Radioiodine therapy in patients with Graves’ disease and the effects of prior carbimazole therapy

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ABSTRACT

The use of radioiodine as the first line of treatment in Graves’ disease is restricted in India because of its limited availability and an unrealistic risk perception associated with it. Additionally, the effectiveness of radioiodine ablation in Graves’ disease is influenced by many factors. Prior medical antithyroid therapy is one such important factor. Aims: To analyze the efficacy of low dose radioiodine therapy (5 mCi) in treatment of naive patients of Graves’ disease in comparison to that in which it was already primed with an antithyroid drug, carbimazole. Settings and Design: A non-randomized, interventional study conducted in the Department of Medicine and Endocrinology of a tertiary care institute in South India. Materials and Methods: The study had two groups; Group A (36 treatment naive, uncomplicated Graves’ disease patients) and B (34 Graves’ disease patients on carbimazole prior to radioiodine therapy). Both groups had baseline clinical, biochemical evaluation and were reassessed at 3 and 6 months for evaluating the clinical status for possible documentation of cure. Results: The cure rate was 61.1% in drug naive group and 58.8% in pretreated group at 6 months following radioiodine (P = 0.845). Higher baseline 99mTc technicium (99m Tc) uptake, male gender, BMI and higher baseline free thyroxine (fT4) level predicted treatment failure following radioiodine therapy. Conclusions: Administration of carbimazole prior to low dose radioiodine therapy does not alter the efficacy of radioiodine. Low fixed dose (5 mCi) of radioactive iodine may be a safe and effective primary therapeutic option in Graves’ disease patients pretreated with antithyroid drugs.

Key words: Fixed low dose, Graves’ disease, radioiodine ablation, treatment failure, treatment naïve

INTRODUCTION

Graves’ disease constitutes 60-80% of all cases of thyrotoxicosis worldwide and is caused by circulating autoantibodies that stimulate thyroid stimulating hormone (TSH) receptor on the thyroid gland. Treatment options for Graves’ disease include antithyroid drugs, radioiodine, and surgery (thyroidectomy). Radioiodine (RAI) is a safe, definitive, and cost effective modality of treatment which is used as the first line of treatment for Graves’ hyperthyroidism by most of the endocrinologists in the USA and elsewhere.[1] In India, however, there is reluctance to use RAI as the first line of treatment because of its limited availability and an unrealistic risk perception in both the general public and some medical practitioners. Antithyroid drugs are widely used in India, Europe, and Japan as an initial treatment of Graves’ disease.[2,3] Studies in the past evaluating the effect of antithyroid drugs on efficacy of RAI therapy have been conflicting.

Our study assessed the efficacy of RAI therapy in those who were treatment naïve and compared it with the outcome in those who are already treated with an antithyroid drug.
MATERIALS AND METHODS

This non-randomized interventional study was conducted in Medicine and Endocrinology departments of our tertiary care institute in South India between August 2010 and July 2012 after being approved by the institute ethics committee. All consecutive patients above 18 years of age who were diagnosed to have Graves’ disease during this period and fitting the study protocol were included. The diagnosis of Graves’ disease was based on clinical, biochemical, and scintigraphic evidence. The exclusion criteria were: age <18 years, pregnant/lactating mothers, severe ophthalmopathy, and patients not consenting for RAI therapy. The patients were subdivided into two groups [Figure 1- CONSORT diagram]. The subjects in group A were newly diagnosed Graves’ disease patients receiving beta blocker therapy alone. The group B comprised of Graves’ disease patients who received carbimazole pretreatment. They primarily consisted of patients who were inadequately controlled with antithyroid drugs or were associated with complications.

