid drugs did not influence the outcome

in our study, which might be due to the higher dose of ¹³¹I used as well as due the fact that anti-thyroid drugs were stopped 7 days prior to ¹³¹I therapy, which decreases the incidence of treatment failure.^[20,21] ^{99m}TcO₄⁻ uptake at 20 min showed significant AUC with ROC curve analysis and the cut-off of 17.75% was able to predict treatment failure with sensitivity and specificity of 68% and 66%. Furthermore, patients with ^{99m}TcO₄⁻ uptake greater than 17.75% had odds of 3.14; implying 3 times higher risk for treatment failure than patients with uptake <17.75. This finding is in contrast to the conventional thinking that patients with ¹³¹I or ^{99m}TcO₄⁻ avid disease should achieve better cure rates due to high uptake and consequent higher dose received to thyroid gland. However, ^{99m}TcO₄⁻ uptake might reflect total functioning thyroid volume and might suggest that large functional volumes might require still higher doses to achieve complete remission. Similar results have also been reported by Zantut-Wittmann *et al.*^[11] In a study by Allahabadia *et al.* which included 813 patients the authors concluded that male patients with large goiters are more likely not to respond to a single dose of ¹³¹I even with high doses of 370 MBq and are concordant with our results.^[9] Another study showed that high ¹³¹I uptake is associated with poor outcome and is concordant with our results.^[10] Though we suggest that high ^{99m}TcO₄⁻ uptake might reflect higher functioning thyroid volume, possibility of poor response due to rapid turnover of ¹³¹I pool resulting in low retention of ¹³¹I in thyroid gland cannot be ruled out. However, taking into consideration the results of previous studies it appears that high ^{99m}TcO₄⁻ uptake might more likely represents higher functional volume and thus might require repeated doses of ¹³¹I to achieve a complete cure remains most logical explanation. Limitations of our study are retrospective nature of study, relatively smaller population group of 150 patients. No direct comparison was made with ¹³¹I uptake studies. Furthermore, thyroid volumes were not calculated by USG, but were graded according to WHO grade of goiter scale. Total T3 and T4 values were used for the analysis and not free T3 and T4 levels.

Conclusion

Our study suggests that 80% of the patients achieve complete remission with a single dose of 259–370 MBq. However, male patients and patients with high ^{99m}TcO₄⁻ uptake require additional doses to achieve complete remission. Whether the outcome of these patients can be improved by giving still higher initial doses of ¹³¹I needs to be addressed by further studies.

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