

# Comparison of clinical outcome after a fixed dose versus dosimetry-based radioiodine treatment of Graves' disease: Results of a randomized controlled trial in Indian population

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### ABSTRACT

**Objective:** Two approaches are used to treat Graves' disease with radioiodine (<sup>131</sup>I)—the fixed dose approach and the other based on dosimetry. A prospective study was performed to compare the results of these two approaches in a randomized patient population, as such study is lacking in the Indian population till date. **Materials and Methods:** Patients with Graves' disease were randomized into two groups: (1) Fixed dose group and the (2) Calculated dose group, each comprising of 20 patients. All the patients underwent detailed clinical and biochemical evaluation. Thyroid mass was determined by high resolution ultrasound machine with linear transducer of 7-11 MHz. Patients were given 185-370 kBq (5-10 uCi) of <sup>131</sup>I and 24 hr radioiodine uptake (RAIU) was calculated using thyroid uptake probe and thyroid phantom. Fixed dose group patients were administered 185MBq of <sup>131</sup>I. Calculated dose group patients were given <sup>131</sup>I as per the following formula: Calculated dose = [3700 kBq/g × estimated thyroid wt. (g)] ÷ 24 hr RAIU (%). Success of first dose of radioiodine was defined as clinically/biochemically euthyroid/hypothyroid status at the end of 3 months without the need for further therapy. **Results:** In the fixed dose group, eight patients were hyperthyroid, four were euthyroid, and eight were hypothyroid after the first dose at 3 months. Success rate of first dose was 60%. In calculated dose group, seven patients were hyperthyroid, eight were euthyroid, and five were hypothyroid. Success rate of first dose was 65%. **Conclusions:** There is no statistically significant difference between the success rates of the two methods at 3 months. Hence, fixed dose approach may be used for treatment of Graves' disease as it is simple and convenient for the patient. Longer follow-up with higher number of patients should be done to confirm or contradict our findings.

**Key words:** Comparison, dosimetry, empiric dose, Graves' disease, radioiodine

## INTRODUCTION

Graves' disease is an autoimmune disease caused by autoantibodies (Thyrotropin (TSH) receptor antibodies-TSHR-Ab) that activate the TSH-receptor

(TSHR), thereby, stimulating thyroid hormone synthesis and secretion, and thyroid growth (causing a diffusely enlarged goiter). The resulting state of hyperthyroidism can cause a dramatic constellation of physical and neuropsychological signs and symptoms.<sup>[1]</sup> Diagnosis is usually made on the basis of symptoms, thyroid hormone profile and increased radioactive iodine uptake (RAIU). Thyroid scan may be done to support the diagnosis.

Treatment of Graves' disease includes antithyroid drugs, thyroidectomy, and radioactive iodine <sup>131</sup>I. Radioiodine (<sup>131</sup>I) has been used for treatment of Graves' disease for many decades. The high-energy beta emissions of <sup>131</sup>I (606 keV) make it very useful for therapy of Graves' disease.<sup>[2]</sup> Beta

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particles released in decay of iodine destroy the follicular cells leading to decreased production of thyroid hormones. However, dosing regimens vary from methods aiming primarily at a cure for Graves' disease, using larger doses of  $^{131}\text{I}$ , to methods using smaller doses, which sometimes aim at a euthyroid outcome.<sup>[3]</sup> Despite the long experience with radioiodine for hyperthyroidism, controversy remains regarding the optimal method to determine the activity that is required to achieve an optimal radiation dose to the thyroid gland and a subsequent optimal clinical outcome.<sup>[4,5]</sup> Many different strategies have been used to approach the ideal activity of  $^{131}\text{I}$  for hyperthyroidism. In general, two methods are available to determine the activity:

1. Standardized activity estimation, using a fixed activity for all patients irrespective of gland size and RAIU.<sup>[6]</sup>
2. Dosimetry-based calculation taking 24 hr RAIU in combination with an estimation of the weight of the thyroid gland.

Currently, there are very few studies comparing the success of radioiodine therapy using these two different approaches i.e. fixed dose and calculated dose. No such study has been performed comparing the clinical outcome using these two methods in the Indian population, which has seen a transition over the last 3 decades from an iodine deficient to an iodine sufficient population. In this study, we aimed to compare the clinical outcome after a fixed dose versus dosimetry-based radioiodine treatment approach of Graves' disease.

