Original Article

Impact of lithium on radioactive iodine therapy for hyperthyroidism

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ABSTRACT

Context: Radioactive Iodine (RAI) is a common therapy for hyperthyroidism. However hyperthyroidism recurs or persists in 15-18% of patients after RAI. Studies report variable percentage of failure after RAI therapy depending on several variables including I^{131}. Lithium enhances efficacy of treatment by increasing RAI retention in the thyroid. **Aims:** To evaluate the efficacy of Lithium to RAI therapy in terms of cure, reduction of mean thyroid volume, and its safety. **Settings and Design:** A prospective comparative study. **Subjects and Methods:** Forty hyperthyroid patients were assigned to two groups, RAI alone and RAI plus lithium and followed for 1 year. Lithium was given in a dose of 900 mg/day in three divided doses for 6 days starting on the day of RAI therapy. Total T3, total T4, and thyroid-stimulating hormone (TSH) were done at baseline, 2,4,6,9, and 12 months. Ultrasound of thyroid was done at baseline and at the end of 1 year. Monitoring was done for side effects of lithium and RAI therapy. **Statistical Analysis:** Cure rate and time to cure were assessed by Chi-square test. Mean change in thyroid volume was compared by student's t-test. $P < 0.05$ was considered significant. **Results:** RAI combined with lithium had a trend towards better cure rate (90%) compared to RAI alone (70%) (P 0.11). Mean time taken to cure was 4.69 months in RAI plus lithium and 7.12 months in RAI alone (P 0.001). Mean change in thyroid volume was similar in both the groups ($P = 0.75$). There were no side effects of Lithium or RAI. **Conclusions:** RAI therapy combined with lithium showed a trend towards higher cure rate, safe and time to cure was less than RAI alone. Hence RAI combined with lithium is a better option in the management of hyperthyroidism than RAI alone.

Key words: Hyperthyroidism, lithium, Radioactive Iodine

Introduction

Radioactive Iodine (RAI) is widely used for hyperthyroidismdue to Graves' disease either as a first-line treatment or when hyperthyroidism relapses after antithyroid drug treatment.[1-4] Hyperthyroidism recurs or persists in 15-18% of patients after RAI.[5] Studies report variable percentage of failure after RAI therapy, depending on several variables including I^{131}.[6,7] Boelaert K, Syed AA *et al.* studied cure rate of hyperthyroidism according to amount of I^{131} administered. Patients treated with a single 16 millicurie (mCi) dose of I^{131} had a greater cure (84%) as compared with those treated with either 5 mCi (63%) or 10 mCi (75%) ($P < 0.001$).[6] Failure of RAI treatment may be influenced by several factors, including prior thionamide treatment, large goitre, high Radio iodine uptake (RAIU)), TSH Receptor antibodies (TRAb) titers.[6,7] However, the efficacy of RAI is dependent on its persistence in the thyroid gland. The increased turnover of radioiodine in hyperthyroidism leads to its rapid discharge from the gland. Lithium can be used as an adjuvant to enhance efficacy of RAI therapy. Lithium accumulates in the thyroid[8] and increases RAI retention without affecting RAIU.[9] The addition of lithium to RAI has been associated with increase in radiation dose delivered to thyroid.[10] Whether this results in higher cure rate of hyperthyroidism is still a matter of argument.[11,12] Furthermore, potential toxicity of lithium raised some concern about its use in combination with RAI for hyperthyroidism.[13]

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The aims of the present study were to evaluate whether lithium offers an additional value to RAI in term of cure of hyperthyroidism, time to cure, reduction of mean thyroid volume, and whether it was safe at the doses used.

