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 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, 99mTc-pertechnetate (99mTcO4-) 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 99mTcO4- uptake were associated with treatment failure. On receiver operating characteristic (ROC) curve analysis, area under the curve (AUC) was significant for 99mTcO4- uptake predicting treatment failure (AUC = 0.623; P = 0.039). Optimum cutoff for 99mTcO4- uptake was 17.75 with a sensitivity of 68% and specificity of 66% to predict treatment failure. Patients with >17.75% 99mTcO4- 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 99mTcO4- 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 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 99mTcO4- 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 99mTcO4- 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 99mTcO4- 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 99mTcO4- uptake and the thyroid volume...
measured by ultrasonography (USG) suggesting a potential role of pre-131I treatment 99mTcO4 uptake in predicting the response to 131I. The current study was aimed at finding out if pre-131I treatment 99mTcO4 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 131I 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 131I treatment (259–370 MBq) were included in the study. All the patients were diagnosed to have Graves’s 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 99mTcO4 prior to 131I therapy (within 30 days). Static planar image of head and neck was acquired for a period of 2 min. 99mTcO4 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 131I. 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, 99mTcO4 uptake at 20 min, dose of 131I 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 131I 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. 99mTcO4 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 µg/dl (range 0.4–28), respectively. Binary logistic regression analysis revealed that male sex (P = 0.029) and 99mTcO4 uptake were associated with treatment failure (P = 0.034). On ROC curve analysis, area under the curve (AUC) was statistically significant for 99mTcO4 uptake for predicting treatment failure (AUC = 0.623; P = 0.039). Optimum cut-off for 99mTcO4 uptake was 17.75% with a sensitivity of 68% and specificity of 66% to predict treatment failure. Of 150 patients, 61 had 99mTcO4 uptake >17.75%, and treatment failure was observed in 17/61 (27.86%). Odds ratio was 3.14 (P = 0.014) for patients with 99mTcO4 uptake >17.75% to predict treatment failure. Whereas, only 8 out of 89 patients (8.98%) with 99mTcO4 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 131I 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 were not able to predict treatment failure. The diagnostic potential role of 99mTcO4 uptake in predicting treatment failure was noted in 17/61 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.

**Table 1: 99mTcO4 uptake values and gender in predicting treatment failure to 131I therapy**

| Total number of patients | Treatment failure | No treatment failure | Odds ratio |
|--------------------------|-------------------|----------------------|------------|
| (n=150)                  | (n=25) (%)        | (n=125) (%)          |            |
| 99mTcO4 uptake ≥17.75%   | 17/61 (28)        | 44/61 (72)           | 3.14 for high |
| 99mTcO4 uptake <17.75%   | 8/89 (9)          | 81/89 (91)          | 1.783 for female sex |
| Males (n=39)             | 9 (23.0)          | 30 (77)             |            |
| Females (n=111)          | 16 (14.4)         | 95 (85.6)           |            |

**Figure 1:** 99mTc-pertechnetate thyroid scan of two patients (a) showing very high uptake of 30% and had to be retreated within 1-year of iodine-131 (131I) therapy, (b) showing moderately high uptake of 6% and was euthyroid during 1-year follow-up, after a single dose of 131I 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, aid 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.[8,14] 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] 99mTcO₄⁻ 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 99mTcO₄⁻ 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 99mTcO₄⁻ avid disease should achieve better cure rates due to high uptake and consequent higher dose received to thyroid gland. However, 99mTcO₄⁻ 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 discordant with our results.[10] Though we suggest that high 99mTcO₄⁻ 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 99mTcO₄⁻ 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 99mTcO₄⁻ 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.