## MATERIALS AND METHODS

This was a prospective study conducted jointly by the departments of Nuclear Medicine, Radiodiagnosis, and Endocrinology, All India Institute of Medical Sciences (AIIMS) between July 2009 and June 2011. A total of 40 patients attending the thyroid clinic at the Department of Nuclear medicine, AIIMS, were included in the study. Only patients, who were proven to have Graves' hyperthyroidism, above 18 yrs of age and undergoing their first  $^{131}\text{I}$  therapy for Graves' disease, were included in the study. The study was approved by the institutional ethics committee. Written, informed consent was obtained. Patients were randomized into two groups: Fixed dose group and calculated dose group.

### Methodology

All the patients underwent detailed clinical and biochemical evaluation. Graves' hyperthyroidism was diagnosed on the basis of compatible symptoms, suppressed TSH levels, elevated serum thyroid hormones (total T4 and/or total T3), elevated radioiodine uptake (RAIU), and diffuse gland enlargement (clinically or on imaging when performed).

### Hormone assays

Hormone assays were performed in all patients before radioiodine therapy using the chemiluminescence technique and at 3 months follow-up using following reference ranges: TSH, 0.17-4.0 mIU/L; total T4, 4.5-12.5 ug/dL; and total T3, 70-200 ng/dL.

### Radioiodine uptake (RAIU)

Radioiodine ( $^{131}\text{I}$ ) was procured from BRIT (Board of Radiation and Isotope technology) India. All patients underwent RAIU both before  $^{131}\text{I}$  therapy as well as on 3 month follow-up. 185-370 kBq (5-10 uCi) of  $^{131}\text{I}$ -NaI in liquid form was administered orally. Atomlab 950 (Biodex) thyroid uptake probe was used for RAIU estimation at 2 hours and 24 hours, with pulse height analyzer setting such that the window width was set at 309-420 Kev and the photopeak was set at 364 Kev.

### Thyroid ultrasonography

Determination of thyroid volume was done by high resolution ACUSON S 200 (SIEMENS) ultrasonography machine with a linear transducer of 4-9 MHz frequency for patient in each group before  $^{131}\text{I}$  therapy as well as on 3 month follow up. The formula of Brunn and co-workers was applied for sonographic estimation of total thyroid volume.<sup>[7]</sup>

### Thyroid dose calculation

5 mCi of  $^{131}\text{I}$  was given in patients of fixed dose group. Calculated dose administered to thyroid was based upon estimated weight of the thyroid and 24 hr radioiodine uptake value and was calculated as:<sup>[8]</sup>

Administered dose (mCi) =

$$\frac{100 \mu\text{Ci} / \text{g} \times \text{thyroid estimated wt. in (g)} \times 10^{-3}}{24 \text{ hr RAIU}}$$

### Post-treatment isolation

Women were advised to avoid conception for six months after the therapy. Patients were advised not to have close contact with children and pregnant women as much as possible and follow all the post therapy radiation safety instructions for 1 week.

### Outcome endpoints

Patients were considered to be responders to initial  $^{131}\text{I}$  therapy if, at the 3-month follow-up, they showed biochemical evidence of a euthyroid or hypothyroid state. Persistence of biochemical hyperthyroid state was considered as treatment failure.

### Statistical analysis

Fisher's Exact test was used to compare the biochemical success between the two dose groups at the end of 3 months. Statistical package, STATA 8.0 and Statistical

Package for the Social Sciences (SPSS) 16.0 were used for all the statistical analyses.

## RESULTS

A total of 40 patients (14 male and 26 female) were recruited in this study from January 2010 to October 2010. All patients were proven case of Graves' disease. Out of 40 patients, 36 had received antithyroid drug (ATD) (Carbimazole) before therapy. Mean age of all the patients included in the study was 42.05 ( $\pm 11.94$ ) years with median of 41 years (range 21-65 years) [Table 1 and Figures 1].

The 40 patients were randomized into two groups of 20 each. The calculated dose group consisted of 12 females and eight males while the fixed dose group consisted of 14 female and six males. Various patient parameters assessed are given in [Tables 2 and 3].

Both the patients groups were analyzed for all the pre treatment parameters (RAIU 2 hr, RAIU 24 hr, T3, T4, TSH, Thyroid weight, age, and ATD duration) and there was no statistically significant difference for any parameter [Table 4a and b].

