Optimizing a Single Fixed Dose of Iodine - 131 in the Treatment of Graves' Disease: Experience From an Endemic Iodine Deficiency Goiter Belt in the Himalayan Valley of Kashmir, India

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Abstract

One hundred and twenty-one patients of Graves' disease were prospectively studied for their response to a single fixed dose of I-131. Patients were randomly treated with two different fixed doses of I-131. Sixty four patients belonging to Group-1 received a fixed dose of 185 MBq (Low Dose) and 57 patients belonging to Group-2 received 370 MBq (High Dose) of I-131. Following therapy all patients were evaluated at 3 months. Patients with normal or reduced thyroid hormone levels were termed as responders and those with persistently elevated levels of thyroid hormone were termed as non responders. The response rates among the two groups were analyzed for their statistical significance. Patients treated with the high fixed dose of 370 MBq revealed good response to therapy achieving a rate of 91.22%, while the response rate in the group of patients treated with low fixed dose of 185 MBq of I-131 was found to be significantly lower at 59.37%. On further analysis it was observed that the higher single fixed dose yielded a significantly higher cure rates irrespective of age, sex, thyroidal radioactive iodine uptake and pretreatment hormonal status. There was no significant difference in the overall incidence of post-131 hypothyroidism at the end of 1 and 5 years following I-131 treatment between the two groups of patients treated with low or high single fixed dose of I-131. A steady rise in the percentage of patients becoming hypothyroid was noted between the 1 and 5 year period. The overall incidence of hypothyroidism at one and five years following I-131 therapy was found to be 48 .76% and 82.64% respectively. The incidence of hypothyroidism appears to be higher in the present study, in comparison to several results reported in literature. This could be attributed to increased avidity of radioiodine to the available body iodine pool in the people living in the endemic area of iodine deficiency. Based on the results of this study we conclude that in an endemic area of iodine deficiency, a high single fixed dose of I-131 yields a higher cure rate as in non endemic areas but the incidence of post I-131 hypothyroidism appears to be higher. However this should not discourage physicians from choosing I-131 as the first line therapy for hyperthyroidism, considering the fact that the hypothyroidism is easily managed by thyroid hormone supplementation, it is cost-effective and last but not the least, it (hypothyroidism) is a part of the natural history of Graves' Disease.

Key Words: Graves' Disease, I-131 Therapy, Fixed Dose

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Introduction

Lush and mountainous, the valley of Kashmir is enclosed by the high snow capped ridges of Pir Panjal mountains to the south and west, and Himalayas to the north and east. Pakistan, Afghanistan and China border it from west to east with the plains of India in its south. A 3.5 kilometers tunnel, India's longest, bored through the rugged Pir Panjal mountains connects the valley with the hot plains of rest of the country. Only 15 to 20 % of its 2800 square kilometers rugged terrain is cultivatable and inhabited. For most of its 4 million natives agriculture and to some extent horticulture are the main economy generating activities. Due to long and harsh winters the terraced rice farming on the mountain slopes yields one crop of rice which is barely sufficient to meet the local needs of this staple diet. People are relatively poor with low annual percapita income (1). Iodine rich sea food in very remote land-locked valley is a luxury that most cannot afford. The literacy rate of Kashmiris is 40% as against the national literacy rate of 65.38% (1,2). Goiter is

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endemic in the Valley of Kashmir. In a published report the overall prevalence of goiter among the school going children in Kashmir between the ages of 5 and 15 years is 45.2% (±SEM) with urinary iodine excretion of 49±3.55 µg per gram of creatinine (3). The extremely shy people of Kashmir are casual towards the aesthetic aspects of their goiters but nevertheless seek medical advise when associated with physical symptoms. In a published study of 203 patients of thyrotoxicosis from Kashmir, Graves' disease was the commonest cause, accounting for 63% of patients (4).