Subjects and Methods

The present study included 40 subjects with hyperthyroidism due to Graves' disease who were eligible for RAI therapy attending the Department of Endocrinology and Nuclear Medicine during the period, February 2011 to January 2012. Forty patients were assigned randomly into two groups (RAI alone and RAI plus lithium) with 20 patients in each group based on lot method. Subjects aged 18 yr or more, who choose RAI as the primary modality of treatment for patients with recent onset hyperthyroidism, those on antithyroid drugs and failed to respond to treatment and now choose radioablation as choice of treatment and those with mild or absent Graves' ophthalmopathy were included. Subjects with moderate to severe and sight threatening Graves' ophthalmopathy, prior treatment with RAI, prior thyroidectomy, contraindications to lithium therapy, pregnant and lactating women were excluded from the study. The severity of ophthalmopathy is classified into mild, moderate to severe and sight-threatening based on European Group on Graves' Orbitopathy (EUGOGO) recommendations. Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown were classified as sight-threatening Graves' Orbitopathy (GO). Patients who have any one or more of the following: Lid retraction ≥2 mm, moderate or severe soft tissue involvement, exophthalmos ≥3 mm above normal for race and gender, inconstant, or constant diplopia were considered as moderate-to-severe GO. Patients who have only one or more of the following: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos <3 mm above normal for race and gender, transient or no diplopia, and corneal exposure responsive to lubricants were considered as mild GO.

History and examination was done in all patients. Evaluation was done for thyroid function, thyroid sonography, blood counts, liver function tests, and antithyroid peroxidase antibodies (anti-TPO-Abs). Total T3 (T T3), total T4 (T T4), and TSH were measured before giving RAI, 2, 4, 6, 9, and 12 months after giving RAI therapy. T T3, T T4, TSH and anti-TPO-abs were assayed by chemiluminescence (Roche, ELECSYS 2010, Hitachi high technology corporation, Tokyo, Japan) (Normal values: Serum T T3: 0.20-2.08 ng/ml, serum TT4: 4.5-12.0 μg/dl, serum TSH: 0.30-5.5 μIU/ml, antiTPO-abs: upto 34 IU/ml). We could not perform TRAb for confirmation of Graves' Disease because of economic constrains. A baseline electrocardiography (ECG) was done for all patients and followed up with two dimensional Echo if necessary.

Thyroid sonography was performed at baseline and at the end of 1 year. All patients were followed for 1 year. Thyroid volume was measured by Ultrasonography (MyLab™ classC- Esaote, Italy) using a 7.5 MHz linear transducer and calculated by the ellipsoid model: Width × length × thickness × 0.52 for each lobe.

Patients were considered cured when they become stably euthyroid or develop permanent hypothyroidism. Stable euthyroidism was defined as serum T T3, T T4 within normal range and confirmed during the following 12 month period. Hypothyroidism was defined as increased TSH concentrations with or without low serum thyroid hormones. Hypothyroidism was corrected by giving levothyroxine and the dose of levothyroxine was adjusted based on subsequent thyroid function tests. Patients with persistent hyperthyroidism were managed with carbimazole and followed up for 1 year after RAI therapy.

RAI therapy was the choice of therapy in all the 40 subjects, the indications being failure of antithyroid drugs in some patients and as primary modality of treatment for hyperthyroidism in others. Out of the 40 patients, 24 patients were toxic and were not treated with any antithyroid drugs, prior to the administration of RAI and remaining 16 patients who were using antithyroid drugs were asked to stop antithyroid drugs for 7 days prior to RAI. Thus all the patients were hyperthyroid prior to the start of RAI therapy. The type of radioactive isotope used for the management of hyperthyroidism in the present study was I^{131}. The RAI therapy adopted by our institute is a fixed dose of 5 mCi. However radioactive decay of I^{131} occurs during storage until it was administered to the patient. We measured the radioactivity of I^{131} prior to the administration by radio active isotope dose calibrator. So, the dose administered to the patient was between 4.5-5mCi. RAI was procured from Bombay Atomic Research Centre (BARC) laboratories. Isolation precautions were followed after RAI therapy and patients were monitored for side effects of RAI therapy. The side effects of RAI monitored in our study were actinic thyroiditis, Sialoadenitis, Nausea, vomiting, loss of appetite, dry mouth, taste changes, headache, worsening of ophthalmopathy. Lithium was administered in a dose of 900 mg per day in three divided doses for 6 days, starting on the day of RAI therapy. Monitored for side effects of lithium therapy, those were broadly categorised into Gastro-intestinal (nausea, vomiting and diarrhoea), Cardiovascular (cardiac arrhythmias, hypotension), Central Nervous system (tremor, giddiness, ataxia, nystagmus, confusion, slurred speech, hyper reflexia, muscle twitchings, drowsiness, delirium, coma, convulsions) and Renal system (nephrogenic, diabetes insipidus). Follow up