Patients of both groups (A and B) received fixed dose RAI of 5 mCi after getting informed consent in local language. Antithyroid drugs were stopped 3 days prior to RAI therapy and were restarted 1 week later at half dose, if needed and titrated. Beta blockers were continued through the ablative procedure and intensified if necessary. Patients with mild to moderate ophthalmopathy were taken up for ablation under the cover of steroids. All females of child bearing potential underwent pregnancy testing within 48 hours prior to administration of RAI and were advised to take oral contraceptive pills for at least 6 months post ablation. Radiation safety measures were explained to patients and their attenders. They were advised to report any adverse drug reactions. Parameters were reassessed at 3 and 6 months. Patients were monitored for change in symptoms and worsening of ophthalmopathy. Thyroid profile was obtained at 3 and 6 months. Patients were declared to be cured at end of 6 months if they were euthyroid or hypothyroid based on free thyroxine (fT4) levels.

Hyperthyroidism was defined as serum TSH level less than 0.35 μIU/ml (reference; 0.35-5.5 μIU/ml) with increased serum free T3 (reference; 2.3-4.2 pg/ml) and/or free T4 (reference; 0.89-1.76 ng/dl). All thyroid hormone investigations were done with Advia Centaur CP chemiluminescent Immunoassay System.

Statistical analysis was done using SPSS software version 17 (SPSS Inc., Chicago, Illinois, U.S.A). All continuous data were summarized as mean and standard deviation (SD). Other categorical data were summarized as frequency (percentage). Continuous non-normally distributed data were summarized as median and interquartile ranges (IQR). Cure rate between two groups were compared using Chi square test and relative risk. To compare two continuous data, unpaired t-test was used. In case of non-normally distributed data, Mann-Whitney U test was used. P < 0.05 was considered significant.

RESULTS

The pretreatment baseline characteristics of group A and group B patients are shown in Table 1. There were no significant differences between the two groups with respect to any of the characteristics listed. Out of 34 patients in group B, 13 patients had taken carbimazole for 2-6 months while rest of the 21 patients had taken carbimazole for more than 6 months. Maximum duration of carbimazole therapy was 240 months in one patient. Twelve patients had mild ophthalmopathy (6 with only signs and one had soft tissue involvement of orbit). They received oral prednisolone in dose of 22.5 ± 4.6 mg for 5.8 ± 1.4 weeks for prevention of ophthalmopathy exacerbation.

Outcome of RAI therapy on follow up in groups A and B is summarized in Table 2. In group A, high 99 mTc uptake on thyroid scintigraphy at baseline was significantly associated with treatment failure (P = 0.039) [Table 3]. In group B, male gender, BMI, higher baseline free T3 and free T4 and longer duration of carbimazole therapy were significantly associated with treatment failure [Table 3]. Multivariate logistic regression analysis could not be performed due to small sample size.

Table 1: Comparison of baseline characteristics of patients in groups A and B

| Baseline characteristics | Group A (n=36) | Group B (n=34) | P value |
|--------------------------|---------------|---------------|--------|
| Age in years (mean±SD)   | 40.67±12.13   | 37.38±11.18   | 0.24   |
| Females (%)              | 33 (91.66)    | 25 (73.56)    | 0.09   |
| Weight loss (%)          | 35 (97.22)    | 33 (97.05)    | 1.00   |
| Hyperdefecation (%)      | 17 (47.22)    | 23 (67.64)    | 0.138  |
| Tremors (%)              | 35 (97.22)    | 34 (100)      | 1.00   |
| Oligomenorrhea (%)       | 17 (51.51)    | 18 (72)       | 0.23   |
| Insomnia (%)             | 13 (36.11)    | 12 (35.3)     | 1.00   |
| Weight in kg (mean±SD)   | 43.13±8.42    | 47.6±9.99     | 0.46   |
| BMI in kg/m² (mean±SD)   | 18.36±3.38    | 19.83±3.76    | 0.088  |
| Pulse rate per min (mean±SD) | 108.5±13.11 | 106.6±20.28   | 0.649  |
| Systolic BP in mmHg (mean±SD) | 122.5±17.3    | 125.41±16.38 | 0.473  |
| Diastolic BP in mmHg (mean±SD) | 68.17±12.5  | 70.17±14.39   | 0.433  |
| Ophthalmopathy (%)       | 2 (5.5)       | 5 (14.7)      | 0.253  |
| Atrial fibrillation (%)  | 0 (0)         | 2 (5.8)       | 0.232  |
| fT3 in pg/ml (mean±SD)   | 12.8±5.74     | 11.73±6.82    | 0.479  |
| fT4 in ng/dl (mean±SD)   | 5.82±3.33     | 5.45±3.11     | 0.641  |
| TSH in μU/ml (median, IQR)| 0.02 (0.03) | 0.005 (0.04)  | 0.205  |
| 99 mTc uptake (%) (mean±SD) | 21.63±11.44 | 27.27±16.03   | 0.097  |