Radioiodine (I-131) since its introduction in 1941 has been widely used in the treatment of various types of thyrotoxicosis and lately is being used as the first line therapy in Graves disease (5). I-131 an analogue of naturally occurring stable iodine is produced in a reactor facility. Like stable iodine it is trapped and organified in the thyroid gland to synthesize the thyroid harmones. However unlike stable iodine it emits 2 types of ionizing radiations namely, 364 KeV gamma rays that are useful for imaging the thyroid and 192 KeV beta rays which during their limited passage of 1-2 mm in the thyroid cause necrosis in the adjoining tissue thus alleviating the toxic state by reducing the mass of hyperfunctioning thyroid tissue (6). Deciding the optimal dose of I-131 to induce remission has been a matter of intense debate for over more than half a century (6). One can either use calculated dose, based on various factors like thyroid mass, radioiodine turnover or a simpler fixed dose regimen. There is scanty evidence to support any appreciable advantage of a complex calculated dose regimen over the relatively simple fixed dose regimen in terms of response or prevention of post I-131 hypothyroidism (7). In the present study we have analyzed the outcome of treating Graves' disease with a single fixed dose of I-131 in two groups of patients who were treated with fixed doses of either 185 MBq (Low dose) or 370 MBq (High dose) I-131. Being in an endemic iodine deficiency goiter belt with the possibility of an altered iodine bio-kinetics our endeavor was to find out how our patients with Graves' hyperthyroidism responded to a low and high single fixed dose of I-131, and recommend the optimal single fixed dose (Low or High) in such an environment.

Materials and Methods.

The study group comprised 121 patients of Graves' disease referred to the department of Nuclear Medicine for I-131 treatment at the Sher-I-Kashmir Institute of Medical Sciences, a tertiary care teaching hospital. It was a prospective study done between 1995 and 2005. Depending on the dose availability the patients were administered a calibrated single fixed dose of 185 MBq or 370 MBq of I-131. Prior to the administration of I-131 all the patients were clinically examined and their laboratory parameters were noted. Pregnancy and lactation were ruled out in all the female patients. After explaining the nature of treatment, a written consent was taken from all the patients. Antithyroid drugs were withdrawn a week before the I-131 therapy and not recommended for a minimum of one week after therapy. The dose was administered in a 6 hours fasting state to the patients. In severely symptomatic patients antithyroid drugs and beta blockers were restarted one week after the I-131 therapy. The patients were followed up for evaluation of response at three month intervals. At three months the patients were examined clinically and their thyroid function profile that included a total serum T4, T3 and TSH were performed by radioimmunoassay. Any patient on antithyroid drugs was advised to stop them one week prior to the thyroid hormone tests. Patients documented to have normal or reduced levels of thyroid hormones were termed as responders to I-131 and those with persistently elevated levels were termed as non responders and administered a further dose of I-131.

Statistical Analysis.

The SPSS package (Statistical Programme for Social Sciences Release 12.5.2005, PC windows) was used for the data analysis. In addition to descriptive statistics, the odds ratio analysis, Chi-square test, Wilcoxon signed rank test and student's t test were used for comparison between categorical variables. P value of < 0.05 was taken as statistically significant.

Demographic Profile of patients studied	Value
Total No. of Patients	121
Females	79
Males	42
Females: Males	1.9
Mean Age (Years)	46
Age Range (Years)	17-70
Mean Total Serum T3 (ng/ml)	4.01
Mean Total Serum T4 (µg/Dl)	16.89
Mean RAIU (%)	54.72
Goiter Size. <10cm.	100
Goiter Size. 10cm	21

Table 1: Demographic and Laboratory Profile of the Patients (Pre-I-131Treatment)

	Cured with 1 dose of 185 MBq of I-131(%)	Cured with 1 Dose of 370MBq of I-131(%)	P-Value*	OR
Sex.				
Female	62.16	92.85	<0.05	7.91
Males	55.55	86.66	<0.05	5.2
P-Value*	>0.05	>0.05	--- ---	--- ---
OR	1.31	2.0	--- ---	--- ---
Age.				
40Years	58.82	87.50	>0.05	4.9
40 Years	59.57	92.68	<0.05	8.95
P-Value	>0.05	>0.05	--- ---	--- ---
OR	1.03	1.81	--- ---	--- ---
RAIU (24 Hours).				
50%	61.63	93.99	<0.05	9.76
50%	55.00	87.50	<0.05	5.73
P-Value	>0.05	>0.05	--- ---	--- ---
OR	1.30	2.21	--- ---	--- ---
Serum T4.				
17µg/Dl	64.28	93.85	<0.05	7.4
17µg/Dl	50	85.71	<0.05	6.0
P-Value	>0.05	>0.05	--- ---	--- ---
OR	1.8	2.22	--- ---	--- ---
Goiter Size.				
10cm	60.34	92.85	<0.05	8.54
10cm	50	86.66	>0.05	6.50
P-Value	>0.05	>0.05	--- ---	--- ---
OR	1.5	2.0	--- ---	--- ---

*P-Value= Chi Square test. OR= Odds Ratio.

