

Research paper

The predictive role of 24h RAIU with respect to the outcome of low fixed dose radioiodine therapy in patients with diffuse toxic goiter

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ABSTRACT

Radioactive iodine uptake (RAIU) is a test used to differentiate hyperthyroidism from thyroiditis and to calculate the radioiodine dose for treatment of Graves' disease. We aimed to evaluate the predictive role of 24h RAIU with respect to the outcome of radioiodine therapy in patients with diffuse toxic goiter (DTG). **METHODS:** Case records of patients with DTG treated with radioactive iodine were reviewed retrospectively. Patients were divided into two groups based on 24h RAIU (normal range: 15% - 35% at 24 h): the first group included patients with 24h RAIU values equal to or less than 50%, while the second group included patients with 24h RAIU values of over 50%. Gland size, duration of disease, treatment with antithyroid drugs (ATD) and its duration were the other factors considered. Success of the first dose of ¹³¹I was defined as a euthyroid or hypothyroid status at 12 months post-therapy without the need for additional radioiodine or ATD therapy. Data were analyzed with 95% power and 1% type I error ($\alpha=0.01$). **RESULTS:** Six hundred thirty-three (633) consecutive patients with DTG were given a fixed-dose (5mCi) of radioiodine between January 1987 and December 2006. One hundred seventy-five patients (175) had an RAIU $\leq 50\%$ and 458 patients had an RAIU $> 50\%$. First-dose success rate in the former group was 81.7% and in the second group 68.6% ($p=0.001$). The overall first-dose success was 72%. Multivariate analysis confirmed the significant role of 24h RAIU data to predict a successful outcome. **CONCLUSION:** A 24h RAIU value of $\leq 50\%$ appears to be associated with a significantly better outcome compared to that of a 24h RAIU value of $> 50\%$ in patients with DTG given as treatment a fixed dose of 185 MBq radioiodine.

Key words: Diffuse toxic goiter, First-dose success, Radioactive iodine uptake

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INTRODUCTION

Diffuse toxic goiter (DTG) is the most common etiology of hyperthyroidism, with radioiodine therapy, ATD and surgery being the available modalities for treatment of this condition. Radioiodine therapy is

used as the preferred modality of treatment due to its simplicity, cost-effectiveness and low complication rates.¹⁻³ In addition, it is the treatment of choice in relapsed Graves' disease and hyperthyroidism due to toxic nodules.⁴ However, there is a lack of consensus regarding the ideal dosage of radioiodine therapy. The regimens used include fixed activities (80, 185, 370, 555 MBq) as well as activities calculated on the basis of gland size, radioactive iodine uptake (RAIU), effective half-life of ¹³¹I and target dose.⁵⁻⁹ Multiple factors including use of ATD, age of onset of disease, gender, etiology of the hyperthyroidism, radioiodine dose regimen, goiter size and RAIU are among those investigated to determine response to radioiodine therapy.¹⁰

The RAIU test is an old test and has been used for differentiating thyroiditis from hyperthyroidism, calculation of ¹³¹I dose for thyroid ablation and for prediction of the outcome of radioiodine treatment. The former two indications are well established; however, the last is controversial. The significance of RAIU in the success of the first dose of radioiodine remains uncertain. Generally, high RAIU is widely considered as a favorable factor for the success of radioiodine therapy.¹¹ However, several studies have suggested that there is no relationship between uptake and cure rate in the range of RAIU varying from 30% to 100%.⁷ Recently, an inverse correlation has been found between pre-treatment iodine uptake and a successful outcome.¹² Other authors have observed a poorer outcome in patients with high 24h RAIU after radioiodine treatment for hyperthyroid disease when the therapeutic dose was calculated on the basis of a 24h RAIU.¹³ The aim of our work was to evaluate this debatable issue by designing a statistically sound study with alpha of 0.01 and power of 95% to determine whether a 24h RAIU is useful in predicting the outcome of radioiodine therapy in Graves' disease.

MATERIALS AND METHODS

Our population was composed of patients presenting to our Thyroid Clinic and found to be suffering from diffuse toxic goiter. These patients were given as treatment a fixed-dose of 185 MBq radioiodine between January 1987 and December 2006. Inclusion criteria were: a) patients with diffuse goiter on

