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Treatment of 1035 Hyperthyroid Patients with ^{131}Iodine

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Abstract: Radioiodine (^{131}I) is an effective and cost effective alternative to surgery in the treatment of thyroid hyperfunction. The debate today concerns how ^{131}I should be given, maximum and minimum ablative doses, and factors affecting development of post-^{131}I hypothyroidism. : 1035 hyperthyroid patients treated with weight-adjusted ablative doses of ^{131}I were retrospectively assessed for correlation between treatment outcome and pre-therapy variables such as sex, age, underlying pathology and dose of ^{131}I received. Thyroid hyperfunction was 3.5 times more common in women. The greatest proportion of patients with thyroid hyperfunction was in the 31 to 40 years age group and the smallest proportion in the over-70 age group. The most common underlying pathology was Grave's disease. Men had a lower response rate to ^{131}I therapy, with a 2.4-fold greater probability of hyperthyroidism persisting ($p<0.0001$). The probability of post-^{131}I hypothyroidism decreased with increasing age ($p<0.0001$). The best response to ^{131}I therapy was seen in patients with toxic adenoma, ($p=0.0001$). The incidence of hypothyroidism did not increase when the dose of ^{131}I was increased ($p<0.001$). The average time to develop clinical hypothyroidism was 7.1 months, and ^{131}I was effective in reducing thyroid nodule size. Age, sex and underlying pathology determine response to ^{131}I. Radioiodine therapy was effective in the treatment of 91.2% of hyperthyroidism cases. The short average time between treatment and the onset of hypothyroidism in our subjects means that the need for a follow-up is decreased in most cases.

Key words: Radioiodine, hyperthyroidism, temporary hypothyroidism

INTRODUCTION

Radioiodine (^{131}I) was first used in the treatment of thyroid hyperfunction a half-century ago[1-3]. ^{131}I is effective, and a suitable alternative to surgery, without the latter's complications[4]. Furthermore, the probability of recurrence of hyperthyroidism after treatment with ^{131}I is very low, in contrast to that with anti-thyroid medication[5]. Radioactive iodine therapy of hyperthyroidism is not associated with an increased risk of mutagenesis and carcinogenesis[6-8]. There is no age limit to the use of ^{131}I, though most physicians are loath to prescribe it in children before puberty[9,10]. The most important question in connection with the use of ^{131}I is the occurrence of post-treatment hypothyroidism[11]. Both the therapeutic effects of ^{131}I and the hypothyroidism it induces are caused by the destruction of thyroid tissue by radiation[12-15]. Accordingly, numerous methods have been devised to standardise radiation exposure (i.e. dose) from ^{131}I[16], though reduction of ^{131}I dosage has not been associated with long-term improvements in treatment outcome[17-20]. So, is radiation dosage the only determinant of treatment success? In this study of 1035 hyperthyroid patients treated with ^{131}I, we have assessed the relationship between treatment outcome and the variables of age, sex, underlying pathology and dose of ^{131}I received

MATERIALS AND METHODS

This study was a cross-sectional analysis of 1035 patients with thyroid hyperfunction treated with ^{131}I. A single endocrinologist evaluated hyperthyroid cases between 1988 and 2003. The following variables were ascertained as part of a questionnaire completed for each

Table 1: Aetiology of 1035 hyperthyroid patients

Underlying cause of hyperthyroidism	Patient distribution		Relapse	
	N	(%)	N	(%)
Graves' disease	499	(48.2)	35	(38.5)
Toxic multinodular Goitre	346	(33.4)	38	(41.9)
Hot nodule	190	(18.4)	18	(19.8)
Total	1035	(100)	91	(100)

p = 0.0001

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Table 2: Treatment outcome in 1035 hyperthyroid patients

