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A Randomized Controlled Trial to Evaluate the Adjuvant Effect of Lithium on Radioiodine Treatment of Hyperthyroidism

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Objective: To evaluate the role of lithium (Li) as an adjuvant in radioiodine therapy of hyperthyroidism. *Methods:* A randomized controlled trial was carried out on 350 hyperthyroid patients with a mean follow-up period of 32.3 ± 9.8 months (range, 12–60 months). The patients were randomized into two groups with 175 patients in each group: (1) radioiodine group (controls)—no lithium was given to these patients at any stage of their treatment and (2) radioiodine and lithium group (Li group)—lithium carbonate, 300 mg three times a day, for 3 weeks starting on the day of radioiodine administration. All patients were made euthyroid with antithyroid drugs prior to radioiodine therapy. *Results:* Mean age was 41.8 ± 11.5 years (range, 18–71) in the control group and 41.8 ± 12.2 years (range, 19–73) in the Li group. Mean first dose and cumulative dose of ^{131}I were 229 ± 85 MBq and 326 ± 204 MBq in controls and 233 ± 110 MBq and 344 ± 281 MBq in the Li group. Average number of radioiodine therapy administered was the same (1.4) in both groups. The cure rate (euthyroid plus hypothyroid) after the first dose of radioiodine in the control and the lithium groups was 68.4% and 68.9%, respectively (p = ns). The overall cure rate at the end of the study was also the same in both groups (96.7% and 96.3%, respectively). Even in patients with a rapidly discharging gland or in patients with a large goiter, no significant statistical difference was observed in radioiodine therapy outcome between the two groups. Ten percent of the patients complained of mild to moderate side effects of lithium. *Conclusion:* The role of lithium as an adjuvant in radioiodine therapy of hyperthyroidism is insignificant.

Introduction

RADIOACTIVE IODINE THERAPY for hyperthyroidism was first used in 1941 by physicians at Massachusetts General Hospital in Boston, Massachusetts (1,2). The relatively low cost, convenient half-life of 8 days, and the effectiveness of treatment of hyperthyroidism with radioiodine have led to its widespread adoption, and now, it is a well-established and effective treatment for hyperthyroidism worldwide.

The effectiveness of radioiodine depends on several factors, including previous treatment with antithyroid drugs, goiter size, 24-hour thyroidal radioactive iodine uptake (RAIU), and the rate of release of radioiodine after incorporation into thyroglobulin (3–6).

Several adjuncts have been used with radioiodine to increase its effectiveness. Lithium blocks the release of organic iodine and thyroid hormone from the thyroid gland without affecting thyroidal RAIU (7–10). These effects are mediated either through the potentiation of an iodide-induced block of binding and hormone release (11,12) (perhaps because lithium is concentrated by the thyroid [13] and subsequently increases the intrathyroidal iodide concentration [14,15]), or through inhibition of adenylate cyclase activity and blockage of cyclic adenosinemonophosphate (cAMP)-mediated translocation of thyroid hormone (16). The latter effect, which is probably responsible for the inhibition of hormone release, appears to be caused by the stabilization of thyroid cell microtubules promoted by lithium (17). Accordingly, its use as an adjunct to radioiodine in the therapy of hyperthyroidism was postulated, but information on this subject is limited (18–20). Therefore, we tried to evaluate the role of lithium as an adjuvant in radioiodine therapy of hyperthyroidism critically, because there is no unanimity regarding its use and effect.

Materials and Methods

Sample size

A two-group χ^2 test with a 0.05 two-sided significance level will have 90% power to detect the difference between a group 1 proportion (radioiodine group) of 0.65 and a group

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2 proportion (radioiodine and lithium) of 0.80 (odds ratio, 2.15) when the sample size in each group is 175 patients.

A randomized controlled trial (RCT) on 350 hyperthyroid patients was undertaken from Dec 1994 to Dec 1999 at All India Institute of Medical Sciences, New Delhi, India. patients with severe Graves' ophthalmopathy, previous treatment of hyperthyroidism with radioiodine or surgery, and those with contraindications to lithium treatment were excluded from the study. The patients were randomly assigned to one of two groups with 175 patients in each group; (1) radioiodine group (controls)—no lithium was given to these patients at any stage of their treatment and (2) radioiodine and lithium group (Li group)—lithium carbonate was given in a dose of 300 mg three times a day, for 3 weeks starting on the day of radioiodine administration (after each radioiodine therapy).