**References**

1. Sharma M, Aronow WS, Patel L, Gandhi K, Desai H. Hyperthyroidism. Med Sci Monit 2011;17:RA85-91.
2. Lynn WR, Lynn JA. Tailor treatment to the patient in thyrotoxicosis. Practitioner 2007;251:37,39,41.
3. Lippe BM, Landaw EM, Kaplan SA. Hyperthyroidism in children treated with long term medical therapy: Twenty-five percent remission every two years. J Clin Endocrinol Metab 1987;64:1241-5.
4. Allamnic H, Fauchet R, Orgiazzi J, Madec AM, Genestet B, Lorcy Y, et al. Antithyroid drugs and Graves’ disease: A prospective randomized evaluation of the efficacy of treatment duration. J Clin Endocrinol Metab 1990;70:675-9.
5. Freitas J E. Therapeutic options in the management of toxic and nontoxic nodular goiter. Semin Nucl Med 2000;30:88-97.
6. Reinwein D, Benker G, Lazarus JH, Alexander WD. A prospective randomized trial of antithyroid drug dose in Graves’ disease therapy. European Multicenter Study Group on Antithyroid Drug Treatment. J Clin Endocrinol Metab 1993;76:1516-21.
7. Nota S, Molyvdas-Athanassopoulou E, Siountas A, Dedoussis E, Papanastasiou E, Sparrakos K. Optimizing the protocol for the calculation of the doses of (131)I administered for the treatment of benign thyroid disease. Hell J Nucl Med 2004;7:14-7.
8. Al-Sharif AA, Abujbara MA, Chiachio S, Ajlouni KM, Mariani G. Contribution of radioactive iodine uptake measurement and thyroid scintigraphy to the differential diagnosis of thyrotoxicosis. Hell J Nucl Med 2010;13:132-7.
9. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklin JA. Radioiodine treatment of hyperthyroidism-prognostic factors for outcome. J Clin Endocrinol Metab 2001;86:3611-7.
10. Damle N, Bal C, Single A, Maharan S, Reddy R, Kumar P, et al. Is 185 MBq radioiodine the optimal dose for therapy of pediatric Graves’ disease? J Nucl Med, 2010; 51 (Suppl 2):202.
11. Zantut-Wittmann DE, Ramos CD, Santos AO, Lima MM, Panzan AD, Facuri FV, et al. High pre-therapy [131]I pertechnetate thyroid uptake, thyroid size and thyrostatic drugs: Predictive factors of failure in [131]I iodide therapy in Graves’ disease. Nucl Med Commun 2009;26:957-63.
12. Vieira L de O, Kuhro R, Sapienenza MT, Willegaignon J, Chammas MC, Coura-Filho GB, et al. Correlation between thyroid volume determined either by ultrasound or by scintigraphy and its implications in dosimetric radioiodine calculations in Graves disease treatment. Arq Bras Endocrinol Metabol 2011;55:696-700.
13. Shapiro B. Optimization of radioiodine therapy of thyrotoxicosis: What have we learned after 50 years? J Nucl Med 1993;34:1638-41.
14. Sanayal D, Mukhopadhayay P, Pandit K, Chatterjee J, Raychaudhuri M, Mukherjee S, et al. Early treatment with low fixed dose (5 mCi) radioiodine therapy is effective in Indian subjects with Graves’ disease. J Indian Med Assoc 2008;106:360-1,372.
15. Canadas V, Villar L, Moura E, Brito A, Castellar E. Evaluation of radioiodine therapy with fixed doses of 10 and 15 mCi in patients with Graves’ disease. Arq Bras Endocrinol Metabol 2007;51:1069-76.
16. Collier A, Ghosh S, Hair M, Malik I, McGarvie J. Comparison of two fixed activities of radioiodine therapy (370 vs 555 MBq) in patients with Graves’ disease. Hormones (Athens) 2009;8:273-8.
17. Stokkel MP, Handkiewicz Junak D, Lassmann M, Dietlein M, Luster M. EANM procedure guidelines for therapy of benign thyroid disease. Eur J Nucl Med Mol Imaging 2010;37:2218-28.
18. Andrade VA, Gross J L, Maia AL. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves’ hyperthyroidism: One-year follow-up of a prospective, randomized study. J Clin Endocrinol Metab 2001;86:3488-93.
19. World’s Health Organisation. United Nations Children’s Fund and International Council for control of iodine deficiency disorders and the control through salt iodization, Geneva: WHO/NUT/94.6, World Health Organisation; 1994. p. 1-55.
20. Walter MA, Christ-Crain M, Schindler C, Müller-Brand J, Müller B. Outcome of radioactive therapy without, on or 3 days off carbimazole: A prospective interventional three-group comparison. Eur J Nucl Med Mol Imaging 2006;33:730-7.
21. Pirnat E, Zaletel K, Gabriček S, Hojker S. The outcome of 131I treatment in Graves’ patients pretreated or not with methimazole. Hell J Nucl Med 2011;14:25-9.

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