	Total No. of Patients		Success (Euthyroid)				Failure (Re-treated)				Hypothyroidism after ^{131}I therapy	
			Yes		No		Yes		No			
Gender	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Female	804	(77.7)	280	(85.4)	56	(61.5)	55	(73.3)	749	(78.0)	463	(77.4)
Male	231	(22.3)	48	(14.8)	35	(38.5)	20	(26.7)	211	(22.0)	135	(22.6)
Total	1035	(100)	328	(100)	91	(100)	75	(100)	960	(100)	598	(100)

p<0.0001, p=0.04, p=0.0006

patient at the start of the study: (1) age, (2) sex, (3) treatment outcome (success/failure), (4) severity of post-treatment hypothyroidism, (5) frequency of temporary post-treatment hypothyroidism, (6) number of treatments with ^{131}I before either treatment success or onset of hypothyroidism, (7) stage of thyroid gland enlargement (according to WHO staging) before and after ^{131}I therapy, (8) underlying cause of hyperthyroidism, (9) side effects of treatment and (10) time delay between completion of treatment course and the onset of hypothyroidism.

Radioiodine was given at the maximum permissible (ablative) dose per unit weight of thyroid gland tissue[21,22].

The administrated of doses of ^{131}I was determined by an endocrinologist. For thyroids up to the stage IA, IB 10 mCi, for those at stage II and III about 12 and 15 mCi were administrated, respectively. To 3 cm of size and lower hot nodules 15 mCi and for hot nodule higher than 3 cm, 18 mCi iodine were given. To patients with huge multinodular goiter who were not candidate for surgery due to contraindication such as cardiovascular or pulmonary disorders 20 to 25 m Ci iodine was delivered.

The collected data were stored on a computer database and analysed using the Chi-squared function of the SPSS software package for categorical data.

Table 3: Age distribution and treatment success in 1035 hyperthyroid patients

Age group (ears)	Age distribution		Treatment success (Euthyroidism)			
			Yes		No	
	N	(%)	N	(%)	N	(%)
10-19	62	(6.1)	14	(4.3)	1	(1.0)
20-29	243	(23.8)	54	(16.4)	19	(20.9)
30-39	269	(26.3)	89	(27.1)	25	(27.5)
40-49	224	(21.9)	72	(22.1)	20	(22.0)
50-59	132	(12.9)	54	(16.4)	17	(18.7)
60-69	81	(7.9)	41	(12.4)	9	(9.9)
70-79	11	(1.1)	4	(1.3)	0	(0)
Total	1035	(100)	328	(100)	91	(100)

p = 0.001, p=0.2

Table 4: Distribution by age group of treatment failure and ^{131}I-induced hypothyroidism

Age group (years)	Re-treated with ^{131}I				Hypothyroidism	
	Yes		No			
	N	(%)	N	(%)	N	(%)
10-19	4	(5.4)	58	(6.2)	48	(8.1)
20-29	10	(13.5)	237	(24.7)	168	(28.0)
30-39	14	(18.9)	255	(26.5)	156	(26.1)
40-49	21	(28.4)	207	(21.5)	129	(21.5)
50-59	15	(20.3)	119	(12.4)	64	(10.7)
60-69	8	(10.8)	75	(7.8)	29	(4.8)
70-79	2	(2.7)	9	(0.9)	4	(0.8)
Total	75	(100)	960	(100)	598	(100)

p = 0.0004, p = 0.0001

RESULTS

The common underlying diagnoses were, in descending order of frequency, Grave's disease, Toxic Multinodular Goitre (TMG) and toxic adenomas (Table 1). Thyroid hyperfunction was 3.5 times more common in women than men (Table 2). The largest number of patients belonged to the 31 to 40 age group (26.3%). The smallest number belonged to the over-70 age group (1. 1%) (Table 3). The rate of response to ^{131}I was lower in men than women (p<0.0001) (Table 2), with the former being 2.4 times more likely to suffer from persisting hyperthyroidism (p=0.0001) (Table 2). The probability of post-^{131}I hypothyroidism declined as the patient's age increased (p<0.0001) (Table 4).