SD: Standard deviation; fT4: Free thyroxine; fT3: Free tri-iodothyroxine; TSH: Thyroid stimulating hormone; IQR: Interquartile range, BP: Blood pressure
Table 2: Thyroid profile of groups A and B patients following 3 and 6 months of radioiodine therapy

| Group A | Thyroid status at 3 months (n=36) (%) | fT4 (ng/dl) (mean±SD) | TSH (µIU/ml) (median (IQR)) | Group B | Thyroid status at 3 months (n=34) | fT4 (ng/dl) (mean±SD) | TSH (µIU/ml) (median (IQR)) |
|---------|--------------------------------------|-----------------------|-----------------------------|---------|----------------------------------|-----------------------|-----------------------------|
| Hyperthyroid 18 (50) | 7.06±3.53 | 2.79±1.02 | 0.015 (0.03) | 0.01 (0.04) | Hyperthyroid 15 (44.1) | 6.49±3.15 | 3.99±2.08 | 0.00 (0.05) | 0.01 (0.02) |
| Euthyroid 6 (16.66) | 5.38±3.61 | 1.26±0.23 | 0.03 (0.28) | 0.1 (0.09) | Euthyroid 7 (20.58) | 3.75±2.11 | 1.25±0.26 | 0.00 (0.03) | 0.1 (0.95) |
| Hypothyroid 12 (33.33) | 4.18±2.16 | 0.56±0.35 | 0.02 (0.01) | 8.97 (45.48) | Hypothyroid 12 (35.29) | 5.16±3.27 | 0.53±0.35 | 0.01 (0.09) | 49.77 (86.49) |

| Thyroid status at 6 months (n=36) (%) | fT4 (ng/dl) (mean±SD) | TSH (µIU/ml) (median (IQR)) | Thyroid status at 6 months (n=34) | fT4 (ng/dl) (mean±SD) | TSH (µIU/ml) (median (IQR)) |
|--------------------------------------|-----------------------|-----------------------------|----------------------------------|-----------------------|-----------------------------|
| Hyperthyroid 14 (38.88) | 2.68±1.37 | 0.01 (0.1) | Hyperthyroid 14 (41.17) | 4.39±2.2 | 0.01 (0.13) |
| Euthyroid 6 (16.66) | 1.18±0.26 | 0.01 (0.11) | Euthyroid 6 (17.64) | 1.43±0.16 | 0.01 (0.10) |
| Hypothyroid 16 (44.44) | 0.78±0.47 | 27.25 (44.21) | Hypothyroid 14 (41.17) | 0.56±0.33 | 56.93 (91.02) |

SD: Standard deviation; fT4: Free thyroxine; fT3: Free tri-iodothyronine; TSH: Thyroid stimulating hormone; IQR: Interquartile range

Adverse events

Eight patients experienced pain or soreness in the region of thyroid gland. There were no cases of worsening of symptoms of hyperthyroidism or occurrence of thyroid storm. None of the patients experienced aggravation of ophthalmpathy.