Twenty-three patients among controls and 11 patients from the Li group were lost to follow-up. Therefore, data were analyzed for 152 patients among controls (109 females and 55 males) and 164 patients in the Li group (103 females and 61 males). All patients were evaluated with complete clinical examination, thyroid function tests (triiodothyronine [T_3], thyroxine [T_4], free triiodothyronine [FT_3], free thyroxine [FT_4], and thyrotropin [TSH]), thyroid scan, 2-hour and 24-hour thyroidal RAIU, and thyroid ultrasonography (for morphology and volume estimation).

Goiter was defined according to the definition proposed by the Pan American Health Organization, i.e., a thyroid gland for which the lateral lobes have a volume greater than the terminal phalanges of the thumbs of the person examined is considered goitrous (21). It was measured by high-resolution ultrasound. The length (a), breadth (b), and depth (c) of each lobe and isthmus were measured in centimeters. Then the volume of each was calculated according to the following spherical ellipsoid formula ($V = \frac{\pi}{6} \times a \times b \times c$) and summed to obtain total thyroid volume (22).

All patients had received prior antithyroid treatment with carbimazole and were clinically and biochemically euthyroid at the time of radioiodine therapy. Antithyroid treatment was stopped 72–96 hours prior to the radioiodine therapy and was never reintroduced throughout the study. Radioiodine was administered after obtaining informed consent from the patients. After radioiodine administration, a β-blocker was prescribed to all patients for 6 weeks. Patients who could not tolerate β-blockers (such as asthmatics) received calcium transport blockers.

Postradioiodine therapy assessment (clinical and biochemical) was done at 3-month intervals until patients became euthyroid/hypothyroid and at 6-month intervals thereafter. Patients were considered cured when they became stably euthyroid or developed permanent hypothyroidism. Euthyroidism was considered stable when it persisted for at least 12 months after the first evidence. Another dose of radioiodine was administered to patients with persistent hyperthyroidism at the end of the 3-month follow-up period and was repeated until patients became either euthyroid or hypothyroid.

Statistical analysis

Data were recorded on a predesigned proforma and managed on Excel spreadsheet. All entries were checked for any error. χ^2 test was used to compare the difference in proportions in two groups. STATA 7.0 intercooled version (STATA Corp., Houston, TX) was used for data analysis. In this study, p value < 0.05 was considered as statistically significant.

Results

All patients were followed up to the mean duration of 32.3 ± 9.8 months (range, 12–60 months). There was no significant difference in the clinical and demographic profile of the two groups (Table 1). As expected, most of patients pre-

Table 1. Demographic and Clinical Characteristics of All Patients

Characteristics	*Radioiodine*	*Radioiodine + lithium*
Total number of patients	152	164
Male	54	61
Female	98	103
F:M	1.8	1.7
Age (years)		
Mean ± SD	41.8 ± 11.5	41.8 ± 12.2
(range)	(18–71)	(19–73)
Duration of illness (months)		
(Mean ± SD)	45.4 ± 41.6	37.3 ± 47.9
Type of gland		
Diffuse	132 (86.8%)	134 (81.7%)
Single thyroid nodule	12 (7.9%)	13 (7.9%)
Multinodular goiter	8 (5.3%)	17 (10.4%)
Ophthalmopathy	22 (14.5%)	23 (14%)
Proximal myelopathy	24 (15.8%)	21 (12.8%)
RAIU (%) (Mean ± SD)		
2-hour	35.9 ± 18.4	36.2 ± 20.1
24-hour	63.3 ± 15.9	59.4 ± 17.5
Mean thyroid mass (gm)	45 ± 24	48 ± 29

Characteristics within the two groups were statistically comparable ($p > 0.05$).
RAIU, thyroidal radioactive iodine uptake; SD, standard deviation.

senting with hyperthyroidism had Graves' disease and diffuse swelling of the thyroid. Patients with concomitant nodules were excluded from the study. Graves' disease was diagnosed by using the following criteria (23): (1) Wayne's clinical score diagnostic of thyrotoxicosis (>19); (2) $T_3 > 160$ ng/dL (normal range, 80–160 ng/dL), and/or $T_4 > 12$ μg/dL (normal range, 4.5–11.5 μg/dL), (3) 2 hours and 24 hours thyroid RAIU > 15% and >35%, respectively (normal range, 2 hours: 5–15%; 24 hours: 15–35%); and (4) presence of diffuse thyromegaly. Although 14.5% of the controls and 14% from the Li group had ophthalmopathy, none had severe ophthalmopathy and there was no deterioration in any patient after radioiodine therapy.