Underlying pathology was also studied as a determinant of response to ^{131}I therapy. The most favourable response was seen in patients with toxic adenomas, 44.8% of who became euthyroid whereas 43.6% were hypothyroid after treatment with ^{131}I. Next in rank in terms of treatment response was TMG, with 37.4% of patients becoming euthyroid and 49.5% hypothyroid after ^{131}I therapy. In third place were patients with Grave's disease, with corresponding rates of 23.0 and 68.5% for euthyroidism and hypothyroidism, respectively (Table 5). Euthyroidism persisting for a minimum of 2 years after ^{131}I was most likely to be achieved in patients with, in descending order of probability, toxic adenomas, TMG and Grave's disease. The probability of post-^{131}I hypothyroidism was highest in Grave's disease patients and lowest in patients with toxic adenomas (Table 5).

The incidence of post-treatment hypothyroidism did not increase along with increasing ^{131}I dose (p<0.001) (Table 6). The mean time delay before the onset of

Table 5: Distribution by underlying pathology of therapeutic response to ^{131}I

Underlying pathology	Grave's		Toxic multinodular goitre		Hot nodule	
	N	(%)	N	(%)	N	(%)
Response						
Hypothyroidism	342	(68.5)	172	(49.5)	83	(43.6)
Euthyroidism	115	(23.0)	129	(37.4)	85	(44.8)
Hyperthyroidism	42	(8.5)	45	(13.1)	22	(11.7)
Total	499	(100)	346	(100)	190	(100)

p = 0.0001

Table 6: Distribution of treatment response according to ^{131}I dose received

Dose of ^{131}I received (mCi)	<10		10–15		16 – 20		>20	
	N	(%)	N	(%)	N	(%)	N	(%)
Response								
Hypothyroidism	58	(81.7)	419	(65.5)	69	(51.9)	74	(46.5)
Euthyroidism	11	(15.5)	151	(23.6)	50	(37.6)	59	(37.1)
Hyperthyroidism	2	(2.8)	70	(10.9)	14	(10.5)	26	(16.4)
Total	71	(100)	640	(100)	133	(100)	159	(100)

p = 0.001

Table 7: Treatment response to ^{131}I in 1035 hyperthyroid patients

Response to Treatment	N	(%)
Hypothyroidism	598	(57.8)
Euthyroidism	328	(31.7)
Hyperthyroidism (Treatment Failure)	91	(8.8)
Temporary Hypothyroidism	18	(1.7)
Total	1035	(100)

p=0.0001

hypothyroidism was 7.1 months (7 months 4 days). ^{131}I was effective in reducing nodules size ($p<0.001$). ^{131}I therapy was effective in hyperthyroidism treatment in 91.2% of the cases (Table 7).

There were 18 cases of temporary hypothyroidism, 15 women and 3 men. The underlying diagnosis was Grave's disease in 11 cases, TMG in 5, and toxic adenomas in 2. All of them recovered to euthyroid status within 12 months of ^{131}I therapy.

DISCUSSION

The present study has the advantage of a larger sample size than previous similar studies and assesses more variables than its antecedents.

Thyroid hyperfunction is more frequent in women than men. One study gives a female-to-male ratio of 3.8:1[7], which is very close to the ratio of 3.5:1, which we obtained. The most common underlying diagnosis in our patients was Grave's disease (48.2%). This is in agreement with other investigations in this field, which yield a frequency range of 60 to 90% for Grave's disease in hyperthyroid populations. The next frequent underlying disorders were TMG and toxic adenomas, respectively[23]. The age distribution of our patients was also in agreement with the majority of studies published[6,7,22-27]. 91.2% of our patients had a favourable response to ^{131}I, with 31.7% remaining euthyroid for 2 or more years after ^{131}I therapy. The figures obtained by others differ according to the method of ^{131}I administration. One study reported 90% treatment efficacy with ^{131}I[26], whilst the other two studies give figures of 80%[25] and 77.5%[28].