### Treatment outcome between the two dose groups

At 3 months post radioiodine therapy, 25 (62.5%) patients were considered as treatment success biochemically. Four patients were euthyroid, eight hypothyroid, and 8 hyperthyroid in fixed dose group (60% success), while eight patients were euthyroid, five hypothyroid, and seven hyperthyroid in the calculated dose group (65% success). Fisher's Exact test was used to compare the success rate between the two dose groups at the end of three months. The test shows that there was no statistically significant difference ( $P = 1.00$ ) between the two groups [Table 5].

**Table 1: Patient characteristics and pre and post radioiodine therapy investigation results**

	N	Mean	95% CI	SD	Median	Min.	Max.
Age	40	42.05	38.23-45.87	11.94	41	21	65
Dose	40	5.46	4.66-6.26	2.50	5	2.4	14
RAIU 2 hr (Pre)	40	37.49	31.71-43.26	18.06	34.3	4.9	77
RAIU 2 hr (Post)	40	16.17	11.74-20.60	13.85	10.55	0.5	48.7
RAIU 24 hr (Pre)	40	62.90	58.9-66.85	12.37	61.05	34.8	92
RAIU 24 hr (Post)	40	27.74	20.60-34.87	22.31	22.65	0.3	73.3
T3 (pre)	40	346.93	303.82-390.02	134.76	365	115	560
T3 (post)	40	192.28	147.56-37.00	139.83	172.5	37	714.3
T4 (pre)	40	15.81	14.17-17.45	5.13	16.5	4.86	26.5
T4 (post)	40	8.64	6.75-10.52	5.88	7.6	0.56	20.97
TSH (pre)	40	0.26	0.04-0.46	0.65	0.01	0.0001	3.5
TSH (post)	40	18.35	7.10-29.59	35.16	0.6	0.0001	126
Thyroid weight (pre)	40	34.13	27.89-40.35	19.47	27.8	9.1	88.6
Thyroid weight (post)	40	17.71	14.47-20.93	10.09	17.35	4.5	45.5
Rx duration	36	22.37	10.77-33.96	34.26	6	0	144

Age (in years), dose (in mCi), RAIU (in %), T3 (in ng/dL), T4 (in ug/dL), TSH (in mIU/L), thyroid weight (in g), Rx-Pre treatment duration (in months). SD: Standard deviation, CI: Confidence interval, RAIU: Radioiodine uptake, TSH: Thyrotropin

**Table 2: Patient characteristics and pre and post radioiodine therapy investigation results in calculated dose group**

	N	Mean	95% CI	SD	Median	Min.	Max
Age	20	42.85	37.50-48.19	11.43	41.5	21	65
Dose	20	5.93	4.27-7.57	3.52	4.3	2.4	14
RAIU 2 hr (Pre)	20	37.06	28.71-45.39	17.82	33	4.9	68.2
RAIU 2 hr (Post)	20	15.53	9.31-21.73	13.28	9.4	0.5	44.5
RAIU 24 hr (Pre)	20	60.70	55.04-66.35	12.09	59.05	34.8	92
RAIU 24 hr (Post)	20	27.23	16.82-37.63	22.23	22.65	0.4	73.3
T3 (pre)	20	357.41	292.56-422.24	138.54	360	115	560
T3 (post)	20	169.50	122.40-216.59	100.63	172.5	50	460
T4 (pre)	20	16.87	14.48-19.26	5.10	16.5	6.9	26.5
T4 (post)	20	7.96	5.39-10.52	5.48	6.85	0.56	16.5
TSH (pre)	20	0.24	0.002-0.48	0.51	0.008	0.0001	2
TSH (post)	20	14.11	-0.511-28.721	31.23	0.6	0.0001	108
Thyroid weight (pre)	20	35.94	25.21-46.66	22.92	24.85	13.3	88.6
Thyroid weight (post)	20	18.01	13.54-22.46	9.53	17.9	5.1	40.9
Rx duration	20	26.39	6.80-45.97	41.84	4	0	144

Age (in years), dose (in mCi), RAIU (in %), T3 (in ng/dL), T4 (in ug/dL), TSH (in mIU/L), thyroid weight (in g), Rx-Pre treatment duration (in months). SD: Standard deviation, CI: Confidence interval, RAIU: Radioiodine uptake, TSH: Thyrotropin