palpation and/or thyroid scan, b) off ATD for at least three days prior to the 24h RAIU test, c) no history of intake of other medications potentially interfering with the 24h RAIU test and d) 24h RAIU values which excluded subacute thyroiditis or extrathyroidal thyrotoxicosis. Patients excluded from this study were those having: a) multinodular goiter, b) solitary autonomously functioning nodule, c) history of intake of other medications potentially interfering with the RAIU test. RAIU was performed in our Department of Nuclear Medicine at 2h and 24h after oral administration of 185-370kBq (5-10 μ Ci) ¹³¹I with normal laboratory values being 5-15% at 2h and 15-35% at 24h. Clinical examination, RAIU, thyroid profile and detailed history relevant to the disease were reviewed. As per our Institutional Protocol, the gland size had been graded from 0-3 (0-not palpable/normal, 1-mildly enlarged, 2-moderately enlarged, 3-grossly enlarged) before therapy. According to RAIU, the patients were classified into two groups: 1) a low uptake group with a 24h RAIU equal to or less than 50% and 2) a high uptake group with 24h RAIU of more than 50%. Age, sex, duration of disease, treatment with ATD and its duration were also reviewed. Post-therapy follow-up was performed every three months via clinical, biochemical and RAIU examination for a period of one year. Our patients were classified into persistent hyperthyroid, euthyroid and hypothyroid groups based on the follow-up biochemical and clinical assessment. First-dose success was defined as euthyroidism or hypothyroidism and no requirement for repeat radioiodine/ATD therapy during the year-long follow-up period, while first-dose failure was defined as persistent hyperthyroidism necessitating further treatment with radioiodine/ATD.

For our statistical analysis SPSS software was used. We performed the Chi-square test to check the dependence of individual explanatory variable and outcome variable in the absence of other explanatory variables. However, since univariate analysis does not give any indication of the significance of an explanatory variable in the presence of other such variables, we used multivariate analysis. In our analysis, we have used the dichotomous logistic regression method. The beta coefficients were calculated using maximum likelihood estimation (Table 4). The goal of the analysis using this method was to find the best

fitting yet biologically most reasonable model to describe the relationship between an outcome and a set of explanatory variables. We have also calculated odds ratio for each significant explanatory variable.

RESULTS

A total of 633 patients (449 female, 184 male) with diffuse toxic goiter were included in our study. Mean age of our patients was 38.2yr (range 14 - 75yrs). As for age, 488 patients were ≤ 45 yrs at the time of radioiodine ablation while the remaining 145 were > 45 yrs. According to 24h RAIU, there were 175 patients in the low uptake group and 458 in the high uptake group. Four hundred fifty-five patients (455) achieved cure with a single dose of ^{131}I and the remaining 178 patients needed more than one dose. Table 1 compares different patient variables between the groups of patients successfully treated with the first dose of radioiodine and the patients who had

persistent hyperthyroidism after the first dose of radioiodine. Table 2 compares different variables between the patients with high and low radioiodine uptake. Thus, the overall first-dose success was 72%. Success rate in females (449) was 73.9% and in males (184) it was 66.8% (p -value = 0.07). The success rates were comparable between the younger and older patient groups (73.3% in ≤ 45 yrs group and 66.9% in the > 45 yrs group; $p = 0.13$). First-dose success rate was 81.7% in the low uptake group and 68.1% in the high uptake group, a difference which was significant ($p = 0.001$).

For post-hoc univariate analysis considering the influence of duration of disease, patients were divided into two groups: group 1 with ≤ 12 months duration and group 2 with > 12 months duration of disease. First-dose success rate in the two groups was 75.9% and 68.3%, respectively ($p = 0.03$). In the assessment of the effect of ATD, 505 patients had already taken

Table 1. comparison of characteristics of patients with first dose success versus first dose failures

		First dose		P Values
		Success	Failure	
Age (yrs)	Mean	38	39	0.25
	Median	38	38	
	Range	15-75	14-70	
	SD	9	10	
	≤ 45 Yrs	73.3%	26.7%	
	> 45 yrs	66.9%	33.1%	
Sex	Male	123 (66.8%)	61 (33.2%)	0.07
	Female	332 (73.9%)	117 (26.1%)	
24h RAIU %	Mean	60	65	0.001
	SD	17	17	
Duration of disease (months)	Mean	29	38	0.008
	Median	18	24	
	SD	37	39	
	≤ 12 months	75.9%	24.1%	
	> 12 months	68.3%	31.7%	
ATD intake	+	352 (69.7%)	153 (30.3%)	0.004
	-	103 (80.5%)	25 (19.5%)	
ATD intake	≤ 1 Yr	70.4%	29.6%	0.55
	> 1 Yr	68.5%	31.5%	
Total		455 (71.9%)	178 (28.1%)	

Table 2. Comparison of characteristics of patients with RAIU $\leq 50\%$ versus those with RAIU $> 50\%$

