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RESEARCH

Lithium-enhanced radioactive iodine ablation of hyperthyroid patients

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Objective: The objective of this study was to compare the effect of adjuvant lithium therapy on the efficacy of radioactive iodine therapy in hyperthyroidism.
Methods: This was a prospective simple randomised comparative, experimental cohort study of hyperthyroid patients for radioactive iodine (RAI) ablation therapy. A total of 163 of the 185 hyperthyroid patients recruited completed the study. Cure was defined by achievement of euthyroidism or hypothyroidism.
Results: From of total of 163 patients, 75 received RAI alone and 88 received RAI with lithium. Those who received RAI with adjuvant lithium showed a higher cure rate (78.4%) compared with those who received RAI only (68.1%) ($p = 0.002$). At one month post RAI therapy, 27.4% of patients who received RAI with adjuvant therapy were cured. This finding showed a trend of being significant compared with just 14.5% cure rate in the group of patients who received RAI alone ($p = 0.08$). This is an indication of a faster cure rate for patients receiving RAI with lithium. Difference in mean T4 concentration at three months between RAI only (17.67 pmol/l) and RAI with lithium (11.55 pmol/l) was significant with a small size effect ($U = 2328.5$, $Z = -2.700$, $p = 0.007$, $r = 0.01$). A significant drop in T4 concentrations was observed between the baseline and one-month visit with small effect size ($p = 0.001$, $r = 0.287$) in patients who received both RAI and lithium.
Conclusion: Adjuvant lithium therapy increases the efficacy of radioactive iodine treatment in hyperthyroidism by increasing overall cure rate and also shortening the time to cure.

Keywords: hyperthyroidism, lithium, radioactive iodine ablation, thyroid stimulating hormone, thyroxine

Introduction

Radioactive iodine (RAI) ablation therapy with Iodine-131 (I-131) for hyperthyroidism has existed for over 60 years ever since Saul Hetz performed the first RAI treatment of Graves' disease on March 31, 1941. It has been used widely either as first-line treatment or when there is recurrence or persistence of hyperthyroidism after a course of antithyroid drug treatment.[1,2] The goal of RAI therapy is a stable restoration to euthyroid state or to render the patient permanently hypothyroid. Provided enough radiation is deposited in the thyroid gland, this mode of therapy is highly effective. Therefore, any intervention that seeks to increase activity and or uptake of the radioactive iodine is most probably going to improve the efficacy of RAI treatment.

Some factors have been shown to influence the outcome of radioactive iodine treatment. These include larger-volume thyroid glands, severe hyperthyroidism,[3–5] sex, and antithyroid drug pre-treatment.[3,6] Other factors that have been shown to affect I-131 therapy outcomes include the 24-hour radioactive uptake, and the presence or absence of nodules in the goitre,[3,7] as well as other iodine-containing medications and preparations (e.g. amiodarone, intravenous contrast) that are used close to therapy.[8,9]

In a study presented over a decade ago, the nuclear medicine group at the Johannesburg hospital noted treatment failure or persistence of hyperthyroidism in about 10% of 805 patients who received RAI.[10] Generally, literature reports between 10% and 20% treatment failure.[11,12] A long-term follow-up study by Metso *et al*. showed that in 25% of patients, two to six RAI treatments were needed to achieve either a hypothyroid or a euthyroid state.[10] Also, retreatment with radioiodine was necessary in 10–30% of patients with toxic adenoma and 6–18% of those with toxic multinodular goitre.[11] This has therefore led to the quest for cheaper and more effective ways of improving the efficacy of RAI.

Lithium is a drug used in treatment of psychiatric disorders like manic-depressive psychosis and for prophylaxis of bipolar affective disorders.[13] The most essential clinically relevant action of lithium on the thyroid is the inhibition of thyroid hormone release, which results in the development of hypothyroidism and goitre.[14] Also, lithium acts by altering signal transduction within the cell and the function of insulin-like growth factor as well as activation of a tyrosine kinase to encourage the proliferation of cells,[14,15] which further potentiates its hypothyroidal and goitrogenic effects. Lithium is also known to inhibit colloid formation, and is involved in blocking organic iodine as well as thyroid hormone release from the thyroid gland without an effect on the radioiodine uptake.[7,11,13] This directly leads to increased radioiodine retention in the thyroid gland.