was done at 2, 4, 6, 9, and 12 months. Each follow-up visit included clinical and biochemical assessment.

The study was approved by the ethical committee of the institution.

Statistical analysis

Statistical analysis was done with SPSS 20.0. Baseline values were expressed as mean ± SD. The baseline characteristics of the two groups were compared by student's *t* test and cure rate, time to cure were assessed by chi- square test. Mean change in thyroid volume was compared by student's t test. $P < 0.05$ was statistically significant.

Results

The baseline characteristics of the 40 subjects (29 females, 11 males) are shown in Table 1 and were similar in both groups except for sex distribution. All the 40 patients included in our study were diagnosed as Graves' disease.

Outcome of therapy

The outcome of therapy in the RAI alone and RAI plus lithium is shown in Figure 1. In the RAI alone, 12 of 20 (60%) patients became euthyroid and 2 of 20 (10%) patients became hypothyroid whereas, 6 of 20 (30%) patients remained hyperthyroid. In the RAI plus lithium, 11 of 20 (55%) patients became euthyroid, 7 of 20 (35%) became hypothyroid whereas 2 of 20 (10%) remained toxic towards the end of study.

Outcome of therapy when Goitre volume <20 ml or >20 ml

Table 2 shows the outcome of therapy when further analyzed based on mean thyroid volume whether it was >20 ml or <20 ml. Among patients with goitre volume <20 ml, there was 100% cure rate in RAI plus lithium compared to 75% in RAI alone. Similarly in patients with goitre volume >20 ml, hyperthyroidism was cured in 83% in RAI plus lithium than 69% in RAI alone. So addition of lithium showed a trend towards better cure rate in RAI plus lithium group.

Cure rate

Figure 2 shows the cure rate in both the groups. In the RAI group, 14 of 20 (70%) patients were cured, whereas in the RAI plus lithium group, 18 of 20 (90%) were cured. However cure rate was not statistically significant ($P = 0.114$).

Table 1: Baseline characteristics of RAI alone and RAI plus lithium

	RAI alone	RAI+lithium	*P* value
Patients (M/F)	20 (9/11)	20 (2/18)	0.01
Mean age (years)	37.30±12.73	35.85±7.54	0.66
Smokers (%)	10	15	0.63
Ophthalmopathy (%)	15	10	0.59
Onset of hyperthyroidism (months)	15.45±10.77	19.65±20.99	0.43
Mean thyroid volume (ml)	28.15±12.40	26.70±15.84	0.74
Mean serum T T3 (ng/ml)	3.57±1.38	3.65±1.51	0.78
Mean serum T T4(μg/dl)	21.74±4.29	21.48±4.97	0.79
Anti TPO Ab (IU/ml)	385±235	296±213	0.22
I^{131} administered dose	4.85±0.87	4.70±0.47	0.50
ATD usage number (%)	7 (35)	9 (45)	0.41