		RAIU $\leq 50\%$	RAIU $> 50\%$	p-values
First dose success		81.7%	68.6%	0.001
Age (yrs)	Mean	38	38	> 0.99
	Median	38	38	
	Range	18-70	14-75	
	SD	9.5	9.5	
Sex	Male	62 (33.7%)	122 (66.3%)	0.19
	Female	113 (25.2%)	336 (74.8%)	
Duration of disease (months)	Mean	31.7	31.9	0.95
	Median	18	18	
	SD	37.4	37.4	
ATD intake \pm		132/43	373/85	0.41

an ATD and the remaining 128 patients were drug naive at the time of radioiodine therapy. The former population had a success rate of 69.7% as against the latter population with a success rate of 80.5%. Patients not treated with ATD had a significantly better outcome compared to those with prior ATD treatment ($p = 0.004$). In the assessment of the effect of duration of ATD intake, it was observed that 292 patients who had taken the drug for a period of more than one year had a success rate of 68.5%, whereas 213 patients who had taken ATD for a period of less than one year had a success rate of 70.4% ($p = 0.55$).

Out of 631 patients (gland size of two patients was not recorded in the chart), 82 did not have goiter and their success rate was 90.2%. Two hundred eighty-eight (288) patients had mild goiter and their success rate was 79.5%. Two hundred forty-four (244) patients had moderate goiter and their success rate was 58.6%. Finally, 17 patients had severe goiter and their success rate was 41.2% (Table 3). Gland size and success rate of ablation were thus inversely related ($p < 0.001$). To summarize, univariate analysis revealed gland size, 24h RAIU, treatment with ATD and duration of disease as statistically significant variables affecting outcome of radioiodine therapy. Multiple logistic regression analysis was applied. Since two observations were missing on gland size, 631 sample observations were taken into consideration for multivariate analysis. The 24h uptake and gland size remained significant. On the basis of the Wald test statistic, the most important variable affecting the success rate was gland size (41.5) and followed by 24 hour uptake (4.1).

Table 3. Success rate with relation to gland size

Number of patients	Thyroid enlargement	Success rate
82	Nil	90.2%
288	Mild	79.5%
244	Moderate	58.6%
17	Severe	41.2%

Table 4. Logistic regression output analysis

	Beta	S.E.	LOWER	UPPER	Wald	df	Sig.	Odds ratio		
								EXP(B)	LOWER	UPPER
X1_24hr_Uptake_Coded(1)	.479	.236	.015	.942	4.102	1	.043	1.614	1.016	2.565
X2_sex(1)	-.577	.207	-.982	-.171	7.764	1	.005	.562	.374	.843
X3_Age_Coded(1)	-.365	.220	-.797	.067	2.741	1	.098	.694	.451	1.069
X4_GLAND_SIZE					41.485	3	.000			
X4_GLAND_SIZE(1)	2.620	.633	1.380	3.860	17.145	1	.000	13.734	3.974	47.463
X4_GLAND_SIZE(2)	1.617	.525	.589	2.645	9.499	1	.002	5.038	1.802	14.088
X4_GLAND_SIZE(3)	.669	.521	-.351	1.690	1.652	1	.199	1.953	.704	5.419
X5_Disease_duration_Coded(1)	.135	.323	-.499	.768	.174	1	.677	1.144	.607	2.156
X6_ATD(1)	.551	.298	-.033	1.135	3.414	1	.065	1.734	.967	3.110
X7_drug_duration_coded(1)	.000	.306	-.599	.600	.000	1	.999	1.000	.549	1.823
Constant	-.315	.509	-1.313	.683	.382	1	.536	.730		

DISCUSSION

A large number of studies have addressed the issue of the response of radioiodine therapy in relation to 24h RAIU. Several studies have described a favorable outcome of radioiodine therapy in patients with high 24h RAIU,^{7,14} while most published reports yield contradictory results.^{15,16} These contradictory results notwithstanding, high 24h RAIU is still regarded as an important factor in the success of radioiodine therapy.¹¹ Decreasing the iodide pool by a low iodine diet¹⁷ or increasing the retention of iodine in the thyroid gland by administering lithium carbonate have previously been proposed by several studies.¹⁸ However, the use of lithium is not a generally accepted option as adjuvant to increase the first-dose success of radioiodine therapy.¹⁹ A recent study found an inverse relationship between pretreatment iodine uptake and post-treatment outcome.¹² Patients with the lowest RAIU showed highest success at 18 months after therapy; the cure rate decreased with increasing pretreatment uptake. Another study suggested poorer outcome in patients with high 24h RAIU after radioiodine treatment for hyperthyroid disease when the therapeutic dose was calculated on the basis of 24h RAIU.¹³ In their study of radioiodine therapy of diffuse goiter, Catargi *et al.* found that mean uptake of a group of patients that remained hyperthyroid after one year follow-up was significantly higher compared to that of the euthyroid group.²⁰