The aim of this study was to compare the effect of adjuvant lithium therapy on the efficacy of radioactive iodine therapy in hyperthyroidism.

Subjects and methods

Study design

This was a prospective simple randomised comparative, experimental cohort study of 185 hyperthyroid patients for radioactive ablation therapy in our centre in Johannesburg between February 2014 and September 2015. Of the 185 patients recruited, 163 completed the study.

Selection of patients into the two arms of the study was done by simple randomisation. Every other patient received RAI with adjuvant lithium as they presented on day of treatment. The physician administering the capsules on the day decided in which group (RAI only or RAI with adjuvant lithium) to put the first patient to be treated on the day. No factors were considered in deciding which patient entered which arm of the study, thus eliminating all possible biases in patient selection.

Hyperthyroid patients referred for radioactive iodine ablation were recruited after thorough explanation of the study and signed consent.

The aetiology of hyperthyroidism in all patients was established based on the clinical history and physical examination, biochemical profile (TSH, TSH receptor antibody), thyroid sonography and/or scintigraphic imaging of the thyroid. The clinical history and examination, as well as serum urea and creatinine in some cases, also helped exclude patients who fell short of the inclusion criteria. All patients had a thyroid scan confirming hyperthyroidism before treatment with radioactive iodine.

Inclusion criteria

All the hyperthyroid patients, both Graves' disease and Plummer's disease (toxic multinodular goitre and toxic adenoma) were referred for radioactive iodine-131 ablation.

Exclusion criteria

Patients who declined the request to participate in the study, those with active ophthalmopathy, psychiatric patients and those already on lithium treatment were excluded. Also excluded from the study were patients with contraindications to lithium therapy such as lithium allergy, renal dysfunction, cardiac dysfunction and prolonged QT intervals (in patients who complained of cardiac complications and/or had ECG prior to therapy).

Patients with previous thyroid surgery were excluded from the study.

Treatment

Some patients were pretreated with neomercazole. This was withdrawn at least 5–7 days before the RAI treatment. As part of patient preparation protocol in our department, patients were also questioned on iodine use (drugs like amiodarone, multivitamins and food supplements, intravenous contrast) prior to therapy. Patients were also advised to be nil per os from the midnight before therapy to improve radioactive iodine absorption whilst a pregnancy test in female patients was mandatory. The patients who met the eligibility criteria were allocated into two parallel groups on the day of treatment; the first group was the control group, which received a fixed dose of radioactive iodine-131 only. The second group received a fixed dose of radioactive iodine-131 plus lithium carbonate (800 mg) daily for seven days, starting from the day of RAI administration. The lithium was started on the day of radioactive iodine administration first to reduce the number of hospital visits and also for the convenience of patients, as some of the patients were referred from outlying hospitals.

The dose of radioactive iodine given was 10 mCi (370 MBq) for Graves' disease, 20 mCi (740 MBq) in two weekly fractionated doses for toxic adenoma and 30 mCi (1110 MBq) in three weekly fractionated doses for toxic multinodular goitre. This was in accordance with department protocols on management of hyperthyroid patients where fixed doses are preferred to calculated doses that may be cumbersome. The fractionation of doses also avoids having to admit the patients.

Patients with nodular disease received the seven-day course of lithium only once, after the first dose of 10 mCi I-131.