One study showed that treatment success depends on the pre-treatment size of the thyroid gland: the smaller the gland, the higher the cure rate[29]. The incidence of hypo - or euthyroidism does not increase when the dose of ^{131}I given is increased (Table 6). In fact, we found an inverse relationship between the two. Huysmans *et al*,[30] study, did not find any significant difference between the two approaches comparing treatment outcome for ^{131}I prescribed on a per-weight basis with treatment outcome when ^{131}I is given in proportion to the rate of iodine uptake by thyroid tissue. A similar study concluded that the best method of calculating ^{131}I dosage is based on unit-weight-of-thyroid-tissue, since long-term follow-up failed to detect any significant difference in incidence of hypothyroidism between the two aforementioned methods[31].

In this study, we used the maximum permissible weight-adjusted (ablative) dose of ^{131}I. The average delay between treatment and onset of hypothyroidism was 7.1 months, which is close to the figure of 6 months in another study[26]. The advantage of this relatively short transition period was that it obviates the need for prolonged follow-up in this group of patients. Most reports in the field agree[21,22] with this finding. Therefore, ^{131}I should be prescribed on a per-weight basis since, the latter method is less expensive and less time-consuming in addition to the advantages[32].

Apart from initial gland size, factors determining response to ^{131}I therapy in our study included the underlying cause of hyperthyroidism, age and sex.

Thyroid hyperfunction is less frequent in men than women but associated with more severe symptoms. Men also have a lower response rate to ^{131}I therapy[33], with a 2.4-fold greater probability of hyperthyroidism persisting. Six times as many women as men became euthyroid after ^{131}I therapy, this being a reflection of the more frequent need for re-treatment in men.

One factor affecting the need for re-treatment with ^{131}I was underlying pathology. Patients with TMG required re-treatment most frequently, but patients with toxic adenomas least frequently (p=0.04). Patients with TMG in general showed the greatest variation in response to ^{131}I. This may be attributed to the activation of previously inactive or suppressed areas within the thyroid gland following ^{131}I therapy.

Age was also a determinant of response to ^{131}I. As age increases, the probability of post-^{131}I hypothyroidism decreases. Post-^{131}I hypothyroidism is most likely to occur in the third decade of life and least likely in the eighth decade. The need for re-treatment also increases with age, corresponding to the reduced probability of hypothyroidism (Table 3). We found no significant association between age and euthyroidism in our patients.

The present study showed that ^{131}I therapy is effective (91.2% favourable response rate) and has few side effects. There was only one case of thyroiditis and one case of submandibular adenitis in our sample study of 1035 patients. The gland size regards to reduction in a subgroup of patients after treatment with ^{131}I. This was in agreement with published research confirming radioiodine therapy as an effective method of reducing thyroid gland size[14,15,34,35].

The proportion of patients with toxic adenomas who progressed to hypothyroidism was higher (43.6%) in the present study than in the Allahabadia study (31.7%)[33]. Adoption of the dose/area ratio method[28] may help to reduce this figure. We observed 18 cases of temporary post-^{131}I hypothyroidism. All eighteen patients recovered to euthyroid status between 7 and 12 months after completion of ^{131}I therapy. Present rate of temporary hypothyroidism (1.7%) differs markedly from a similar Japanese study, in which 260 patients with Grave's disease were monitored for 1 to 15 years following treatment with intermediate doses of ^{131}I[19]. The incidence of temporary hypothyroidism in Japanese patients was 15%, with an average time of 12 months to euthyroid recovery. In the latter study, levels of TSH-receptor antibodies (anti-TSHR) were high (more than 5 times of upper normal limit) in 78% of the patients with temporary hypothyroidism[19]. We were unable to ascertain anti-TSHR status in our patients because of the retrospective nature of the study.

In conclusion, a weight-adjusted ablative dose of ^{131}I was effective in 91.2% of subjects, obviated the need for prolonged follow-up, and appeared to be a suitable mode of administration for ^{131}I. Given the exceptional efficacy and infrequent and tolerable side effects of ^{131}I in the treatment of thyroid hyperfunction, further investigation is required to elucidate the factors that determine satisfactory response to ^{131}I therapy as well as to reduce the incidence of post-therapy hypothyroidism.

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