While the cure rate (stably euthyroid and hypothyroid) after the first dose of radioiodine was 68.4% in controls and 68.9% in the Li group, the final cure rates at the end of the follow-up were 96.7% and 96.3%, respectively, requiring almost similar mean numbers of radioiodine therapy. Of those patients who required only one dose of radioiodine, 45 (29.6%) patients among controls and 52 (31.7%) patients in the Li group became hypothyroid after the mean duration of 9.9 ± 9.4 and 12.3 ± 11.5 months, respectively. The difference was statistically not significant. Moreover, 39 (25.7%) patients among controls and 43 (26.2%) patients in the Li group became hypothyroid within 1 year (p = ns). Details of radioiodine therapy in all patients are given in Table 2.

On detailed group-wise analysis, there were 132 patients (81 females and 51 males) with a mean age of 41.1 ± 11.4 years, among controls and 134 patients (78 males and 56 males) with a mean age of 40.3 ± 11.1 years in the Li group with Graves' disease. Mean first dose and mean cumulative dose of radioiodine in both the groups of patients were not statistically different from each other. Cure rate after one dose of radioiodine (70.5% vs. 71.6%) and overall cure rate (97% vs. 96.3%) at the end of the follow-up period was almost the same in both the groups in patients with Graves' disease. Details are given in Table 3.

When nodular toxic glands are analyzed further, there were 12 patients with autonomous functioning thyroid nodule (AFTN) and 8 with toxic multinodular goiter (TMNG) among controls, and 13 patients with AFTN and 17 with TMNG in the Li group. Patients with AFTN or TMNG (from both groups) required more radioiodine therapies and more radioiodine (either as first dose or cumulative dose). In patients with AFTN, while one dose cure rate was 58% among controls and 69.2% among Li group patients, the overall cure rate was 91.7% and 100%, respectively, in both groups. In patients with TMNG, while one dose cure rate was 50% among controls and 52.9% among Li group patients, the overall cure rate was 100% among controls and 94.1% among lithium-treated patients. These outcomes were almost the same as in patients with Graves' disease. However, in contrast, most of the cured patients were euthyroid. No statistical difference in amount and number of radioiodine therapy used and final outcome was observed between controls and Li group patients with either AFTN or TMNG. Radioiodine therapy details of these patients are given in Table 4.

There were 7 patients among controls and 16 patients in the Li group with rapid wash-out of radioiodine from the thyroid gland. in these patients 2-hour RAIU was equal to or more than 24-hour RAIU. These patients required greater amounts of radioiodine and higher numbers of radioiodine therapies than other patients with hyperthyroidism. Overall cure rates were also lower. However, there was no statistical difference in the amount of radioiodine used and radioiodine therapy outcome among such patients from both groups. While the cure rate after the first dose of radioiodine was 57.1% in controls and 56.3% in the Li group, the final cure rate at the end of follow-up was 85.7% and 81.3%, respectively, on both groups. Details are given in Table 5.

There were 79 patients with goiter mass measuring 40 g or less and 73 with a mass measuring more than 40 g among controls, and 67 patients with a mass measuring 40 g or less and 97 with a mass measuring 40 g in Li group. Patients with more than 40 g of goiter or more (from both groups) required more radioiodine therapies and the cure rate (stably euthyroid and hypothyroid) after one dose of radioiodine or overall cure rate was also far lower. However, no statistical difference in amount and numbers of radioiodine therapy used and final outcome was observed between controls and Li

