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Research paper

Comparison of two fixed activities of radioiodine therapy (370 vs. 555 MBq) in patients with Graves' disease

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ABSTRACT

OBJECTIVE: Radioiodine therapy is the most commonly used therapy for patients with Graves' disease (GD) in the United Kingdom. It is considered safe, effective and relatively inexpensive. The aim of our study was to examine the outcome of 131Iodine therapy in patients with GD when two different activities of 131Iodine were used. DESIGN: A retrospective audit was undertaken to compare the efficacy of 370 (10 millicuries) versus 555MBq (15 millicuries) radioiodine therapy in patients with Graves' disease over a period of ten years. RESULTS: Overall, 90% of the patients had a successful outcome from treatment with no significant difference in the success rate between the lower and higher activities or between genders. CONCLUSIONS: 555 MBq of radioiodine was no more effective than 370 MBq in managing patients with Graves' disease. We therefore recommend that the higher activity should not be routinely used in these patients.

Key words: Graves' disease, **H**yperthyroidism, Hypothyroidism, Radioiodine therapy

INTRODUCTION

The aim of radioiodine therapy in Graves' disease is to destroy sufficient thyroid tissue to cure hyperthyroidism, a process that renders the patient either euthyroid or hypothyroid. Radioiodine therapy induces an intense radiation thyroiditis and subsequent fibrosis, thereby destroying the synthetic capacity of the thyroid.[1] "Ablative" concept of radioiodine therapy is a well accepted form of therapy. This form of therapy is the most commonly used therapy for patients with Graves' disease in the United Kingdom.[2,3] It is considered safe, effective and relatively inexpensive. However, there is a lack of consensus as to what dosage of radioactive iodine should be used and whether the aim of treatment is to render the patient euthyroid for a period of time or hypothyroid.[4-7] Different methods have been used for determining the activity that is administered to these patients. Techniques have varied from fixed activities to elaborate calculations based on gland size, iodine uptake and iodine turnover.[8]

The two District General Hospitals in Ayrshire, Scotland, have historically used two different fixed activities of radioiodine therapy to treat thyrotoxic

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patients. The aim of this audit was to compare the efficacy of 370 (10 millicuries) versus 555MBq (15 millicuries) radioiodine activities for therapy in patients with Graves' disease over a period of ten years.

SUBJECTS AND METHODS

Patients

Details of all the patients who received radioiodine therapy for thyrotoxicosis in Ayrshire and Arran during the period 1997 to 2007 were available on the NHS Ayrshire and Arran Department of Nuclear Medicine database. One in four patients diagnosed with Graves' disease and treated with radioiodine were randomly selected for the audit. The diagnosis of Graves' disease was made on the basis of elevated Free T4 or Total T4 with suppressed TSH concentrations and clinical examination (presence of two of the following three: diffuse goitre, eye signs specific for Graves' disease, pre-tibial myxoedema), and supported by other investigations (such as the presence of TSH-Receptor antibodies or radionuclide imaging).

Baseline Clinical Data before 131Iodine therapy

Baseline characteristics obtained included age at diagnosis, gender, Free T4 levels and Thyroid Stimulating Hormone (TSH) plus the presence or absence of Graves' ophthalmopathy. Patients were categorised as having received carbimazole (Carb), propylthiouracil (PTU), previous radioiodine treatment or no therapy prior to receiving 131Iodine treatment. Previous radioiodine treatment (if any) was also documented along with the presence of Graves' ophthalmopathy using the Clinical Activity Score.[18] Patients with moderate to severe Graves' ophthalmopathy did not receive radioiodine therapy.

Anti-thyroid drugs were discontinued 5-7 days before radioiodine was administered and were not restarted unless there was evidence of persistent or worsening hyperthyroidism at the first visit six weeks post-treatment. Beta-blockers were not systematically stopped and were allowed for symptom control during the period of pre-radioiodine administration and for a few weeks thereafter.