Follow-up

All patients were followed up for three months (12 weeks) from the date RAI was administered, which was selected as the first day. The end point of three months was based on findings that hyperthyroid patients who fail to respond to RAI therapy after three months can be retreated, as treatment failure can be assumed in such circumstances.[2,16,17] Also, it is not uncommon in our unit to receive referrals for retreatment of patients 3–4 months post RAI therapy. As the aim was not to interfere with the normal or routine clinic follow-ups, patients were reviewed at the endocrine clinics at 4–6 weeks and at 12 weeks post-ablation with thyroid functions (TSH, T4 and/or T3), as is the protocol in the hospitals involved. All the blood tests were done at the National Health Laboratory Services (NHLS) and results were accessed through their database.

Lithium adverse effects were assessed by the clinical signs and symptoms reported by the patient post-administration.

Definition of cure

Cure was defined as the achievement of euthyroidal or hypothyroidal state 3 months post RAI therapy. Normal range values for TSH, T4 and T3 were based on the values defined by the National Health Laboratory Services (NHLS), which are given as: TSH normal range: 0.35–5.50 mIU/L. Hyperthyroidism was diagnosed when TSH remained suppressed, euthyroidism when TSH was within the reference range and primary hypothyroidism when TSH exceeded the reference range.

Statistical analysis

Data were analysed using SPSS 20® (IBM Corp, Armonk, NY, USA). Results were presented as mean +/– SD for normal distribution and for skewed distribution as median. Baseline values were expressed as percentages for qualitative variables and for quantitative variables as mean +/– SD. The baseline characteristics of the two groups (RAI only and RAI with adjuvant lithium) were compared by nonparametric Mann–Whitney test for quantitative variables or by the Pearson chi-square test or Fisher's exact test for qualitative variables where applicable. The time trend of serum T4 concentration in the two treatment groups was compared using the Wilcoxon signed rank test and the Friedman test.

Ethics

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Clearance certificate number M130848).

Results

A total of 185 patients were recruited to this study; 163 patients met the inclusion criteria and had reached the end point at the time of data analysis; one patient was dropped from the study due to symptoms suggestive of lithium side effects; another two patients were excluded due to them being hypothyroid and euthyroid at the time of RAI treatment (i.e. TSH > 0.35); 10 patients were lost to follow-up and hence no TFT results were available from three months; nine patients recruited had not reached end point at the time of data analysis.

Table 1: Baseline clinical and biochemical features of patients received RAI alone and patients who received RAI with adjuvant lithium

Features	RAI only	RAI + lithium	*p*-value
Patients (M/F)	75 (11/64)	88 (9/79)	0.6545
Age	48.40 ± 12.04	43.68 ± 13.24	1.0000
Graves' disease	62 (83%)	72 (82%)	1.0000
Toxic nodular disease	13 (17%)	16 (18%)	1.0000
Pretreatment with ATDs	55 (57%)	42 (43%)	0.6605
BaselineT4 (pmol/l)	33.72 ± 20.50	34.83 ± 24.55	0.637
Baseline TSH (mIU/l)	0.04	0.05	0.253

Note: Data are presented as mean ± SD or number (%).

Amongst the 163 patients submitted for final analysis, 75 received RAI alone whilst 88 received RAI with lithium. Baseline clinical and biochemical findings of these two groups of patients are given in Table 1 Generally, the two treatment groups did not differ in their main clinical and biochemical features.

Cure rate

Of the 163 patients enrolled, 111 (68.1%) achieved cure (i.e. euthyroid or hypothyroid) at 12 weeks follow-up post RAI therapy whilst 52 (31.9%) remained hyperthyroid.

For the patients who received RAI only, 42 (56%) were cured whilst 33 patients (44%) remained hyperthyroid after three months. In the patients who received RAI with adjuvant lithium therapy, however, 69 patients (78.4%) were cured whilst only 19 patients (21.6%) remained hyperthyroid at the end point of the study. This represents an increase in percentage of patients cured (22.4 percentage points) in those who received RAI with adjuvant lithium therapy over the patients who received RAI only ($p = 0.002$).

At one month post RAI therapy, 20 (27.4%) patients who received RAI with adjuvant therapy were cured compared with just eight (14.5% cure rate) in those who received RAI alone. This finding of a 12.9% difference in cure rates showed a trend towards statistical significance ($p = 0.08$).