ATD: Antithyroid drug, RAI: Radioactive Iodine, TPO: Thyroid Peroxidase

Table 2: Outcome of therapy when mean thyroid volume <20 ml and >20 ml

	Goitre volume <20 ml (%)		Goitre volume >20 ml (%)	
	RAI (*n*=4)	RAI+lithium (*n*=8)	RAI (*n*=16)	RAI+lithium (*n*=12)
Euthyroid	3 (75)	3 (38)	9 (56)	8 (66)
Hypothyroid	0	5 (62)	2 (13)	2 (17)
Hyperthyroid	1 (25)	0	5 (31)	2 (17)
	P=0.14		*P*=0.37	

RAI: Radioactive Iodine

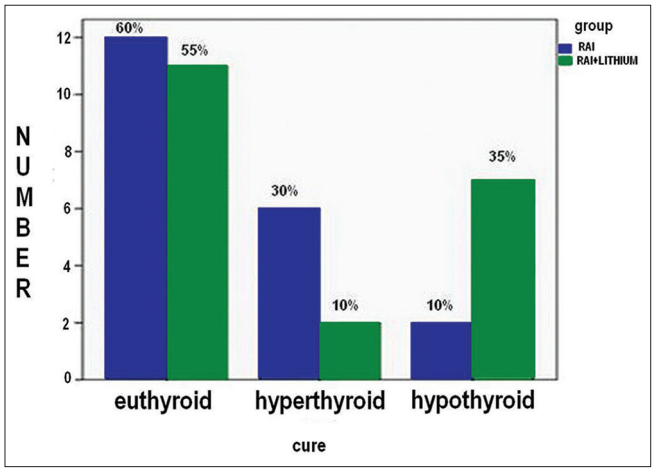

Figure 1: The outcome of therapy in the RAI alone and RAI plus lithium

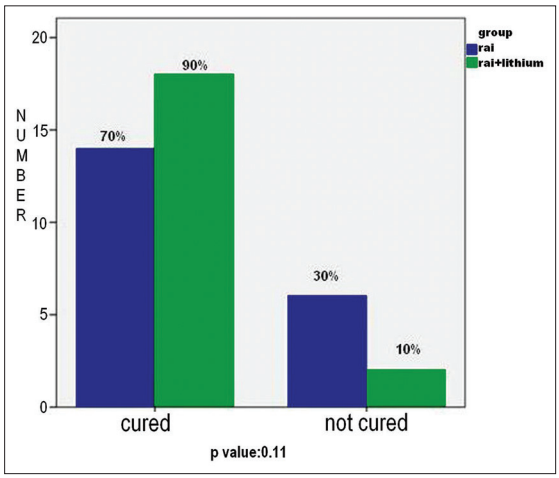

Figure 2: Cure rate in both the groups

Cure time

Mean time taken to cure was 4.69 months in radioiodine plus lithium and 7.12 months in radioiodine alone ($P = 0.001$). RAI plus lithium group cured earlier than RAI alone which was statistically significant. Figure 3 shows mean time (months) taken to reach euthyroidism and hypothyroidism in the two groups.

Anti thyroid drugs

The type of antithyroid drug (ATD) used in both groups before and after RAI are shown in Table 3 and Table 4. There was significant reduction of usage of ATD in RAI plus lithium group compared to RAI alone after radio-iodine therapy ($P = 0.01$).

Outcome of thyroid volume

Mean thyroid volume at baseline was 28.15 ± 12.40 ml in RAI alone and 26.70 ± 15.84 ml in RAI plus lithium ($P = 0.74$). At the end of study, the mean thyroid volume was 9.75 ± 6.13 ml in RAI alone and 9.10 ± 6.79 ml in RAI plus lithium which was similar in both the groups. (P value 0.75). There was significant reduction of goitre volume in both RAI alone and RAI plus lithium towards the end of the study ($P = 0.0001$). However the reduction of goitre volume was same in both the groups. Figure 4 shows mean thyroid volume at baseline and at the end of 1 year in both groups.