**Table 3: Patient characteristics and pre and post radioiodine therapy investigation results in fixed dose group**

	N	Mean	95% CI	SD	Median	Min.	Max.
Age	20	41.25	35.31-47.18	12.69	41	24	62
Dose	20	5.00	5.00-5.00	0.00	5	5	5
RAIU 2 hr (Pre)	20	37.93	29.15-46.70	18.75	35.55	12.4	77
RAIU 2 hr (Post)	20	16.82	9.92-23.70	14.72	11.9	1	48.7
RAIU 24 hr (Pre)	20	65.10	59.21-70.97	12.57	65.25	43.4	87
RAIU 24 hr (Post)	20	28.25	17.50-38.98	22.95	20.9	0.3	69.1
T3 (pre)	20	336.45	273.91-398.98	133.62	365	140	557.6
T3 (post)	20	215.07	135.48-294.64	170.04	172.5	37	714.3
T4 (pre)	20	14.75	12.38-17.11	5.05	15.73	4.86	21.3
T4 (post)	20	9.32	6.36-12.27	6.32	9.7	0.72	20.97
TSH (pre)	20	0.27	(-) 0.08-0.63	0.78	0.013	0.0001	3.5
TSH (post)	20	22.60	4.32-40.86	39.04	0.65	0.0001	126
Thyroid weight (pre)	20	32.31	24.97-39.64	15.68	30.55	9.1	64.9
Thyroid weight (post)	20	17.41	12.32-22.48	10.86	15.25	4.5	45.5
Rx duration	16	17.34	5.76-28.92	21.73	14.5	0	84

Age (in years), dose (in mCi), RAIU (in %), T3 (in ng/dL), T4 (in ug/dL), TSH (in mIU/L), thyroid weight (in g), Rx-Pre treatment duration (in months).  
SD: Standard deviation, CI: Confidence interval, RAIU: Radioiodine uptake, TSH: Thyrotropin

**Table 4a: Mean, F-ratio, and significance level obtained by ANOVA between the two dose groups**

	Mean (calculated dose group)	Mean (fixed dose group)	F-ratio	Significance level
RAIU 2 hr Pre	37.06	37.93	0.02	P=0.881
RAIU 24 hr Pre	60.70	65.10	1.27	P=0.267
T4 Pre	16.87	14.75	1.75	P=0.194
Thyroid weight Pre	35.94	32.31	0.34	P=0.562
Age	42.85	41.25	0.18	P=0.677

ANOVA: Analysis of variance, RAIU: Radioiodine uptake

**Table 4b: Rank and significance level obtained by Kruskal-Wallis test between the two dose groups**

	Rank (calculated dose group)	Rank (fixed dose group)	Significance level
3 Pre	21.50	19.50	P=0.588
TSH Pre	19.67	21.33	P=0.643
Rx duration	18.62	18.34	P=0.936

TSH: Thyrotropin

**Table 5: Comparison of clinical/biochemical success between calculated and fixed dose group**

	Clinical success (group)		Biochemical success (group)	
	Calculated dose	Fixed dose	Calculated dose	Fixed dose
Hyperthyroid	3	2	7	8
Euthyroid/Hypothyroid	17	18	13	12
Total	20	20	20	20

P=1.00

## DISCUSSION

Although there is general consensus that radioiodine is a safe and effective treatment for Graves' hyperthyroidism, debate remains in terms of the optimal method for calculating the dose and even what the criteria should be for defining optimal method. This is due to several factors,