For Graves' patients, there was a statistically significant increase of 22.1% in cure rate when patients who had RAI with adjuvant lithium were compared with patients who received RAI only at three months follow-up ($p = 0.012$). This shows an association, with a small effect size, between adjuvant lithium therapy and increased cure rate in Graves' disease patients (phi = 0.235, $p = 0.007$). In nodular disease patients, though there was an increase in cure rate of 11.2% in patients who received RAI with adjuvant lithium over RAI alone, this was not statistically significant ($p = 0.151$).

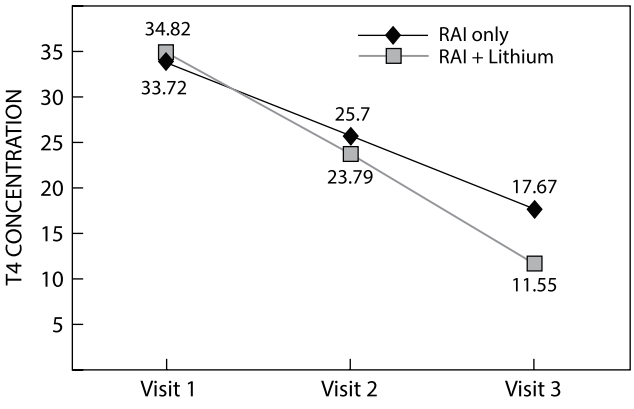

Figure 1: Mean T4 concentration between the RAI only and RAI with lithium groups over the three visits.
Note: Y-axis demonstrates T4 concentration in pmol/l.

T4 concentration

Figure 1 demonstrates mean T4 concentration between the RAI only and RAI with lithium groups over the three visits; baseline (V1), one month (V2) and three months (V3).

There was no statistically significant difference in mean free T4 concentration between the two groups at baseline (U = 2977, Z = –0.415, $p = 0.678$, r = 0.003) and one month post-treatment (U = 1611.5, Z = –1.282, $p = 0.200$, r = 0.01). However, difference in mean T4 concentration at three months between RAI only (17.67 pmol/l) and RAI with lithium (11.55 pmol/l) was significant with a small size effect (U = 2328.5, Z = –2.700, $p = 0.007$, r = 0.01).

Also, decrease in T4 concentration from baseline to the three-month visit in the two groups was significant ($p = 0.000$ in both groups). In patients treated with RAI only, this significant decrease was observed from between the second and third visits with moderate effect ($p = 0.000$, r = 0.341) and the baseline and third visits, also with moderate effect size ($p = 0.000$, r = 0.428). For patients who received both RAI and lithium, a significant drop in T4 concentrations was observed between the baseline and one-month visit with small effect size ($p = 0.001$, r = 0.287), second and third visits also with small effect size ($p = 0.000$, r = 0.455) and the baseline and third visits, which showed a large effect size ($p = 0.000$, r = 0.579).

Discussion

Cure rate

The results from this study clearly showed that addition of adjuvant lithium to RAI therapy is beneficial in the treatment of hyperthyroidism with a higher proportion of patients who received adjuvant lithium (78.4%) cured at the end point of the study (three months after RAI administration) compared with those who received RAI only (56%). Lithium treatment resulted in an additional 22.4% increase in cure rate three months post RAI therapy. Our findings are comparable to those from Martin *et al.*, the Pisa group and Zha *et al.*[7,11,18,19] The lower proportions of cure rate observed in our study compared with those from Martin *et al.* and the two studies from the Pisa group can be attributed to the shorter end point of three months in our study compared with at least one year in the others. It is noteworthy that our findings differed from that of Bal *et al.*, who found no difference between the RAI only group and RAI with adjuvant lithium group[20] with cure rates of 68.4% and 68.9% respectively. The reason for the lower cure rate and lack of difference between the RAI only and RAI with lithium groups was not stated and was more likely not investigated by the authors.