Discussion

American thyroid association (ATA) and American Association of Clinical Endocrinologists (AACE) guidelines for management of thyrotoxicosis 2011, recommend a single dose of 10-15 mCi for optimal treatment of Graves’ disease.[4] There is evidence that 10 mCi results in hypothyroidism in 69% at 1 year[6] and 15 mCi results in hypothyroidism in 75% at 6 months.[5] But in our study, we limited the dose of RAI to 5 mCi taking into consideration the resource limited setting and economic logistics available in our institute. Interestingly, we found a good cure rate at 6 months using such a low dose of RAI. Our study used a fixed low dose of 5 mCi of RAI in Graves’ disease patients. The observed cure rate was 61.1% (44.44% hypothyroid and 16.66% euthyroid) in group A and 58.8% (41.1% hypothyroid and 17.7% euthyroid) in group B after 6 months of RAI therapy. In group A, 50% of patients had responded (cured) within 3 months of RAI therapy while the response rate in group B within 3 months was 55.9%. Similar reports are there in literature.[7] Watson et al., found a cure rate of 72.4% at 5 years of follow-up but only 15.5% of patients were hypothyroid at the end of 1 year.[8] In an Indian study, using low dose of 5mCi, the cure rate was 82.4% (40% hypothyroid and 42.4% euthyroid) after a median follow-up period of 5 years and the response rate was 55.4% within 6 months.[9]

In our study, we tried to determine the factors that might have influenced the outcome of RAI therapy. In group A, higher 99mTc uptake was significantly associated with therapy failure. It was probably related to high iodine turnover associated with increased 99 mTc uptake. Interestingly, univariate analysis of the baseline characteristics in group B revealed multiple risk factors associated with therapy failure. In group B, male gender, BMI, higher baseline free T3 (fT3) and free T4 (fT4), and shorter duration of prior carbimazole therapy were significant risk factors associated with treatment failure. Multivariate logistic regression

Table 3: Univariate analysis of baseline characteristics in groups A and B patients with persistent hyperthyroidism (treatment failure) and success (hypothyroidism/euthyroidism) after 6 months of radioiodine therapy

| Characteristic | Group A | Treatment failure (n=14) | Treatment success (n=22) | P value | Group B | Treatment failure (n=14) | Treatment success (n=20) | P value |
|----------------|---------|------------------------|-------------------------|---------|---------|------------------------|-------------------------|---------|
| Age in years (mean±SD) | 40.07±11.66 | 41.05±12.68 | 0.818 | 39.21±12.68 | 36.1±10.15 | 0.433 |
| Males | 14 | 3 | 0.267 | 7 | 2 | 0.023 |
| Females | 2 | 19 | 0.523 | 18 | 7 | 0.276 |
| Weight in kg (mean±SD) | 41.85±7.08 | 43.95±9.24 | 0.523 | 45.36±10.71 | 49.2±9.4 | 0.032 |
| BMI in kg/m² (mean±SD) | 17.9±3.2 | 18.65±3.53 | 0.523 | 18.19±3.55 | 20.98±3.55 | 0.032 |
| Ophthalmopathy | 0 | 2 | 0.511 | 2 | 3 | 1.00 |
| fT3 in pg/ml (mean±SD) | 14.48±5.93 | 11.73±5.49 | 0.165 | 15.16±7.07 | 9.33±5.64 | 0.012 |
| fT4 in ng/dl (mean±SD) | 6.95±3.34 | 5.1±3.2 | 0.106 | 6.98±3.34 | 4.38±2.51 | 0.014 |
| TSH in µIU/ml (median (IQR)) | 0.01 (0.04) | 0.02 (0.02) | 0.964 | 0.005 (0.05) | 0.005 (0.02) | 0.382 |
| 99mTc uptake % (mean±SD) | 26.52±8.95 | 18.5±11.93 | 0.039 | 33.6±14.21 | 22.84±16.06 | 0.052 |
| Carbimazole duration in months (median (IQR)) | Not applicable | 3.5 (22) | 21 (33) | 0.009 |
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The treatment

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In our study, 691

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Bonnemma

and 6 months was not statistically significant. Studies in the

past evaluating the effect of administration of antithyroid

drugs prior to RAI therapy have given conflicting results.