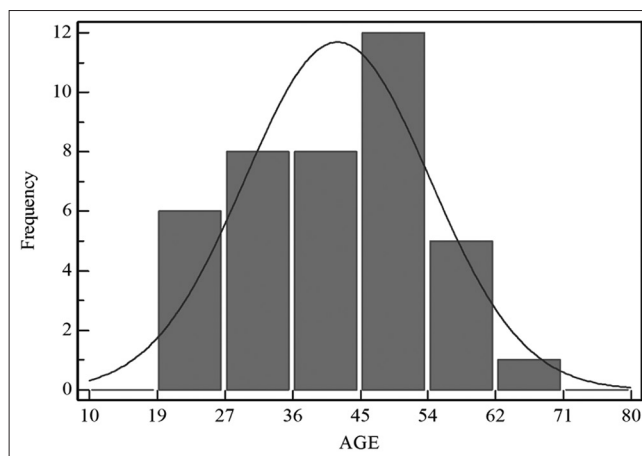


Figure 1: Age histogram of all the patients

including differing goals of treatment (hypothyroidism vs. euthyroidism), and the lack of comprehensive studies relating to the efficacy of different treatment protocols and outcomes.<sup>[9]</sup> Irrespective of the method of dose selection used, some patients develop hypothyroidism in the first year after <sup>131</sup>I; up to 70% in earlier studies, depending on the dose of radioiodine given.<sup>[10]</sup> As hypothyroidism is an unavoidable event in perhaps the majority of <sup>131</sup>I treated hyperthyroidism, some physicians consider that the goal of dosimetry, the avoidance of <sup>131</sup>I-induced hypothyroidism, to be a futile undertaking.<sup>[3,11]</sup> These physicians use ablative doses of <sup>131</sup>I, immediately curing hyperthyroidism, at the cost of inducing irreversible hypothyroidism in nearly all patients treated. Others, however, continue the use of treatment schedules aiming at euthyroidism.<sup>[12]</sup> In an effort to avoid excessive <sup>131</sup>I-induced thyroid damage resulting in hypothyroidism, complex formulae have been in use to calculate the dose needed for curing hyperthyroidism.<sup>[13,14]</sup>

The present study was carried out to directly compare a standard low dose with a calculated <sup>131</sup>I dose for treatment

of Graves' disease. There have been few randomized clinical trials that have directly compared different doses of  $^{131}\text{I}$  in the treatment of thyrotoxicosis. The earliest and largest trial compared a conventional dose [5.18 MBq (140  $\mu\text{Ci}$ )/g adjusted for gland size by palpation, but not for radioiodine uptake] with half-dose [2.59 MBq (70  $\mu\text{Ci}$ )/g] in 546 hyperthyroid patients.<sup>[15]</sup> The mean doses of radioiodine used in this particular study (185 MBq in the fixed dose group and 104 MBq in the half dose group) were much less than those currently used, and results may not be applicable to current practice.

A more recent randomized trial specifically compared a standard activity of 555 MBq  $^{131}\text{I}$  with an activity calculated to deliver 100 Gy to the thyroid, taking into consideration thyroid volume by ultrasound and radioiodine kinetics dose for Graves' hyperthyroidism.<sup>[16]</sup> They found higher success rates (defined as elimination of hyperthyroidism 6 months post treatment) with fixed activity (71%) vs. adjusted activity (58%), a difference that was marginally significant ( $P = 0.05$ ). In a third open randomized trial, 221 consecutive hyperthyroid patients were randomized to receive a fixed dose of iodine-131 (185, 370, or 555 MBq depending upon gland size) or an individualized dose (3.7 MBq/g total thyroid volume by ultrasound adjusted for 24 h radioiodine uptake measurement, to a maximum dose 740 MBq).<sup>[17]</sup> The researchers concluded that a semi quantitative approach is as good as using calculated radioiodine doses and is more cost effective.

In our study, the success rate at 3 months, defined as euthyroidism or hypothyroidism for both the groups, was 62.5% which is comparable with the success rates previously reported. No significant difference was found between success rates of both groups (60% vs. 65%). Also no difference was found with regards to achievement of hypothyroidism in both the groups ( $P = 1.00$ ). For our study, the follow-up period was limited to 3 months. It can be presumed that prolonged follow-up would have resulted in higher proportions of hypothyroidism for it is known that the annual incidence of hypothyroidism after radioiodine therapy is about 3%.<sup>[18]</sup>

Different factors that affect success rate of radioiodine therapy are pre therapy treatment with ATDs and its duration, thyroid gland size, RAIU, and age.<sup>[17,19,20]</sup> Not all authors report the use of antithyroid drugs prior to  $^{131}\text{I}$ -therapy properly. A slightly higher rate of treatment failure due to antithyroid drug use has been shown.<sup>[21]</sup> However, in our study outcome was not found to be associated with age ( $P = 0.809$ ), thyroid gland size ( $P = 0.154$ ) and RAIU 2 hr ( $P = 0.471$ ) and RAIU 24 hr ( $P = 0.318$ ) in fixed dose group and in calculated dose group too outcome was not