The patients and results were reviewed by two Consultant Endocrinologists pre- and post-treatment. Informed written consent was obtained from each participant and the audit was approved by the NHS Ayrshire & Arran Health Board, Clinical Effectiveness Office.

Thyroid function assays and radioiodine treatment

TSH and FT4 were measured using an ADVIA Centaur immunoassay analyser (Bayer Diagnostics, Tarrytown, NJ, USA).[9] All patients received 131Iodine therapy at the Ayr and Crosshouse Hospitals, Ayrshire, United Kingdom. On the day of radioiodine administration pregnancy was excluded in female patients of child-bearing potential/age using an hCG test kit.

The patients from Ayr Hospital received 370 MBq of 131Iodine, whereas patients from Crosshouse Hospital received 555 MBq.

Outcome assessments

Follow-up was left to the discretion of the Clinical Endocrinologists, who monitored for the clinical outcome. All patients were followed up for at least one year following 131Iodine therapy. The primary outcome was each patient's thyroid status within one year of 131Iodine therapy. Euthyroidism was defined as normal serum T4 concentration, regardless of TSH values (without levothyroxine therapy at one year). Hypothyroid patients had elevated serum TSH on two occasions four weeks apart (within 12 months) and required permanent levothyroxine treatment. Persistent/recurrent hyperthyroidism was defined by the presence of elevated Free T4 and suppressed TSH, or by requirement of either anti-thyroid medication, repeat administration of 131Iodine therapy or thyroid surgery within one year of 131Iodine therapy. 131Iodine treatment was considered to be successful if the patient was either euthyroid or hypothyroid (requiring levothyroxine therapy) within one year of 131Iodine therapy.

Statistical analysis

SPSS version 15 was used to analyze the data. For comparison of baseline parameters in the two groups, chi-square and independent samples t-test were used. To assess treatment success against dosage, previous drugs and previous radioiodine treatment, a number of chi-square tests were conducted.

RESULTS

Approximately 1500 patients received radioiodine therapy for thyrotoxicosis in Ayrshire between 1997 and 2007, the majority of whom were diagnosed as having Graves' disease (1312). One in four of these patients with Graves' disease were randomly selected for our audit. Three hundred and twenty-eight cases were identified for analysis. Seventeen cases were excluded as case documentation was inadequate or patient was not completely followed up. Hence, 311 patients with a diagnosis of Grave's disease were included in the study (Table 1). One hundred and eighty-four patients (59.2%) received the larger activity of radioiodine (i.e. 555 MBq). The mean age in the sample was 63.6 ± 15.8 yrs (mean ± standard deviation). There was no significant difference in mean age by activity ($t(282) = 1.83$, $p = 0.07$). Two hundred and sixty-nine of the patients were female (86.5%).There was no significant difference in gender by activity: 89.8% of those receiving low activity were female compared to 84.2% of those receiving higher activity (chi-square (1, N = 311) = 1.96, p = 0.16). There was also no significant difference in mean age by gender ($t(282) = 0.92$, $p = 0.36$) and no significant difference in baseline free thyroxine levels or clinical presence of goitre in the two groups (p= 0.95 and 0.91, respectively).

Overall, 90% of the patients had a successful outcome from 131Iodine treatment (Table 2). There was no significant difference in success rate between the lower and higher activities (chi-square (1, N = 311) = 0.06, p = 0.80).

There were significant gender differences in overall success rates: 91.9% of females had successful treatment compared to 81.8% of males (chi-square (1, N = 311) = 4.46, $p < 0.05$, OR = 2.52). However, there was no significant difference in success rate by activity for either females or males (chi-square (1, N = 269) = 0.11, p = 0.74 for females; chi-square (1, N = 42) = 0.20, p = 0.66 for males).

Two hundred and sixty-two (79.9%) of the pa-

Table 1. Pertinent data in the two groups (high and low activity).