Bonnemma et al., reported a higher treatment failure rate

following RAI therapy when propylthiouracil was given as

an adjunctive treatment.14 Connell et al., pretreated patients

with carbimazole before RAI therapy and discontinued the

drug 5 days prior to RAI administration.15 The treatment

failure rate at 1 year follow-up was higher in patients who

received prior carbimazole (75% vs 55%) when compared to

those who received RAI alone. Andrade et al., discontinued

methimazole 4 days prior to RAI therapy and did not

demonstrate any effect on cure rate following RAI therapy.14

Bonnemma et al., reported similar results when methimazole

was discontinued 6 days prior to RAI therapy.17

In a recent meta analysis that included 14 randomized

controlled trials, antithyroid drugs potentially increased the

rate of treatment failure when they were given in the week

before RAI treatment.18 However, ATA guidelines, 2011

suggest that discontinuing methimazole 3-5 days before

the administration of RAI is sufficient to wane off the

radioprotective effect of methimazole so that it does not

influence the efficacy of RAI.4 It is important to note from

our study that giving antithyroid drug cover prior to RAI

therapy did not reduce the effectiveness of RAI therapy,

provided it was stopped 3 days prior to RAI administration.

One patient in group A and two patients in group B

relapsed at 6 months after becoming euthyroid and

hypothesis respectively at 3 months. All of these patients

had persistently suppressed TSH level at end of 3 months

despite normal or low fT4 level. ATA guidelines, 2011

recommend that patients who have persistent, suppressed

TSH with normal fT4 level following RAI ablation should

be monitored closely for either relapse or development of

hypothyroidism.16 Uy HL et al., reported that transient

hypothyroidism can occur following RAI therapy with

subsequent recurrent hyperthyroidism.19 In our study,

out of 42 patients who were rendered either euthyroid

or hypothyroid at end of 6 months, TSH level remained

suppressed in 14 patients. These patients need to be followed

closely for a longer period to look for relapse in the future.

In our study, we administered RAI to newly diagnosed

Graves’ disease patients who were antithyroid drug

naive (group A). Radioablation was done after ensuring

adequate beta blockade. Few patients complained of pain

in the region of thyroid gland post ablation but there were

no cases of worsening of thyrotoxicosis or thyroid storm

in either group. All patients tolerated RAI therapy well with

marked clinical improvement in a study by Vijayakumar

et al.20 Our study demonstrated that RAI can be given

safely as the first line of treatment to patients with Graves’

disease without fear of thyroid storm.

The strength of our study is a low dropout rate of only

15% across the across the study period. There are very few

studies in India evaluating the efficacy and safety of RAI

and our study is the first one of its kind in south India. Our

study has certain limitations too. The study population was

small with a shorter duration of follow up. The cure rate

is expected to be much higher with longer follow up. Cure

rate can be expected to increase very significantly if it was

reassessed further down the time scale. We did not assess

the iodine status and thyroidal volume status of the study

subjects. Our study is not a randomized controlled trial and

there was a significant bias as evident by the presence of

heterogeneous population in group B. Comparison between

group A and group B could not be made conclusively due to

this bias, though incidentally, the baseline characteristics of

both groups matched. Some of study patients were required
to be put on antithyroid drugs following RAI and hence the
cure rate cannot be expected to exactly reflect the effect of
RAI. Most of our patients belong to lower or middle

socioeconomic strata hailing from a lesser iodine sufficient

areas and thereby our results may not be generalizable to

those patients from higher socioeconomic strata.

**Conclusion**

Low fixed dose (5 mCi) of RAI is a safe and effective

primary therapeutic option in Graves’ disease patients
without severe ophthalmopathy. Higher baseline 99 mTc uptake, male gender, BMI and higher baseline free T4 level may predict treatment failure following RAI therapy. A higher dose of RAI may be considered in these patients to improve the cure rate. Administration of carbimazole prior to RAI therapy does not alter the efficacy of RAI according to our study.

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