Radioactive iodine in the treatment of Graves' disease

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ABSTRACT

Objectives: This study was performed to evaluate the efficacy of radioactive iodine ^{131}I therapy of Graves' hyperthyroidism at Sultan Qaboos University Hospital, Oman and to determine the optimal dose of ^{131}I needed to achieve the euthyroid or hypothyroid status.

Methods: The medical records of 366 patients with Graves hyperthyroidism who received a single dose of ^{131}I at Sultan Qaboos University Hospital, Oman between 1991 and 1999 were reviewed. The diagnosis was based on clinical, biochemical grounds and ^{99m}Tc thyroid scintigraphy. The patients were followed up for a minimum period of 12 months. For the analysis, the patients were divided into 6 groups according to the ^{131}I dose administered: Dose one (350-399), dose 2 (400-449), dose 3 (450-499), dose 4 (500-549), dose 5 (550-599) and dose 6 (≥600) MBq.

Results: Fifty-eight percent of all the patients were hypothyroid after 3 months. Three hundred and twenty two patients (88%) were treated by a single dose of ^{131}I in 12 months (85.5% hypothyroid and 2.5% euthyroid). Forty-one patients (11.2%) required a 2nd ^{131}I dose and only 3 patients required 3 doses of ^{131}I. The best cure rate (93%) was observed in group dose 5 (574.0 ± 16.4 MBq) which however, was not significantly different from other dosage levels. The female to male ratio was 2:1 and the cure rates were not gender or age related.

Conclusion: Treatment of Graves' hyperthyroidism from a single ^{131}I dose is our aim, rather than avoidance of hypothyroidism. Our results indicate that cure rates are higher with larger doses of ^{131}I except in group dose 6 (special category of patients). In the future, fixed doses would be adopted in our radioactive iodine treatment practice guidelines. As the majority of our patients were hypothyroid at 3 months regular monthly follow-up is essential. Whenever appropriate, physicians are encouraged to consider early referral of Graves' hyperthyroidism patients for radioactive iodine treatment as it is cheap, effective, easy to administer and free from serious side effects.

Keywords: Graves' hyperthyroidism, radioactive iodine therapy.

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In 1941 radioactive iodine was used for the first time by physicians at Massachusetts General Hospital in Boston.[1,2] Radioactive iodine treatment (RAIT) for thyrotoxicosis is proved to be cheap, effective, easy to administer and free from serious side effects. Despite more than 50 years experience with RAIT, no unanimity exists regarding dose (D) selection, although certain guidelines have become generally accepted. Five approaches had been used: (1) small doses repeated as necessary, (2) a large ablative D, (3) a "sliding scale" based on thyroid size, (4) a standard formula for administered D based on estimated thyroid size, and (5) precise dosimetry for the administered D.[3] Hypothyroidism is common after RAIT of Graves' hyperthyroidism (GH) and can occur weeks, months, or even years later.[4]

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Recognizing these imperfections, some investigators have suggested that patients are best treated by a single "thyroablative D", arguing that the aim is cure of hyperthyroidism, larger doses accomplish cure with more certainty, and that the inevitable hypothyroidism develops under physician control. This approach raises a new question: in the trade-off between curing hyperthyroidism and radiation risk, how much ^{131}I should be considered as appropriate dosage? To answer this question, we evaluated in a retrospective study, the proportion cured by a single RAIT in 366 patients with GH treated with different doses of ^{131}I at Sultan Qaboos University Hospital (SQUH), Oman over a period of 8 years.