When we grouped patients according to their diagnosis, that is, Graves' disease and nodular disease, we noted a trend not different from the general trends discussed above. Graves' disease patients who received adjuvant lithium showed a significant 22.1% increase in cure rate over those who received RAI alone and also demonstrated a positive association between Graves' disease and adjuvant lithium and increased cure rates in Graves'

patients who received RAI therapy. Though patients with nodular disease also showed a similar trend, with a 24% increase in cure in patients who received adjuvant lithium over patients who received RAI alone, this was not significant statistically. This can probably be explained by the small number of nodular disease patients who enrolled in the study (a total of 30 with 14 receiving RAI alone and 16 receiving RAI with adjuvant lithium). The increased cure rate in nodular patients, however, is corroborated by Martin *et al.*, who showed that adjuvant lithium doubled the chance of cure with RAI therapy.[18] For these patients in particular, this finding is very important as nodular disease patients generally have lower cure rates and a higher likelihood for retreatment compared with Graves' patients.[2]

The cure rates achieved in our study (56% for RAI only and 78.4% in those receiving RAI with adjuvant lithium) were found to be generally lower compared with those achieved in similar studies, which had cure rates greater than 80%.[7,11,18,19] This, however, can be explained by the fact that our study had a shorter endpoint of three months post RAI therapy in comparison with the other studies where follow-up lasted at least a year post-therapy. We defined cure in our study using TSH values. It is, however, known that changes in TSH after RAI therapy usually lag behind changes in T4 and T3 concentration and hence, given time, more patients are likely to achieve cure as observed in the other studies with longer follow-up periods. For patients receiving RAI only, our findings of cure rates of 55.7% for Graves' patients and 57% in nodular disease patients was not so different from the 50% cure at three months seen in Graves' patients[11] or the 55% cure rate at three months in toxic multinodular disease.[2]

Time to cure

Our study showed that 12.9% more patients who had adjuvant lithium therapy achieved cure one month post RAI therapy compared with those who received RAI only. The trend towards statistical significance shown by this finding, together with the fact that at three months 78.4% of patients who received adjuvant lithium compared with only 56% of patients who had RAI alone were cured, supports the theory that adjuvant lithium leads to prompter control of hyperthyroidism. Our findings were in agreement with those of Martin *et al.* and the Pisa group who both found a significant reduction in time to cure in their studies.[7,18] A later study by the Pisa group also supported our results as they found that 50% of patients who received adjuvant lithium were cured in two months compared with the RAI only group, which had 50% cured in three months.[11]

This prompter control of hyperthyroidism is likely due to the fact that release of organic iodine as well as thyroid hormones is blocked by lithium without affecting radioactive iodine uptake (RAIU) by the gland.[7,19] In fact Plazinska *et al.* even went further to show that adjuvant lithium is able to increase thyroidal radioiodine uptake in patients with a low baseline RAIU, that is RAIU less than 30.[21] Zha *et al.* also found that in patients treated with adjunct lithium during RAI therapy the mean radiation absorbed dose rate in the anterior neck was significantly higher than that with RAI alone.[19] Adjunct lithium can increase radiation dose to the thyroid by an average of 39%.[22] All the above together leads to a prolonged effective half-life of I-131, leading to a more effective action of dose administered. One study showed effective half-life was prolonged significantly by a factor of 1.61 +/– 0.49 in patients who received adjuvant lithium.[22]

This finding is very significant because of the immense benefits of early control of hyperthyroidism, especially in the elderly and patients with concomitant cardiovascular diseases who require rapid restoration to euthyroidism (with or without T4 replacement). Also, patients receiving RAI often complain of unpleasant symptoms because of unstable thyroid hormone levels until cure is achieved. Therefore, adjuvant lithium shortening time to cure even by a few weeks may reduce these fluctuations in hormone concentration and will be of great clinical benefit to most recipients of RAI.

