

Comparing the effect of adjuvant lithium therapy on the efficacy of radioactive iodine therapy in hyperthyroidism

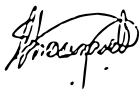
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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Nuclear Medicine.

Johannesburg, 2015

Declaration

I, Emmanuel Nii Boye Hammond, declare that this research report is my own work. It is being submitted for the degree of MMed (Nuc Med) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



DR ENB Hammond

On this 4th day of April 2016.

For my family..... Love you always!

Publications and presentations

This work has never been published.

It has never been presented at a congress.

Abstract

INTRODUCTION: Radioiodine ablation therapy with Iodine-131 (I-131) has been used in the treatment of hyperthyroidism for over 60 years. Lithium, a drug used in the treatment of psychiatric disorders is known to accumulate in the thyroid, increasing radioiodine retention by blocking its release and inhibiting thyroid hormone release without affecting thyroid iodine uptake.

AIM: 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 ablation therapy.

Results: Amongst the 163 patients submitted for final analysis, 75 received RAI alone whilst 88 received RAI with Lithium. Those who received RAI with adjuvant lithium showed a higher cure rate (78.4%) compared to those who received RAI only (68.1%) ($p = 0.002$). At 1 month post RAI therapy, 27.4% of patients who received RAI with adjuvant therapy were cured compared to just 14.5% cure rate in those who received RAI alone, a trend of being statistically significant ($p = 0.08$) and indicating a faster cure rate for patients receiving RAI with lithium. Difference in mean T4 concentration at 3 months between RAI only (17.67pmol/l) and RAI with Lithium (11.55pmol/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 3 months visit in both groups were significant ($p = 0.000$ in both groups). However, significant drop in T4 concentrations were observed between the baseline and 1 month visit with small effect size ($p = 0.001$, $r = 0.287$) patients who received both RAI and lithium.

CONCLUSION: Adjuvant lithium therapy increases efficacy of radioactive iodine treatment in hyperthyroidism by increasing overall cure rate and also shortening the time to cure.

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O for a thousand tongues to sing

My great Redeemer's praise,

The glories of my God and King,

The triumphs of His grace!

.....Charles Wesley

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1. Introduction

1.1. Rationale

Radioiodine 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 31st March 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. The goal of radioactive Iodine (RAI) treatment 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 likely going to improve the efficacy of RAI treatment.

Lithium, a drug used in psychiatric disorders, is known to accumulate in the thyroid. When given together with I-131, it increases radioiodine retention by blocking its release and inhibiting thyroid hormone release without affecting thyroid iodine uptake. A blind randomized control study by Bogazzi et al (1999) demonstrated that a short course of lithium therapy given concomitantly with RAI resulted not only in a higher cure rate, but also a prompter control of hyperthyroidism.

This study aims at establishing the impact of adjuvant Lithium therapy on the efficacy of RAI in hyperthyroid patients from a heterogeneous population as found in South Africa.

1.2. The thyroid Gland

1.2.1. Brief Anatomy

Located anteriorly in the neck at the level of the C5—T1 vertebrae and lying deep to the sternothyroid and sternohyoid muscles, the thyroid gland primarily comprise of right and left lobes anterolateral to the larynx and trachea (1, 2). These lobes are joined together over the trachea, by a relatively thin

isthmus, commonly anterior to the second and third tracheal rings. A thin fibrous capsule surrounds the thyroid and sends septa deeply into the gland(1, 2). These septa divide the gland into lobules which are made of large numbers of closed follicles filled with a secretory substance called colloid (3). These follicles are also lined with cuboidal epithelial cells which secrete into the interior of the follicles(3)

The normal thyroid in an adult gland weighs between 15 to 20 g with the lateral lobes measuring about 4 to 5 cm from superior to inferior poles and are 1.5 to 2 cm wide(4). The capsule is attached to the cricoid cartilage and superior tracheal rings by dense connective tissue. Normal variations in the structure of the thyroid gland include the presence of a remnant of the thyroglossal duct called the pyramidal lobe which is found in approximately 50% of people usually above the isthmus (1, 2, 4).

The well vascularized thyroid, per gram of tissue of any organ, has one of the highest rates of blood flow in the body(5) . It has a rich capillary network that that is supplied by the inferior and superior thyroidal arteries (2). The superior thyroid arteries supplying the antero-superior aspect of the gland usually arise from the external carotid arteries. The inferior thyroid arteries are the largest branches of the thyrocervical trunks arising from the subclavian arteries and supply the postero-inferior parts of the gland, as well as the inferior poles (1, 2).

A thyroid plexus of veins is usually formed on the anterior surface of the thyroid by superior, middle and inferior thyroid veins which respectively drain the superior, middle and inferior poles. The superior and middle thyroid veins drain into the internal jugular veins and the inferior thyroid veins drain into the brachiocephalic veins(1, 2)

1.2.2. Brief Physiology

Thyroxin (T4) is the primary biologically active hormones secreted by the thyroid (about 93%), together with lesser quantities of triiodothyronine (T3) (about 7%)(3). Both these hormones are amino acids

which contain iodine. Thyroxin is deiodinated at its site of action in peripheral tissues to the much more biologically active T3 (3, 5). It is conceptually helpful to see T4 as form in which the hormone is stored and transported and T3 as the active metabolic form (3). Also small amounts of other compounds, including the biologically inactive reverse triiodothyronine (3, 3', 5'-triiodothyronine, RT3) are found in thyroid venous blood(3).