Methods. In the Sultanate of Oman, RAIT, at present, is confined at SQUH, Muscat. The medical records of all patients with GH treated with ^{131}I from May 1991 through to December 1999 were reviewed. A total of 366 cases were selected with definite evaluation and diagnosis of GH prior to RAIT and a follow up period ensuring permanent treatment of hyperthyroidism. All patients with toxic nodules and patients who underwent previous thyroid surgical intervention were excluded. Twenty patients were also excluded due to lost of follow up or their care was transferred to their local hospital immediately post RAIT. The diagnosis of GH was based on clinical grounds, biochemically on raised serum levels of free thyroxine (FT_4) (> 20pmol/L), free triiodothyronine (FT_3) (> 5.3pmol/L) and suppressed thyroid stimulating hormone (TSH) (less than 0.49 m IU/L) using micro particle enzyme immunoassay, and increased diffuse uptake in ^{99m}Tc thyroid scintigraphy (uptake of more than 4%). The majority of the patients received anti-thyroid drugs (ATDs) for more than 6 months prior to the referral for RAIT. In addition to a low-iodine diet, ATDs were discontinued 5 days prior to RAIT. The term "cure" used is not totally true because to what happen substitution of a disease difficult to control (GH) by another disease easier to manage (hypothyroidism). The need for lifelong thyroxine replacement was carefully explained to the patients and accompanying relatives and a printed leaflets was provided with general information of RAIT to participate in making the final decision. Irrespective to the size of the goiter, the uptake scan, duration of the illness, duration, type and D of ATDs used, the ^{131}I dosage was divided retrospectively into 6 groups of D: D1 (350-399 MBq), D2 (400-449 MBq), D3 (450-499 MBq), D4 (500-549 MBq), D5 (550-599 MBq) and D6 (≥600 MBq). D6 dosage was noted to be given to patients with large goiter (grade 3 according to the World Health Organization [WHO] criteria), severe thyrotoxicosis and with cardiac complications. The patient was considered to be treated post-RAIT if his/her TSH was normal or elevated (TSH >0.46 m IU/L) for more than 6-months without any ATDs. The patients were reviewed clinically and biochemically at approximately 3, 6, 9, 12 months after treatment, and then at 3 months intervals until they were cured. Severely thyrotoxic patients were given ATDs 48 hours post-RAIT and continued for 4 weeks. If the patient was still overtly, clinically and biochemically hyperthyroid, a 2nd D was considered after 6 months and the 3rd D 12 months from the 1st RAIT. However, mild hyperthyroid patients were followed for 12 months before being subjected to a 2nd D of RAIT.

Statistical methods. An appropriate Pearson's and Mantel Haenzel Chi-square tests were used, to analyze categorical variables. Spearman's rho statistic was used to test linear correlations between variables. The data are largely descriptive. Where appropriate data are organized as means, standard deviation (SD) or standard errors (SE). The t-test was used to test the significance of the difference between sample averages of the demographic variables. The analysis,[5] and graphics were carried out using the Statistical Package for Social Sciences software (SPSS) (Version 10.0),[6] with a P value of < 0.05 is considered statistically significant.

Results. Out of the 366 cases, the female to male ratio was 2:1. The average age for females were 37.5 (SD 12.8) and males were 39 (SD 12.5), with no significant difference in age versus gender distribution **(Table 1)**. There was no significant difference between the mean dosages of ^{131}I given to female and male patients. However, age was positively correlated with dosage, older patients were given higher D of ^{131}I (rho =0.37, $p<0.001$). **Table 2** shows the cure rate in each of the 6 groups categorized according to ^{131}I administered D. The overall cure rate was 88%. No statistical significant difference was found between the cure rate in the 6 groups, but the best cure rate (93%) was obtained in group D5 with a mean D of ^{131}I of 574.0 ± 16.4 MBq. Despite a higher ^{131}I D, group D6 showed a lower cure rate (85.3%) than group D5. The cure rate was not dependent on age or gender. The overall non-cure rate was only 12% (44 patients). Of these, 41 required a 2nd D and only 3 needed a 3rd D of RAIT to achieve cure. The overall response from all the groups within the 1st 3 months post ^{131}I was the following: 58.4% of patients became hypothyroid, 13.6 % became euthyroid and 28% hyperthyroid, and by the end of 12 months the percentages were 85.5% hypothyroid, 2.5% euthyroid and 12.0% hyperthyroid. Thus, the majority of the patients became hypothyroid within the first 3 months (**Figure 1**). Two cases had transient hypothyroidism reversing to hyperthyroidism and requiring a 2nd D of ^{131}I.

Table 1 - Statistics summary of study factors by categories of iodine-^{131} dosage.

Factors		D1 350-399 MBq	D2 400-449 MBq	D3 450-499 MBq	D4 500-549 MBq	D5 550-599 MBq	D6 ≥600 MBq	Overall
n		32	42	46	98	80	68	366
Gender (F:M)		5:2	1:8	1:7	1:8	2:2	1:7	2:0
Age in years								
Female	Mean	30.5	32.1	36	34.5	42	45.2	37.5
	SD	10.1	11	12.7	11.2	13.5	11.3	12.8
Male	Mean	41	29.8	38	36.6	42.4	44.8	39
	SD	13.1	10.4	10.2	11.2	13.6	12.3	12.5
Overall	Mean	32.1	31.3	36.7	35.2	42.1	45	38
	SD	11.1	10.7	11.7	11.2	13.5	11.6	12.7
Dose								
Female	Mean	369.6	415.3	476.2	519	574.4	623.9	516.9
	SD	36.4	14.3	18.4	16.2	17.4	28.2	83.7
Male	Mean	390	419.4	481.2	519.2	573.1	623.5	528
	SD	7	14.3	15.9	15.8	14.1	21	71.9
Overall	Mean	372.8	416.7	478.4	519.1	574	623.8	520.9
	SD	34.3	14.3	17.3	16	16.4	26.5	80

n - number, F:M - female male ratio, D - dose, SD - standard deviation

Table 2 - The distribution of the radioiodine dosage groups and the outcome by the end of 12 months (single ^{131}I dose).