found to be associated with age ( $P = 0.211$ ), thyroid gland size ( $P = 0.768$ ) and RAIU 2 hr ( $P = 0.738$ ) and RAIU 24 hr ( $P = 0.944$ ). Duration of ATD treatment was also not found to have any significant impact on treatment outcome both in fixed dose ( $P = 0.785$ ) and calculated dose ( $P = 0.320$ ). This finding is most likely to be because of the fact that ATD was stopped 7 days before giving therapy in both groups. Smaller sample size in the present study and a shorter follow-up duration (3 months) might explain these findings. Sustained euthyroidism would clearly be the most desirable outcome, but this appears to be a futile objective, because high rates of cumulative hypothyroidism are reported in most series.<sup>[3,11,12]</sup> Our study showed 13 out of 40 patients to be hypothyroid at 3 month follow-up (eight patients in fixed dose group and five patients in calculated dose group). However, it is possible that some of these cases represented transient hypothyroidism.<sup>[22,23]</sup> But thyroxine replacement therapy of hypothyroidism is now safe, inexpensive and easily monitored by TSH measurement.<sup>[16]</sup> Furthermore, one must also remember that compared with the morbidity of continuing hyperthyroidism, sufficiently substituted hypothyroidism scarcely influences the quality of life of the patient affected. This has led some groups to suggest a larger initial radioiodine dose with achievement of hypothyroidism to minimize the need for retreatment and the morbidity and medical costs associated with ineffective primary treatment.

For studies calculating lowest effective radioiodine dose using dosimetric analysis, different parameters that determine the radioiodine dose are thyroid volume, RAIU and iodine half life.<sup>[2,3,10]</sup> In our study, calculated  $^{131}\text{I}$  dose was based upon ultrasonography estimation of thyroid gland size and radioiodine uptake at 24 h. Only a single observer was used to estimate thyroid size in an effort to minimize interobserver variability. However, our use of the radioiodine uptake at 24 h does not make any adjustment for iodine kinetics. Some groups have advocated additional uptake measurements after 24 h to characterize the rate of radioiodine turnover, which is then incorporated into the radioiodine treatment dose.<sup>[8,9,24]</sup> Because of these differences, we cannot definitely state that a more finely adjusted dose based upon thyroid radioiodine turnover would not give superior results to a fixed dose, as has been implied.

Ideally, the rate of euthyroidism should correlate with the applied activities of radioiodine, while too low activities would result in persistent hyperthyroidism and overdosing would induce hypothyroidism and in between these extremes an ideal activity would be observed. However, thus far the ideal way to determine activity does not exist,

mainly because treatment success depends on the absorbed dose and not on the applied activity. Individualized methods make important assumptions with respect to the kinetics of radioiodine. All included studies used the 24 h radioactive iodine uptake to determine activity. However, this uptake method may be inaccurate due to the fact that the biological half-life of radioiodine is variable and that it assumes a first order kinetic model, which may be too simplistic.<sup>[18]</sup> Moreover, dosimetric formulas take into account individualized iodine metabolism, but ignore several other factors also known to affect treatment outcome, such as patient age, gender and severity of hyperthyroidism. Also, the individual thyroid metabolism seems to fluctuate over time. Thus, the uptake of a test activity of radioiodine does not necessarily correlate with the uptake of the therapeutic activity several days to weeks later.<sup>[25]</sup> Since there will always be some time between the application of the uptake measurement and the therapy with <sup>131</sup>I, this problem cannot be overcome with dosimetry. These considerations make clear that calculated methods to determine activity may also not be optimal.

Although radioactive iodine is relatively inexpensive, costs of treatment are increased if there is a requirement for complex measurements of radioiodine uptake, turnover, and thyroid volume. The combined technical and professional costs for performing two radioiodine uptake measurements and a thyroid ultrasound may exceed the cost of the radioiodine treatment itself. Some groups have even proposed a role for positron emission tomography in dose calculation, which would clearly add considerably to costs.<sup>[26,27]</sup> Our study also suggests that a fixed dose approach works as well and could lead to greater patient convenience while at the same time reducing medical costs.<sup>[11]</sup> A large study by Damle *et al.*, in 633 patients with diffuse toxic goiter also suggested that first dose success of a fixed 185 MBq dose radioiodine is high when assessed over a period of 1 year.<sup>[28]</sup>

Irrespective of the treatment goal, radioactive treatment should be performed according to the ALARA ('as low as reasonable achievable') principle. This means that for a predefined therapeutic goal, the lower the administered activity better it is from the radiation safety point of view.

Our study had certain limitations: Firstly, the sample size was small as only 40 patients were enrolled in this study, and secondly, the follow-up duration was only 3 months, hence the actual incidence of hypothyroidism/euthyroidism in the present patient population might not represent the final outcome at a later stage. A larger follow-up study with longer follow-up duration might address these issues.

We conclude that a fixed low dose of radioiodine is as effective as a dosimetrically calculated dose. Hence, it can be used as a more convenient and cost effective method for radioablation of Graves' disease. This is only a preliminary study in Indian population. Further, large scale studies can be carried out further to prove or contradict our findings.

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