Goitre volume reduction was further analyzed based on goitre volume <20 ml or >20 ml. There was 70% reduction of goitre volume in RAI alone, whereas 72% reduction in RAI plus lithium in subjects with goitre volume <20 ml. Similarly there was 65% reduction of goitre volume in RAI alone and 66% reduction in RAI plus lithium in patients with goitre volume >20 ml. There was significant reduction of goitre volume towards the end of study. However the reduction of goitre volume was same in both the groups. So, addition of lithium did not have much effect on the reduction of goitre volume.

Table 3: Type of ATD used before RAI

	RAI (%)	RAI+lithium (%)
Carbimazole	6 (30)	9 (45)
PTU	1 (5)	0
Not used	13 (65)	11 (55)

P=0.41, ATD: Antithyroid drug, RAI: Radioactive Iodine, PTU: Propylthiouracil

Table 4: Type of ATD used after RAI

	RAI (%)	RAI+lithium (%)
Carbimazole	13 (65)	5 (25)
Methimazole	1 (5)	0
Not used	6 (30)	15 (75)

P=0.01, ATD: Antithyroid drug, RAI: Radioactive Iodine

Outcome of T T3

The mean T T3 values at baseline and at follow up of 2, 4, 6, 9 and 12 months is shown in Figure 5. Mean T T3 concentrations did not differ at baseline in both groups.

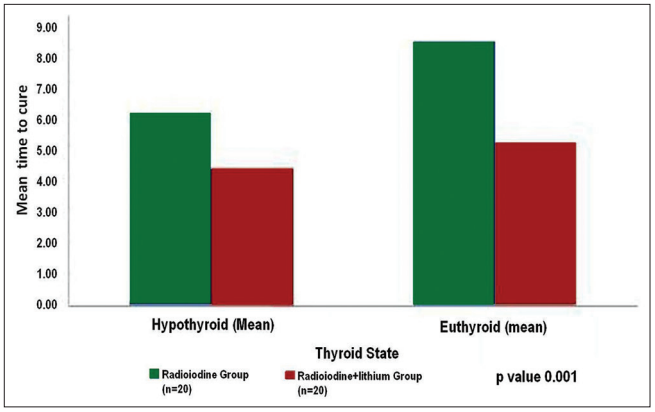

Figure 3: Mean time (months) taken to reach euthyroidism and hypothyroidism in the two groups

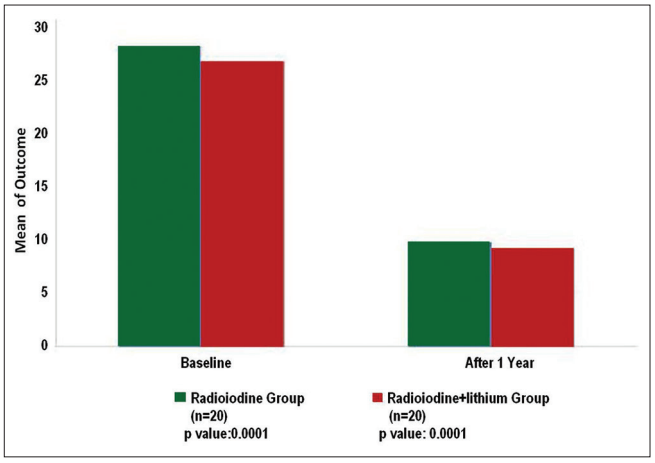

Figure 4: Mean thyroid volume at baseline and at the end of 1 year in both groups. There was significant reduction of goiter volume in both RAI alone and RAI plus lithium towards the end of the study ($P = 0.0001$)

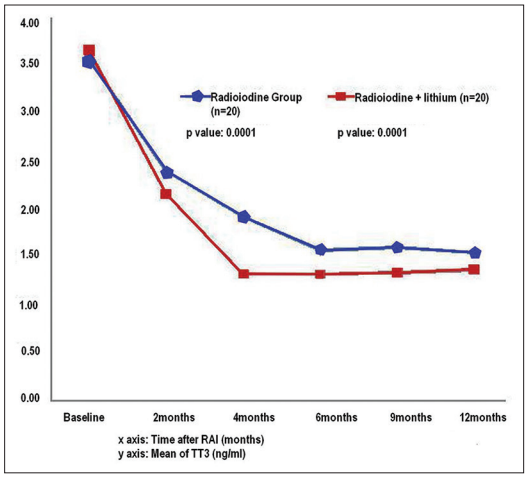

Figure 5: Outcome of T T3. There was significant reduction of T T3 in RAI and RAI plus lithium groups towards the end of study ($P = 0.0001$)