Table 2. Responses to low and high doses of I-131 Therapy

Results

The demographic and pre-treatment laboratory profile of the patients is given in Table 1. There were 79 female and 42 male patients. Among 79 female patients 37 were treated with a single fixed dose of 185 MBq of I-131 and 42 were treated with a single fixed dose of 370 MBq of I-131. The response rate at 3 months was 62.16% for the low dose and 92.85% for the high dose. There was significantly higher cure rates among females treated with 370 MBq of I-131. Among 42 male patients, 27 received a low dose of (185 MBq) I-131 and 15 patients received a high dose (370 MBq) of I-131. In the male patients also the cure rate at 3 months was significantly higher among those receiving 370 MBq of I-131 .Odds ratio of a successful cure rate with a higher dose of 370 MBq was 7.91 and 5.2 among female and male patients respectively. There was no difference in response rate to either a low or high dose among females and males. In this study group 33 patients were 40 years or less, and 88 patients were over 40 years of age. There was a significantly higher cure rate among patients who were 40 years or more and who were treated with a single fixed dose of 370 MBq. Among patients of 40 years or less a high single fixed dose did not seem to have a significant difference in cure rate when compared to low dose though the odds ratio of 4.9 was favorable for the high single fixed dose. A higher cure rate was observed among patients given a higher single fixed dose irrespective of their pre treatment radioiodine uptake values (Table 1).

All the patients had an elevated serum T4 levels with a mean pre treatment level of 16.89µg/dL. Patients were grouped into those with pre treatment T4 level greater than17 µg/dL and those with levels less than 17µg/dL .The cure rate was significantly higher in both the groups among patients treated with a higher single fixed dose , with an odds ratio of 7.4 and 6.0 for high and low single fixed dose respectively. A high single fixed dose had a significantly higher cure rate when given to patients with a goiter size of 10 cm or less and also among patients with goiters of more than 10 cm. The overall response in terms of cure rate was 91.22% for 57 patients treated with a high single fixed dose of 370MBq and 59.37% for the 64 patients treated with a low single fixed dose of 185 MBq of I-131. The difference was significant (Table 3). The incidence of post I-131 hypothyroidism at 1 and 5 years among patients treated with a low or high single fixed dose of I-131 did not show

Dose	Total No. of Patients	Response to treatment	P value
185 MBq (Low Dose)	64	38 (59.37%)	<0.05*
370 MBq (High Dose	57	52 (91.22%)	
Total	121	90 (74.38%)	

*P value: Chi square test

Table3: Overall Response to Single Dose of I-131

any significant difference (Table 4). However in both groups the percentage of patients becoming hypothyroid at 5 years (post I-131) was significantly higher when compared to the rate at 1 year post I-131. The overall incidence of hypothyroidism in the entire study group was 48.76% at 1 year and 82.64% at 5 years. The difference was significant. The overall response to single fixed dose (Low & High) of I-131was 74.38%. When we looked at the overall results it appears that there is a significantly higher cure rate among patients receiving a higher single fixed dose of 370 MBq of I-131 irrespective of sex, age, the hormonal levels, RAIU and the goiter size. There is no significant difference in the incidence of post I-131 hypothyroidism. An interesting observation in this study was that in no patient was I-131 chosen as the initial treatment option. Patients were managed with anti-thyroid drugs, beta blockers and anxiolytics for a time period ranging from 10 days to 12 years with an average hold up period of 3 years prior to administration of I-131.

Discussion

Iodine deficiency resulting in endemicity of goiter has been documented in Kashmiris. Amongst the profile of other thyroid disorders, thyrotoxicosis is also prevalent in the Valley of Kashmir, with Graves' hyperthyroidism accounting for 63% of such cases (4). In the present study we observed that anti thyroid drugs were still the first line of treatment for hyperthyroidism including Graves' hyperthyroidism. All the patients in the present study were managed with anti thyroid drugs for an average period of 3 years before contemplating I-131 treatment. The skepticism on the part of treating physician in using I-131 as the first line therapy in Graves' disease is perhaps due to ignorance of its utility and irrational fears about radiation induced genetic damage and malignancy (11-13). Anti thyroid drugs though effective in Graves' disease do not produced a sustained long term remission and may be associated with side effects and problems of compliance (14,15). Surgery is no longer a preferred method of treating Graves' disease except for cosmetic reasons in very large goiters (16,17). I-131 is increasingly being used in the first line therapy for Graves' hyperthyroidism in the developed countries. An appropriate dose of I-131 in Graves' hyperthyroidism has been debated hotly but a strong consensus in favor of using a fixed dose regimen seems to be emerging in the recent past (8-10). Time consuming and complicated dosimeteric methods that take into consideration the total thyroid mass and its iodine turnover do not seem to have any potential advantage over the fixed dose methods (8-10). Better cure rates with a higher single fixed dose of 370 MBq are well established (18). Most of such data is from non iodine deficient countries in the developed world. Kashmir being an iodine deficient area, an attempt was made to find out how Graves' disease responded to the high (370 MBq) and low (85 MBq) single fixed dose of I-131. Our observations of a significant difference in cure rates of 59.37% and 91.22% between low single fixed dose and high single fixed dose respectively in patients of Graves' disease were almost similar to the results reported in a previous study by Nordyke et al (19). Nordyke et al reported a cure rate of 66.6% and 84.6% in low and high dose groups respectively in their study based on larger number of patients that included all types of hyperthyroidism without specifically addressing the response among patients of Graves' disease (19). The single most constraint in using a high single fixed dose of I-131 is a possible increase in the rate of subsequent