Table 2. Details and Outcome of Radioiodine Therapy in All Patients

Characteristics	*Radioiodine*	*Radioiodine + lithium*
First dose of radioiodine (mean ± SD)	229 ± 85.1 MBq (6.2 ± 2.3 mCi)	233 ± 110 MBq (6.3 ± 2.96 mCi)
Cumulative dose of radioiodine (mean ± SD)	326 ± 204 MBq (8.8 ± 5.5 mCi)	344 ± 281 MBq (9.3 ± 7.6 mCi)
Average number of radioiodine therapy required	1.4	1.45
One dose given	104 (68.4%)	113 (68.9%)
Two doses given	37 (24.3%)	35 (21.3%)
Three or more doses given	11 (7.3%)	16 (9.8%)
Cure rate with single dose of radioiodine		
Hypothyroid	45 (29.6%)	52 (31.7%)
Euthyroid	59 (38.8%)	61 (37.2%)
Final outcome at the end of the study		
Hypothyroid	59 (38.8%)	61 (37.2%)
Euthyroid	88 (57.9%)	97 (59.1%)
Hyperthyroid	5 (3.3%)	6 (3.7%)

Characteristics within the two groups were statistically comparable ($p > 0.05$).
SD, standard deviation.

Table 3. Radioiodine Therapy Details in Patients with Graves' Disease

Characteristics	*Radioiodine*	*Radioiodine + lithium*
Total no of patients	132	134
First dose of radioiodine (mean ± SD)	210.9 ± 59.2 MBq (5.7 ± 1.6 mCi)	196.1 ± 55.5 MBq (5.3 ± 1.5 mCi)
Cumulative dose of radioiodine (mean ± SD)	284.9 ± 151.7 (7.7 ± 4.1 mCi)	292.3 ± 229.4 (7.9 ± 6.2 mCi)
Average number of radioiodine therapy required	1.2	1.41
One dose given	93 (70.5%)	96 (71.64%)
Two doses given	30 (22.7%)	25 (18.66%)
Three or more doses given	9 (6.8%)	13 (9.7%)
Cure rate with single dose of radioiodine		
Hypothyroid	48 (36.4%)	48 (35.82%)
Euthyroid	45 (34.1%)	48 (35.82%)
Final outcome at the end of the study		
Hypothyroid	57 (43.2%)	56 (41.79%)
Euthyroid	71 (53.8%)	73 (54.48%)
Hyperthyroid	4 (3%)	5 (3.73%)

Characteristics within the two groups were statistically comparable ($p > 0.05$).
SD, standard deviation.

group patients with either 40 g or less or greater than 40 g of goiter. In patients with 40 g or less of goiter, whereas the one-dose cure rate was 86.1% among controls and 85.1% among Li group patients, the overall cure rate was 100% in both groups. In patients with more than 40 g of goiter, where the one-dose cure rate was 56.2% among controls and 57.7% among the Li group patients, the overall cure rate was 93.2% among controls and 93.8% among lithium-treated patients. Radioiodine therapy details of these patients are given in Table 6.

Discussion

More than 50 years of experience with the use of radioiodine in the treatment of hyperthyroidism has shown that it is a safe and effective form of therapy. Several adjuvants had been postulated to potentiate the effectiveness of radioiodine to achieve the maximum therapeutic response per millicurie administered or to reduce the total body radiation by retaining the radioiodine in thyroid gland, such as, large goiters, patients with low RAIU, patients with rapid turnover and discharge of radioiodine, or in young patients. It is believed that lithium can significantly affect the kinetics of iodine by reducing its release from the thyroid gland, thus increasing its retention (9–12,16,17). however, no study has demonstrated that the radiation dose absorbed by the thyroid gland is greater in lithium-treated patients. Moreover, these studies did not demonstrate any impact of lithium in terms of the overall outcome (euthyroidism and/or hy-