	Low activity (370MBq)	High activity (555MBq)	Overall
n (%)	127(40.8)	184 (59.2)	311
Mean age (SD)	65.6 (15.8)	62.2 (15.7)	63.6 (15.8)
% of females	89.8	84.2	86.5
Patients with goitre n (%)	86 (68)	121 (66)	66.5
Baseline Free T4 (pmol/l)	38.1 (3.06)	37.8 (3.03)	37.9 (3.04)
mean (SD) (normal range: 9 – 24 pmol/L)			
Successful outcome n (%)	115 (90.6)	165 (89.7)	(90)

Table 2. Success rate by activity, gender and previous PTU/carb therapy and previous RI therapy.

	% success rate of those with low activity (370MBq) (n)	**% success rate of those with high activity (555MBq) (n)**	**Overall (%) success rate (n)**
Females (86.5)	92.1 (114)	91.0 (155)	91.4 (269)
Males (13.5)	76.9 (13)	82.8 (29)	81.0 (42)
Given PTU/carb (79.9)	89.6 (96)	89.3 (150)	89.4 (246)
Not given PTU/carb (20.1)	93.5 (31)	91.2 (n34)	92.3 (65)
Previous RI treatment (12.9)	85.7 (21)	89.5 (19)	87.5 (40)
No previous RI treatment (87.1)	91.5 (106)	89.7 (165)	90.4 (271)
Overall	90.6 (127)	89.7 (184)	90.0 (311)

PTU: propylthiouracil, Carb: carbimazole, RI: Radioiodine

tients in our audit received anti-thyroid medication before radioiodine administration. All the patients that received anti-thyroid medication were started on carbimazole and the nine patients who developed side-effects (commonly rash) were switched to propylthiouracil (PTU). There was no evidence that this had any effect on the success rate (chi-square (1, N=311)=0.47, p=0.49). In addition, there was no significant difference in success rate by activity in those with and without carbimazole or PTU pre-treatment (chi-square (1, N=127)=0.43, p=0.51 for low activity; chi-square (1, N=184)= 0.10, p=0.75 for high activity).

A small number of patients (40=12.2%) had had previous radioiodine treatment. There was no significant difference in the efficacy of treatment between those who received pre-treatment (with radioiodine) and those who did not (chi-square (1, N=311)=0.33, p=0.57). Nor was there any significant difference in success rate by activity for those with or without previous radioiodine treatment (chi-square (1, N=127)=0.69, p=0.41 for low activity; chi-square (1, N=184)=0.001, p=0.98 for high activity).

DISCUSSION

The use of radioiodine in hyperthyroidism is increasing, particularly in younger patients with Graves' disease where the likelihood of success (i.e. lack of relapse) with anti-thyroid drugs is modest.[10] Although there is general consensus that radioactive iodine is safe, cheap and effective for the treatment of Graves' thyrotoxicosis, there remains a lack of consensus as to what dosage should be used. Several factors have been considered as influencing the outcome of radioiodine treatment. Previous studies have suggested that patients with larger volume thyroid glands and severe hyperthyroidism are more likely to fail to respond to a single administration of radioiodine.[11] Techniques have also been undertaken to assess gland size (estimated either clinically or with imaging) and doses have been calculated on the basis of gland size, iodine uptake and sometimes iodine turnover.[12] The use of this methodology adds to the complexity of the procedure and significantly increases the cost related to therapy.[13] As radioactive iodine therapy is relatively inexpensive, incurring further cost to determine the administered activity clearly needs to be justified.

Our audit could potentially have included over 1500 patients. The great majority had Graves' disease, with much smaller numbers having other causes of thyrotoxicosis such as multinodular goitre (MNG) and toxic adenoma. With such small numbers, it would have been difficult to demonstrate and interpret any possible difference in the comparative efficacy of 370 and 555 MBq of radioiodine therapy in these other causes. It therefore seemed sensible to concentrate our audit on patients with Graves' disease. Given the sample sizes in this study, the power of the statistical test undertaken was sufficient to determine a 10% difference in success rates (power=0.84*). If the full audit had been used instead of the 1 in 4 sample, then the power would have been sufficient to reduce this to 5% (power=0.81*). The small increase in precision would not have justified the extra time and effort involved. Hence, our audit demonstrated that administering the larger activity of radioiodine therapy (555MBq) has little, if at all any, added effect in patients with Graves' disease when compared to 131Iodine therapy with 370 MBq.