In the RAI alone, there was a gradual fall of T T3 levels up to 6 months of follow up after which the T T3 levels were stable. In the RAI plus lithium group, there was a steep fall in level of T T3 up to 4 months after which the level stabilized. There was significant reduction of T T3 in both the groups towards the end of the study compared to baseline ($P = 0.0001$).

Outcome of T T4

The mean T T4 values at baseline and at follow up of 2, 4, 6, 9 and 12 months is shown in Figure 6. Mean T T4 values at baseline were similar in both two groups. In RAI alone, mean T T4 values showed gradual fall up to 6 months of follow up after which remained stable. In the RAI plus lithium, there was a steep fall in level of T T4 up to 4 months after which the level stabilized. There was significant reduction of T T4 in both the groups towards the end of the study compared to baseline ($P = 0.0001$).

Outcome of Graves' ophthalmopathy

There were five patients with ophthalmopathy in our study, out of which, three patients were in RAI alone and two patients were in RAI plus lithium. All the five patients had mild ophthalmopathy and no patient in either group had worsening of ophthalmopathy during the study.

Side effects of lithium and RAI therapy

No side effects of either RAI therapy or lithium were observed during the study.

Discussion

The present study showed that RAI plus lithium had a trend towards better cure rate than RAI alone. The RAI plus lithium had a cure rate of 90% while the RAI alone had a cure rate of 70% ($P = 0.11$). The small sample size

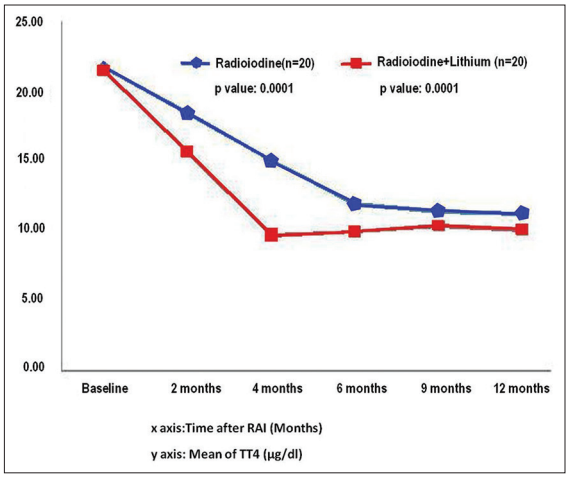

Figure 6: Outcome of T T4. There was significant reduction of T T4 in RAI and RAI plus lithium groups towards the end of study ($P = 0.0001$)

in our study might have precluded statistical significance. Lithium can affect the kinetics of iodine by reducing its release from the thyroid gland and thus increase its retention in the gland.[5,14] Addition of lithium to RAI has been associated with an increase in the radiation dose delivered to the thyroid.[10] Whether this results in higher cure rate of hyperthyroidism is still a matter of argument. Conflicting results have been reported on this issue.[11,12,15] Fausto Bogazzi *et al.*, in their study published in 1999 showed a cure rate of 72% in those treated with RAI alone and 83% in those treated with RAI and lithium, which was statistically significant.[11] In a recent study in 2010 involving a larger cohort, the same authors showed a higher cure rate with RAI plus lithium ((91%) vs RAI alone (85%).[5] Another study by same author published in 2002 showed higher cure rate in RAI plus lithium (G2, G3 groups) (92%) compared to RAI alone (G1 group) (67%).[10] In a retrospective cohort study by N.M.Martin *et al.* showed a cure rate of 93.1% in RAI plus lithium versus 83.5% in RAI alone.[16] Thus present study was in agreement with earlier studies. Whereas, a study by Bal *et al.* from India showed a cure rate after the first dose of radioiodine in the control and lithium groups was similar (68.4% and 68.9% respectively).[12] Similarly a study by Brownie and Turner *et al.* showed that in patients with 35-55 g goitres, addition of lithium to RAI did not produce a higher cure rate after 3 years follow-up period.[15] The radioiodine dose used by Bogazzi *et al.* was 520-530 millibecquerel (mBq), by N.M. Martin *et al.* was 550-570 mBq, by Bal *et al.* was 230 mBq and our study used around 185 mBq. This suggests that the difference in the cure rate might also depend on the dose of radioiodine used.