Table 4. Radioiodine Therapy Details in Patients with AFTN and TMNG

	Patients with AFTN		*Patients with TMNG*	
Characteristics	*Radioiodine*	*Radioiodine + lithium*	*Radioiodine*	*Radioiodine + lithium*
Total no of patients	12	13	8	17
First dose of radioiodine (mean ± SD)	400 ± 81 MBq (10.8 ± 2.2 mCi)	403 ± 141 MBq (10.9 ± 3.8 mCi)	315 ± 137 MBq (8.5 ± 3.7 mCi)	389 ± 144 MBq (10.5 ± 3.9 mCi)
Cumulative dose of radioiodine (mean ± SD)	581 ± 266 MBq (15.7 ± 7.2 mCi)	540 ± 233 MBq (14.6 ± 6.3 mCi)	585 ± 352 MBq (15.8 ± 9.5 mCi)	607 ± 451 MBq (16.4 ± 12.2 mCi)
Average number of radioiodine therapy required	1.42	1.46	1.87	1.7
One dose given	7 (58%)	9 (69%)	4 (50%)	9 (53%)
Two doses given	5 (42%)	3 (23%)	2 (25%)	6 (35.2%)
Three or more doses given	—	1 (8%)	2 (25%)	2 (11.8%)
Cure rate with single dose of radioiodine				
Hypothyroid	—	1 (7.7%)	—	1 (5.9%)
Euthyroid	7 (58%)	8 (61.5%)	4 (50%)	8 (47%)
Final outcome at the end of the study				
Hypothyroid	1 (8.3%)	3 (23.1%)	2 (25%)	2 (11.8%)
Euthyroid	10 (83.4%)	10 (76.9%)	6 (75%)	14 (82.3%)
Hyperthyroid	1 (8.3%)	—	—	1 (5.9%)

Characteristics within the two groups were statistically comparable ($p > 0.05$).
AFTN, autonomous functioning thyroid nodule; TMNG, toxic multinodular goiter; SD, standard deviation.

Table 5. Radioiodine Therapy Details in Patients with Rapid Washout of Radioiodine from Thyroid Gland

Characteristics	*Radioiodine*	*Radioiodine + lithium*
Total no of patients	7	16
First dose of radioiodine (mean ± SD)	248 ± 137 MBq (6.7 ± 3.7 mCi)	247 ± 130 MBq (6.68 ± 3.5 mCi)
Second dose of radioiodine (mean ± SD)	185 MBq (5 mCi)	231 ± 81 MBq (6.3 ± 2.2 mCi)
Third dose of radioiodine (mean ± SD)	296 MBq (8 mCi)	185 MBq (5 mCi)
Cumulative dose of radioiodine (mean ± SD)	396 ± 315 MBq (10.7 ± 8.5 mCi)	400 ± 252 MBq (10.8 ± 6.6 mCi)
Average number of radioiodine therapy required	1.57	1.63
One dose of ^{131}I given	4 (57.1%)	9 (56.3%)
Two doses of ^{131}I given	2 (28.6%)	4 (25%)
Three doses of ^{131}I given	1 (14.3%)	3 (18.7%)
Cure rate with single dose of radioiodine		
Hypothyroid	1 (14.2%)	3 (18.8%)
Euthyroid	3 (42.9%)	6 (37.5%)
Final outcome at the end of the study		
Hypothyroid	1 (14.3%)	3 (18.75%)
Euthyroid	5 (71.4%)	10 (62.5%)
Hyperthyroid	1 (14.3%)	3 (18.75%)

Characteristics within the two groups (either with ≤ or > 40 g of goiter) were statistically comparable ($p > 0.05$).
SD, standard deviation.

pothyroidism) in these patients. however, they demonstrated that these end points are achieved earlier after radioiodine therapy in lithium-treated patients.

The beneficial effects of lithium have been reported in cases of radioiodine therapy of thyroid carcinoma (24–27). However, in cases of hyperthyroidism, few such studies have been conducted. Turner et al. (18) reported that low-dosage lithium therapy increases the retention of a standard-therapy dose of radioiodine and seems to be a useful adjunct to radioiodine therapy in patients with rapid thyroidal turnover and particularly in young patients (18). However, in a later study the same group reported that the addition of lithium to radioiodine did not produce a higher rate of cure after a 3-year follow-up period (19). In another study, Bogazzi et al. (20) showed that radioiodine plus lithium allows more rapid control of hyperthyroidism than radioiodine alone, although the two groups did not significantly differ at the end of the study as far as final outcome was concerned.