An adequate radiation dose from radioiodine therapy is necessary to prevent either persistent or recurrent hyperthyroidism. Sustained euthyroidism would clearly be the most desirable outcome, but this would appear to be futile. Irrespective of the administered radioiodine activity, a number of studies have demonstrated an annual incidence of hypothyroidism of approximately 2-3% many years after therapy.[19]

There has been concern that thyrotoxic patients receiving radioiodine therapy may release thyroid hormones into the circulation from thyroid follicular cell disruption following therapy. Worsening thyrotoxicosis and even thyroid storm have been reported.[20] As a result, many patients, including most patients in this audit, are rendered euthyroid prior to radioiodine therapy. Pre-treatment of patients with propylthiouracil has been reported to be associated with relative radio-resistance and hence the possible need for a larger activity of radioiodine. Carbimazole pre-treatment does not appear to affect the outcome.[21] It has also been suggested that patients with Graves' disease do not require pre-treatment with anti-thyroid drugs. Approximately one fifth of our

patients did not receive anti-thyroid medication prior to radioiodine therapy and there was no difference in their outcomes.

The degree of hyperthyroidism and presence or absence of goitre has been suggested as influencing response to radioiodine.[14] Patients in the low and high activity groups had similar prevalence of hyperthyroidism and goitre. Hence, this did not interfere with the interpretation of our results.

The Royal College of Physicians clinical guidelines reviewed papers studying cancer induction rates in populations following radioiodine administration and reported that increased incidence of thyroid cancer post treatment is more likely to be associated with the underlying thyroid disease than the radioiodine treatment.[15,16] They also found no evidence of increased incidence of leukaemia, but there was a possible increased incidence of small bowel cancer and gastric cancer. There are several potential benefits to using a smaller (370MBq) radioiodine activity. The International Commission on Radiological Protection (ICRP) recommends the "linear-no threshold" model for radiation risk.[22] Therefore, a 33% reduction in the administered activity should result in a 33% reduction in the relative risk of cancer induction.

Restrictions on behaviour of out-patients post treatment can also be reduced with the administration of a lower activity. When 555MBq is administered, the Medical and Dental Guidance Notes suggest a maximum restriction period of 25 days to ensure that radiation dose to members of the public is kept below 1mSv. For an activity of 370MBq, this period can be reduced to 21 days, conferring obvious benefits to patients, families and their carers.[17] Another potential environmental benefit of administering a lower activity would be a reduction in the release of 131Iodine via the sewage system. In addition, with the administration of 370MBq radioiodine an approximate 10% saving can be made on the cost of each 131Iodine capsule.

In this audit, 370 and 555 MBq of radioiodine, were equally effective in destroying sufficient thyroid tissue to cure hyperthyroidism by rendering the patient either euthyroid or hypothyroid. In the long run, almost all patients will possibly be rendered hypothyroid and require replacement therapy. As 555 MBq of radioiodine was no more effective than 370 MBq in managing patients with Graves' disease, we would recommend that the larger activity should not be routinely used in these patients.