The significance of our study is that our patients with diffuse toxic goiter received exactly the same dose. The data, therefore, reflect a homogenous treatment modality. Our sample size is large enough for acceptance or rejection of the hypothesis that lower RAIU leads to a better outcome after ¹³¹I therapy with 95% power and 1% type 1 error ($\alpha = 0.01$). However, the duration of disease, ATD and their duration and gland size are potentially important factors which could affect the outcome. Increasing gland size would be expected to lead to high uptakes. Hence, the major issue here was whether the high uptake group had more patients with grade 2 and 3 goiter as compared to the low uptake group, thus leading to lower cure rates when a fixed dose of 185 MBq ¹³¹I was used. We did a logistic regression analysis taking all these factors into account. The success rate

in the low uptake group was still significantly better than the high uptake group. Out of 455 patients with a first-dose success, we found that 249 (54.7%) were euthyroid and 206 (45.3%) were hypothyroid at 12 months after therapy. Thus, there was a higher rate of euthyroidism with fixed dose 185 MBq (5 mCi) radioiodine therapy. Physicians who advocate high dose radioiodine ablation of Graves' disease put forth the argument that leaving behind thyroid tissue partially damaged by radiation has potential risk of malignancy. The long-term risk of malignancy developing in such a gland, particularly in adults, is negligible. However, in pediatric Graves' disease the risk of malignancy in radiation injured residual thyroid tissue is not well established. A recent review by Verburg *et al.* concluded that the risk of malignancies after radioiodine therapy of benign thyroid disease is not increased.²¹

Duration of disease and treatment with ATD were found to be significant in the univariate analysis but not significant in multivariate analysis, indicating that these may be secondarily related to other factors like the aggressiveness of the disease which necessitates initial antithyroid drug treatment. It is also known that patients with severe hyperthyroidism may not respond to a single fixed low dose of radioiodine. Odds ratio for 24h uptake was 1.6 (CI=1.02-2.56), which indicates that if 24h uptake changes from >50% to \leq 50%, the probability of success increases 1.6-fold. Thus, we can conclude that as uptake decreases, probability of success increases. Odds ratio for gland size was 13.7 (CI=3.97-47.46), implying that if gland size changes from severely enlarged to not enlarged, probability of success increases 13.7-fold. When gland size changes from severely enlarged to mildly enlarged, probability of success increased 5.0-fold. Thus, as gland size decreases, probability of success appears to increase. In other words, larger glands need higher radioiodine therapy dose for a successful outcome with single dose.

Several hypotheses may be proposed to explain this apparently paradoxical observation, i.e. that lower 24h RAIU produces higher success rate with a fixed dose of radioiodine. Firstly, there could be a biologically different response of the follicular cells in the form of decreased radiosensitivity in response to higher

RAIU.²² A two-compartmental model suggesting less possibility of cure in patients with high RAIU in comparison with the low 24h RAIU group has been postulated if the same target dose is delivered.²³ Also, altered iodine kinetics in the subsequent ¹³¹I therapy has been described after using ¹³¹I for 24h RAIU. This could be due to stunning of the thyroid following low dose of ¹³¹I used for 24h RAIU, although this is extremely rare. Studies have shown the phenomenon of stunning in thyroid cancer, but the radioiodine dose used in the whole body scan was almost one thousand times the 24h RAIU dose.²⁴⁻²⁶ Another hypothesis could be that high uptake values lead to lower effective intrathyroidal half-life of radioiodine, but this is speculative and needs to be confirmed by further studies. In addition, our findings may have been influenced by the short duration of follow-up, i.e. one year, and longer follow-up is needed to confirm these. Moreover, there seem to be three shortcomings in our study that deserve mention. Firstly, the gradation of gland size was not done using neck ultrasound, which would have been a fully objective method. Secondly, whether the patients were iodine deficient or iodine-sufficient was not known, but there may be a similar proportion of patients of both types in the high as well as the low uptake group. Lastly, the success rate of radioiodine may change on prolonged follow-up as detection of delayed hypothyroidism increases with longer follow-up. Nevertheless, our data suggest that the hypothesis that we sought to verify may be correct and high uptake may in fact be an adverse factor as far as outcome of the first dose of radioiodine therapy is concerned, and that low 24h RAIU may not be a contraindicating factor as is commonly perceived. The data also highlight the fact that a fixed dose of 185 MBq (5 mCi) produces satisfactory and comparable results in glands with an RAIU less than or equal to 50% and smaller glands. However, its routine use in glands showing more than 50% uptake and larger gland size may not achieve equally good results and may need higher administered activity of ¹³¹I to achieve higher first-dose success rate.

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