Many investigators have reported that pretreatment with

Table 6. Radioiodine Therapy Details in Patients with ≤ and > 40 g Goiter

	Patients with ≤ 40 g goiter		*Patients with > 40 g goiter*	
Characteristics	*Radioiodine*	*Radioiodine + lithium*	*Radioiodine*	*Radioiodine + lithium*
Total no of patients	79	67	73	97
First dose of radioiodine (mean ± SD)	211 ± 59 MBq (5.7 ± 1.6 mCi)	189 ± 48 MBq (5.1 ± 1.3 mCi)	248 ± 104 MBq (6.7 ± 2.8 mCi)	266 ± 129 MBq (7.2 ± 3.5 mCi)
Cumulative dose of radioiodine (mean ± SD)	244 ± 118 MBq (6.6 ± 3.2 mCi)	218 ± 107 MBq (5.9 ± 2.9 mCi)	411 ± 241 MBq (11.1 ± 6.5 mCi)	433 ± 326 MBq (11.7 ± 8.8 mCi)
Average number of radioiodine therapy required	1.18	1.15	1.66	1.63
One dose given	68 (86.1%)	57 (85.1%)	41 (56.2%)	56 (57.7%)
Two doses given	8 (10.1%)	10 (14.9%)	24 (32.9%)	25 (25.8%)
Three or more doses given	3 (3.8%)	—	8 (10.9%)	16 (16.5%)
Cure rate with single dose of radioiodine				
Hypothyroid	32 (40.5%)	34 (50.8%)	17 (23.3%)	18 (18.5%)
Euthyroid	36 (45.6%)	23 (34.3%)	24 (32.9%)	38 (39.2%)
Final outcome at the end of the study				
Hypothyroid	36 (45.6%)	37 (55.2%)	22 (30.2%)	24 (24.7%)
Euthyroid	43 (54.4%)	30 (44.8%)	46 (63%)	67 (69.1%)
Hyperthyroid	—	—	5 (6.8%)	6 (6.2%)

Characteristics within the two groups were statistically comparable ($p > 0.05$).
SD, standard deviation.

an antithyroid drug (ATD) results in relative radioresistance, necessitating a larger dose of radioiodine than would otherwise be required (4,28–34). This may relate to the short biologic half-life of radioiodine because of thyroidal iodine depletion from the ATD, a small iodine pool (because of blockade of organification of iodide and decreased reuse of deiodinase-mediated intrathyroidal iodide by ATD), and rapid turnover (34). However, we cannot comment on this issue, because all our patients had received ATD prior to radioiodine therapy. Again, for the same reason, we cannot comment on the effectiveness of radioiodine plus lithium in the initial control of clinical signs and symptoms of hyperthyroidism, because our patients had already been made euthyroid with antithyroid drugs before recruitment into the study and patients in both groups had almost same mean values of T_3 and T_4 to start with. Again, it was almost similar at the first visit after radioiodine therapy in both the groups.

In our study, mean first dose and mean cumulative dose of radioiodine in both groups of patients were not statistically different from each other. As far as the cure rate was concerned, again, there was no statistically significant difference in the outcome of radioiodine therapy in patients in whom only radioiodine was given versus patients in whom radioiodine and lithium was given, be it the outcome of a single dose of radioiodine therapy or the final outcome at the end of the study. Similarly, when data were analyzed separately from the different type of gland, namely Graves' disease or nodular goiter (AFTN or TMNG), no difference in outcome of radioiodine therapy was observed in patients in whom only radioiodine was given versus patients in whom radioiodine and lithium was administered. Even in patients with rapid thyroidal iodine turnover and in patients with large goiter (> 40 g), where theoretically lithium should have increased the efficacy and potency of radioiodine therapy, no statistically significant difference in the outcome of radioiodine therapy in the two groups was observed.

Moreover, 10% of the patients complained of mild to moderate side effects of lithium therapy, such as nausea, vomiting, giddiness, mild diarrhea, etc. In view of these findings it seems unnecessary to complicate radioiodine therapy with lithium, because it hardly makes any impact on the overall outcome.

Conclusion

This study, with 90% power to detect the true difference, demonstrates that addition of lithium as an adjuvant during radioiodine therapy does not result in any significant improvement in the cure rate of patients with hyperthyroidism. This lack of difference was also observed in the subgroups of patients with large goiter and patients with rapidly discharging gland.

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