Another important result of our study was that addition of lithium as adjuvant therapy to RAI allowed a prompter control of hyperthyroidism than RAI alone thus confirming results of previous studies. Mean time taken to cure was 4.69 months in RAI plus lithium and 7.12 months in RAI alone ($P = 0.001$). RAI plus lithium group cured earlier than RAI alone which was statistically significant. Median time taken to reach cure was 60 days in RAI plus lithium and 90 days in RAI alone in a study by Fausto Bogazzi *et al.* The difference in the time taken to cure between our study and study by Bogazzi *et al.* could be because of high RAI dose used and longer duration of lithium (12 days) compared to our study (6 days). In an another study by N.M. Martin *et al.*[16] showed that there was a significant reduction in the time to cure in the RAI plus lithium group (10.5 weeks) compared with RAI alone (12 weeks) ($P = 0.02$). Prompt control of hyperthyroidism is important in some patients such as elderly or those with underlying cardiac problems like arrhythmias, ischemic heart disease etc., who need rapid cure.

The third important result of our study was goitre volume reduction. Goitre shrinkage occurred in both the groups

significantly compared with baseline. However, the reduction of goitre volume was same in both the groups. So the addition of lithium did not have much effect on the reduction of goitre volume. This observation was in agreement with earlier studies.[5,11]

Mean serum T T3, T T4, did not differ in the two groups at baseline and there was a steep fall of T T4 and T T3 in RAI plus lithium within 4 months on follow up. So the addition of lithium to RAI in our study might have contributed for the steep fall in the levels of T T3 and T T4 levels at 4 months. This rapid control may be beneficial in patients with cardiac arrhythmias, ischemic heart disease and older people.

Five patients who had mild ophthalmopathy did not have worsening of ophthalmopathy during follow up. The combined treatment with RAI plus lithium might also be favorable for Graves' ophthalmopathy, because of the lower risk of recurrence of hyperthyroidism, which is known to affect negatively the course of eye disease.[17]

There were no side effects either with RAI or lithium in the present study, thus proving the safety of RAI and lithium therapy in the management of hyperthyroidism.

The results of present study showed that the addition of lithium was beneficial for hyperthyroid patients treated with RAI. However, we did not measure I^{131} radioactivity in the thyroid gland after radio ablation. So we could not confirm the radio retention effect of lithium. Finally, the lithium regimen used was cheap, safe, and may avoid further requirement of RAI therapy. The limitations of the study were small sample size and failure to measure serum lithium concentrations.

In conclusion RAI therapy combined with lithium showed a trend towards higher cure rate but does not reach statistical significance, probably requires larger sample to confirm. This study also suggests that a short course of lithium was safe and beneficial for patients treated with RAI, increasing the cure rate and shortening the cure time. The addition of lithium did not have much effect on the reduction of goitre volume. There were no side effects of lithium or RAI therapy in our study. Hence RAI therapy combined with lithium may be better option in the management of hyperthyroidism due to Graves' disease than RAI alone. Our study used low dose of radioiodine and short course of lithium and showed similar results with earlier studies.

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