Group dose intervals	Cure Yes	Cure No	Total	Proportion cured	SE
350-399	26	6	**32**	0.81	0.07
400-449	34	8	**42**	0.81	0.06
450-499	41	5	**46**	0.89	0.05
500-549	89	9	**98**	0.91	0.03
550-599	74	6	**80**	0.93	0.03
≥600	58	10	**68**	0.85	0.04
Total	**322**	**44**	**366**	**0.88**	**0.02**

SE - standard error

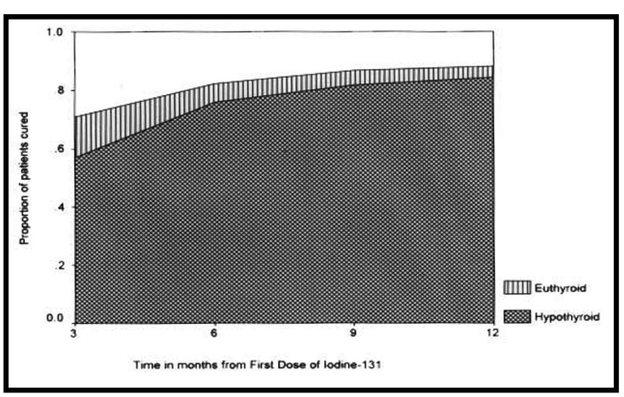

Figure 1 - Cumulative proportion of patients treated with a single ^{131}I dose over a one year period.

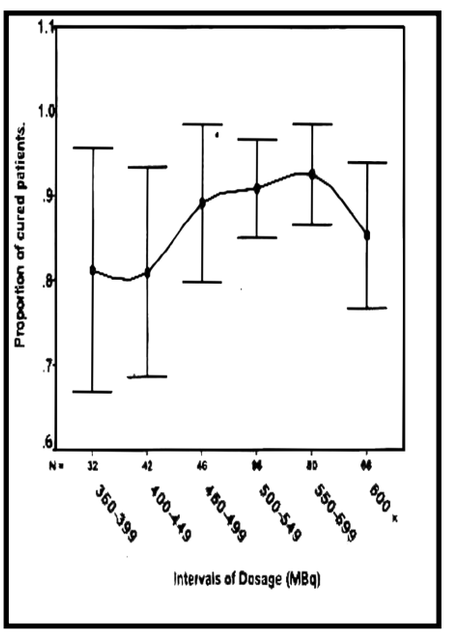

Figure 2 - Proportions of patients cured by a single ^{131}I dose versus dosage groups, by the end of 12 months. (Bar = 95% confidence interval and n - number of patients in each dosage group).

Although there were some patients experience transient radiation thyroiditis post ^{131}I, not a single case of thyroid storm was found. There were no serious complications in our patients post RAIT.