Time after treatment	185 MBq (Low Dose)	370 MBq (High Dose)	P-Value*
1 year	43.75	54.38	>0.05
5 years	81.25	84.21	>0.05
P-Value**	<0.05	<0.05	--.--

(Overall rate of hypothyroidism including both schedules of treatment in 121 Patients: 1 Year= 48.76%, 5 Years = 82.64 %.)
* = Chi Square Test, **= Wilcoxon Signed Rank Test.

Table 4: Incidence of Hypothyroidism among Patients of Graves' Disease Treated with a Single Fixed Dose of 185 MBq (Low) or 370 MBq (High) of I-131.

hypothyroidism which has been reported in one of the larger studies from the developed world (54.5% at 1year) (19). Although this data is based on 321 patients of Graves' disease, it does not specify the rates of hypothyroidism separately for low and high single fixed doses of I-131(19). In our study the rates of hypothyroidism at 1 year post 1-131 were observed to be 43.75% and 54.38% for low and high single fixed doses respectively. This difference was insignificant. We also observed that the rate of hypothyroidism at 1 and 5 years post low single fixed dose of I-131 to be 43.75% and 81.25% respectively. This is high when compared to the rates of 15.5% and 27.3% with a similar dose in a published study from the west (20). However our results are close to another published study which reports 1 year post I-131 hypothyroidism rate without specifying the type of hyperthyroidism to be 41.3% with a low fixed dose and 60.8% with a high fixed dose (19). The possible reason for a relatively higher incidence of post I-131 hypothyroidism with both the low and high single fixed dose in an endemic area of iodine deficiency could be an increased avidity of radio iodine to the available body iodine pool.

The overall rate of post I-131 hypothyroidism in the present study was 48.76% and 82.64% at 1 and 5 years respectively. The present study though based on relatively smaller sample size did not show any difference in the incidence of hypothyroidism at 1or 5 years between a low and high single fixed dose of I-131. However more patients were hypothyroid at 5 years post I-131 than at 1year and the difference was significant. The overall cure rate with I-131 including both dose schedules in the present study is 74.38% and this compares with the rate of 69.5% in one of the published studies (19), the difference being statistically insignificant ($P>0.05$).

The present study clearly establishes the fact that a higher single fixed dose of 370 MBq of I-131, irrespective of sex, age, RAIU, thyroid hormonal level and goiter size produces significantly better cure rate among patients of Graves' disease even in an endemic iodine deficiency area like Kashmir. These results are comparable to the results from non endemic areas (18,19).

We observed that our physicians are not inclined to use I-131 as a first line treatment in Graves' disease. Physicians in general and endocrinologists in particular need to be made aware of this modality of treating Graves' disease which is safe, simple to administer and very cost effective. I-131 as the first line treatment for Graves' disease in endemic iodine deficiency areas is recommended as most of such areas are educationally and economically weak and underdeveloped.

Conclusion

From the present study we conclude that Graves' hyperthyroidism reportedly the commonest cause of hyperthyroidism in an iodine deficient area like Kashmir shows significantly higher cure rate to a single high fixed dose of 370 MBq of I-131. The incidence of post I-131 hypothyroidism in an endemic iodine deficient area at 1 and 5 years does not differ among these two single fixed dose schedules. When compared to data from the developed countries, a relatively higher incidence of post I-131 hypothyroidism in an endemic iodine deficient area may be attributable to increased thyroid avidity for iodine in such areas. A study focused on iodine kinetics in an iodine deficient area may answer this question in a more specific and scientific manner. The physicians and patients need to be made aware and educated about the simplicity, effectiveness and safety of I-131 as the first line treatment for the Graves' hyperthyroidism. Iodine deficient areas like Kashmir are also invariably economically and educationally weak making I-131 a logical first choice for treating Graves' disease.

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