T4 concentration

According to the American Thyroid Association (ATA) guidelines (2011) on management of hyperthyroidism, RAI therapy is repeated if hyperthyroidism continues six months after initial RAI or there is minimal response three months after the initial RAI.[2] Since TSH levels may remain suppressed for a month or longer after resolution of hyperthyroidism, the levels are usually interpreted together with serum free T4 and T3 in order to select patients who may require repeat treatment with RAI.

Our study showed that though baseline T4 values were similar in both RAI only and RAI with adjuvant lithium groups, there was a significant difference between the two groups at three months post-therapy as illustrated in Figure 1, with patients who received adjuvant lithium having lower T4 concentration.

It is also worthy of note that our study not only demonstrated a significant decrease in serum T4 concentration at three months for patients who received adjuvant lithium, but also showed a significant decrease from baseline T4 concentration one month post RAI therapy, albeit with a small effect size. However, this was not observed in patients who received RAI alone as the decrease in T4 observed in this group was statistically insignificant. Even more remarkable was the finding that at three months the drop in serum T4 concentrations from baseline values in patients who had adjuvant lithium was of a large effect size whilst those who received RAI only were only of moderate effect.

The foregoing serves to reiterate that adjuvant lithium significantly reduces serum T4 concentration throughout the study. This is achieved by inhibition of T4 release from the thyroid. Lithium is also known to prevent deiodination whilst optimising thyroidal iodine uptake.[14] These findings, especially the significant drop in T4 concentration one month post-therapy, is essential in the elderly and patients with cardiovascular disease, as discussed earlier. This inhibition of T4 release with adjuvant lithium will help in preventing some complications such as thyroid storm that may arise due to release of preformed T4 from destruction of thyroid follicles as a result of RAI therapy.

Lithium adverse effects

In our study, patients received 800 mg of lithium per day for seven days starting on the day of RAI therapy. This dose was chosen for convenience as the lithium in our environment came in 400 mg tablets and hence patients were given two tablets per day. The dose also corresponded with that given by Martin *et al.*, except that they gave lithium for 10 days starting three days before RAI therapy.[18] Our shorter protocol hoped to avoid increasing hospital visits, as one of our objectives was not to interfere with the regular existing hospital visits and protocols.

Only 1 patient out of the initial 185 (0.5%) patients recruited complained of symptoms in keeping with lithium toxicity and hence was excluded from the study. The patient phoned the department and complained of diarrhoea a day post-RAI and was advised to stop the lithium immediately. The low incidence of

side effects can be attributed to a considerably lower dose regimen and shorter period over which it was administered compared with previous studies.[11,20,21] Even in a previous study where 900 mg of adjuvant lithium per day was given for 12 days, occurrence of side effects was insignificant to limit its usage.[11] Hence with our lower dose it is safe to assume that these patients should remain free of adverse effects.

Limitations of study

The study did not evaluate serum free T3 concentration as most patients did not have results for T3 because of the gatekeeper policy of the NHLS. It would have been interesting to see the correlation between T3 and T4 concentrations in the different scenarios we analysed. There may also have been patients with T3 toxicosis who may have presented with normal T4 levels. We would have failed to detect these patients.

In our data analysis, patients with multinodular goitre and toxic adenoma were grouped together due to the small numbers available, even though they received different doses of radioactive iodine. This may have introduced some bias in the analysis of patients with nodular disease.

There are other factors that influence response to radioiodine treatment in hyperthyroidism such as size/volume of the thyroid gland and severity of hyperthyroidism, the effects of which were not studied. The randomisation of patients into the two arms of the study, however, decreases the biases and confounders that these factors could have introduced.

Conclusion

Adjuvant lithium therapy increases the efficacy of radioactive iodine treatment in hyperthyroidism by increasing overall cure rate and also shortening the time to cure. There was a positive association between adjuvant lithium therapy and increased cure rate in Graves' patients. These patients also showed a prompter response to therapy. Adjuvant lithium was also shown to significantly reduce serum free T4 concentration following RAI therapy.

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