Discussion. Radioactive iodine treatment has been increasingly recognized as the treatment of choice for most patients with GH. Our results show that RAIT is very effective in patients with GH, with more than 88% being treated by a single D (overall: 520 ± 80MBq) of ^{131}I. Surprisingly therefore there is still a striking difference between different countries in its use. For a given a 43-year-old woman with moderate Graves' disease,[7] in the United States of America 69% of physicians would use ^{131}I as the initial treatment. This figure is much lower in Europe (22%) and Japan (11%). In our community there is still some concern about the use of radioactive materials. Unfortunately, we have encountered patients who suffered from hyperthyroidism for over five years before being eventually referred for ^{131}I therapy. The preferred thyroid ablation D of ^{131}I varies between individual physicians from 150 to 1100 MBq.[8] It is generally observed that the lower the D of ^{131}I, the greater the chance of recurrent thyrotoxicosis, and the larger the D, the greater the chance for hypothyroidism.[9] Our approach has been to achieve hypothyroidism over a short period of time using a single D of ^{131}I, rather than having hypothyroidism develop insidiously over many years when patients might be lost to follow-up. Our findings are similar to those of Johansen et al[10] in the Kingdom of Saudi Arabia (KSA) and Child et al[11] in the United Kingdom who found that 68% and 67% respectively of their patients were hypothyroid over 12 months period after a single D. Wise et al[12] gave 370 to 444 MBq for small or impalpable thyroids and 550 MBq for larger goiters in 50 patients with diffuse goiter in Australia. Seventy-six percent became hypothyroid in 2-3 months, and 92% in 6 months. But these patients were not rendered euthyroid prior to radio-iodine. In this study the female to male ratio of the 366 Graves' patients studied was 2:1, which is much lower than 7 to 10:1 ratio seen in the western world,[13] but close to the ratio of 1.4:1 in KSA.[10] It seems that GH has a different gender distribution in the Arabian Gulf region compared with the western world, but this finding could be attributed to selection bias. For several reasons, treating physicians are aware that GH males patients tend to relapse more frequently and thus they are referred more readily for ^{131}I therapy than females patients. In addition, pregnancy, consecutive pregnancies and breast-feeding are contraindications for ^{131}I therapy. However, further studies need to be carried out to elucidate this observation. Since long standing hyperthyroidism may suppress pituitary TSH release, this parameter is not useful in the early diagnosis of hypothyroidism in ^{131}I treated patients.[14] Free thyroxine and FT_3 concentrations will normalize long before TSH concentration D. Based on observation of the symptoms of hypothyroidism, once the patients become hypothyroid, they should be started on thyroxine replacement.

Our study indicated that, there is no significant difference in age versus gender distribution. The cure rates were not dependent on age or gender, although it is well known that younger individuals appear to be more at risk for hypothyroidism and men are less likely to have hypothyroidism than women. In evaluating response to therapy, variables such as race, iodine content of the diet, size of the goiter, the uptake scan, duration of the illness and duration, type and doses of ATDs used were not analyzed in the study. Thus, not considering these variables may explain the inconclusive results in the responses of patients to different doses. There was no statistical significant difference found between the 6 groups. However, the cure rates in D1 and D2 groups had wide confidence intervals. Patients with large goiter (WHO grade 3), severe thyrotoxicosis and cardiac complications may require even higher doses than the given D in group D6 (mean of 623.8 ± 26.5 MBq) to avoid relapses (**Figure 2**). The group given D of mean 574 ± 16.4 MBq had the best cure rates although statistically significant optimal D of ^{131}I could not be determined in our study groups. Most of our patients were treated with ATDs as the first-line therapy for a period of at least 6 months and then referred for RAIT (from all over the Oman). The influence of ATDs on the outcome of RAIT has not been analyzed in our patients. However, in the literature this issue is fraught with controversy. Some researchers claim that pretreated patients with ATDs need approximately a 25% increase in the administered ^{131}I D,[4] while others state that there is no influence on the outcome of treatment.[15] The general awareness of the safety and the efficacy of RAIT is on the increase, influenced by various studies showing no evidence of cancer, infertility or abnormalities in the offspring of patients treated with RAIT and its cost effectiveness.[7] The trend observed in our practice is that, increasingly the treating physicians prefer early referral for ^{131}I rather than keeping the patients on ATDs for years. Our aim in the treatment of GH is the treatment of hyperthyroidism rather than avoidance of hypothyroidism, and the sooner the patient is made hypothyroid the better. In this country, this is of significant advantage, as early thyroxine replacement will prevent the development of hypothyroidism, which might otherwise go undiagnosed for long periods with unwanted consequences. In the first 4 years, RAIT was given only as inpatient treatment. However, more and more patients are currently given the treatment on outpatient basis following satisfactory assessment of the social and family set

up, with the proper verbal and written instructions, to minimize radiation exposure to others. It should be standard practice to inform each patient prior to ^{131}I treatment, of the almost certain implication that lifelong thyroxine treatment may be necessary, and the need for lifelong follow-up for thyroid status monitoring. Patients should also be aware that some commonly prescribed medications (iron and antacids) could interfere with T_4 absorption, requiring spacing in time of administration by 4 hours.[7]

In conclusion, treatment of GH is from a single ^{131}I D is our aim, rather than avoidance of hypothyroidism. Our results indicate that cure rates are higher with larger doses of ^{131}I except in group D6 (special category of patients) though the differences among the rates are not statistically significant. Therefore, an optimal D of ^{131}I could not be determined. In the future, fixed doses would be adopted in our RIAT practice guidelines. In addition, the treating physicians should be more aware of the importance of early referral for ^{131}I. As the majority of our patients developed hypothyroidism in the 1st 3 months post RAIT, monthly follow-ups are required to promptly recognize and treat hypothyroidism.

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