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REFERENCES

1. Solomon B, Glinoer D, Lagasse R, Wartofsky L, 1990 Current trends in the management of Graves' disease. J Clin Endocrinol Metab 70: 1518-1524.
2. Radioiodine in the management of benign thyroid disease 2007. Clinical guidelines. Report of a Working Party. The Royal College of Physicians of London.
3. Hedley AJ, Lazarus JH, McGhee SM, et al, 1992, Treatment of hyperthyroidism by radioactive iodine. Summary of a UK national survey prepared for the Royal College of Physicians Committee on Endocrinology and Diabetes. J R Coll Physicians Lond 26: 348-351.
4. Beierwaltes WH 1978 The treatment of hyperthyroidism with iodine-131. Semin Nucl Med 8: 95-103.
5. Bockisch A, Jamitzky T, Derwanz R, Biersack HJ, 1993 Optimized dose planning of radioiodine therapy of benign thyroidal diseases. J Nucl Med 34: 1632-1638.
6. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA, 2003 A randomized comparison of radioiodine doses in Graves' hyperthyroidism. J Clin Endocrinol Metab 88: 978-983.
7. Peters H, Fischer C, Bogner U, Reiners C, Schleusener H, 1995 Radioiodine therapy of Graves' hyperthyroidism: standard vs. calculated 131iodine activity. Results from a prospective, randomized, multicentre study. Eur J Clin Invest 25: 186-193.
8. Berg G, Michanek A, Holmberg E, Nystrom E, 1996, Clinical outcome of radioiodine treatment of hyperthyroidism: a follow-up study. J Intern Med 239: 165-171.
9. Girgensohn S, Liedtke R, Balzer G, Castor S, Hauser M, 1997, Performance of the ACS: Centaur high-capacity, random-access immunoassay system. Clin Lab 43: 975-83.
10. Hedley AJ, Lazarus JH, McGhee SM, et al, 1992, Treatment of hyperthyroidism by radioactive iodine. Summary of a UK national survey prepared for the Royal College of Physicians Committee on Endocrinology and Diabetes. J R Coll Physicians Lond 26: 348-351.
11. de Bruin TW, Croon CD, de Klerk JM, van Isselt JW, 1994 Standardized radioiodine therapy in Graves' disease: the persistent effect of thyroid weight and radioiodine uptake on outcome. J Intern Med 236: 507-513.
12. Safe AF, Maxwell RT, 1990, Efficiency of treatment and monitoring of ablative radio iodine therapy for hyperthyroidism: a DGH centre study. Br J Clin Pract 44: 393-395.

13. Jarlov AE, Hegedus L, Kristensen LO, Nygaard B, Hansen JM, 1995, Is calculation of the dose in radioiodine therapy of hyperthyroidism worth while? Clin Endocrinol (Oxf) 43: 325-329.
14. Kung AW, Pun KK, Lam KS, Choi P, Wang C, Yeung RT, 1990, Long-term results following 131I treatment for Graves' disease in Hong Kong Chinese—discriminant factors predicting hypothyroidism. Q J Med 76: 961-967.
15. Dobyns BM, Sheline GE, Workman JB, Tompkins EA, McConahey WM, Becker DV, 1974 Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the cooperative thyrotoxicosis therapy follow-up study. J Clin Endocrinol Metab 38: 976-998.
16. Holm LE, Hall P, Wiklund K, et al, 1991 Cancer risk after iodine-131 therapy for hyperthyroidism. J Natl Cancer Inst 83: 1072-1077.
17. Medical and dental guidance notes: A good practice guide on all aspects of ionising radiation in the clinical environment. York: Institute of Physics and Engineering in Medicine, 2002.
18. Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, van der Gaag R, 1989 Clinical criteria for the assessment of disease activity in Graves' ophtalmopathy: a novel approach. Br J Ophtalmol 73: 639-644.
19. Cunnien AJ, Hay ID, Gorma CA, et al, 1982 Radioiodine induced hypothyroidism in Graves' disease: factors associated with the increasing incidence. J Nucl Med 23: 978-983.
20. McDermott MT, Kidd GS, Dodson LE, et al, 1983 Radioiodine induced thyroid storm. Am J Med 75: 353-355.
21. Connell JM, Hilditch TE, McCruden DC, Robertson J, Alexander WD, 1984 Effect of pretreatment with carbimazole on early outcome following radio-iodine (131I) therapy. Eur J Nucl Med 9: 464-466.
22. ICRP Publication 99, 2006 Low-dose extrapolation of radiation related cancer risk. Annals of the ICRP 35:4. Elsevier, UK.