Iodine is very important for normal thyroid function as it is a very critical raw material for thyroid hormone synthesis. Iodine is ingested in the form of iodides with about 50mg required each year, or almost 1 mg/week or 150ug daily for normal T4 production in adults (3-5). Iodides ingested orally are absorbed into circulation from the gastrointestinal tract in the same manner as chlorides (5). Over 90% of the iodides are absorbed systemically within 60 minutes of ingestion. Normally a fifth of the ingested iodide is removed from circulation and used in thyroid hormone synthesis whilst the rest is rapidly excreted by the kidneys (3-5).

Iodine is transported against an electrochemical gradient into thyroid follicular cells (3, 5). The basolateral membranes of the thyroid epithelial cells contain Na⁺/I⁻ Symporter (NIS) which transports two Na⁺ ions and one I⁻ ion into the cell against the electrochemical gradient for I⁻, with each cycle (5). This NIS is capable of producing intracellular iodine concentrations 20 to 40 times greater than plasma concentrations involving a secondary active transport process, with the energy provided by Na, K ATPase (5). Regulation of the NIS is by transcription and also by active trafficking into and out of the basolateral membrane of the thyroid epithelial cells; with TSH specifically involved in the induction of NIS expression and its retention in the basolateral membrane where it can facilitate continuous iodide uptake(5).

Pendrin, a membrane-bound iodide-chloride transporter, is involved in transporting the iodine through the apical membrane of the cell (3). Thyroid hormone synthesis begins here with the rapid oxidation of iodide to molecular iodine, promoted by the thyroid peroxidase (TPO) enzyme and the accompanying hydrogen peroxide. In the thyroid cells, the oxidized iodine is associated with an iodinase enzyme that causes it to rapidly bind (within seconds or minutes) with the amino acid tyrosine (3). Thyroglobulin (a molecule containing about 70 amino acids) is synthesised and secreted into the follicles by the endoplasmic reticulum and Golgi apparatus, and almost immediately iodine binds with about a sixth of the tyrosine within the thyroglobulin molecule (3, 5). Tyrosine is first iodized to monoiodotyrosine and then to diiodotyrosine followed by coupling of more iodotyrosine residues in minutes up to even the next few days (3). The major hormonal product of the coupling reaction is thyroxine or T4 (coupling of 2 molecules of diiodotyrosine) and triiodotyrosine or T3 (coupling one molecule of monoiodotyrosine with one molecule of diiodotyrosine, which represents just about a fifteenth of the final hormones)(3, 5). Each thyroglobulin molecule after synthesis of the thyroid hormone has up to 30 T4 molecules and little amounts of T3 molecules. The thyroid gland, usually stores enough hormones for maintenance of T4 and T3 within physiologic serum levels for at least 2 weeks to about 3 months (3, 5).

Thyroglobulin is not released into the circulation in measurable amounts; T3 and T4 are released as free hormones after they are firstly cleaved from the thyroglobulin molecule (5). In response to TSH stimulation the apical surface of the thyroid follicular cell sends out pseudopodal extensions that form pinocytic vesicles by closing around small portions of the colloid which then migrate to the apex of the thyroid cells (3). Digestive vesicles are produced as these colloid containing vesicles immediately fused with lysosomes containing digestive enzymes. Thyroxin and T3 are then released in the free form after the multiple proteinases among the enzymes digest the thyroglobulin molecules, which then diffuse into the surrounding capillaries through the base of the thyroid cell (3, 5).

The process of thyroid hormone production and release discussed above is controlled by a negative feedback loop in which thyrotropin-releasing hormone (TRH) increases secretion of TSH, which stimulates the production and release of T4 and T3 by the thyroid gland, and both hormones in turn inhibit TRH release and TSH secretion (3, 5).

The serum half-life of the thyroid hormones is determined by how strongly they are bound to the carrier proteins. The bond between T3 and its carrier protein is fairly weak, hence a short serum half-life of around 12 hours, while T4 has a lengthier serum half-life of almost 7 days due to the much stronger bond (3, 5). These carrier proteins consist of albumin which has the largest binding capacity to T4, transthyretin (formerly called thyroxine-binding prealbumin), and thyroxin-binding globulin (TBG) (3, 5).

Thyroid hormones action is slow at onset but long in duration (5). About 80% of T4 is converted to T3 by the action of monodeiodinases in the liver and other tissues, and the remaining 20% is conjugated with glucuronide and sulphate in the liver, excreted in the bile and partly hydrolysed in the bowel. The deiodination reactions not only breaks down the hormones, but also to specifically provide a local supply of T3, which the primary facilitator of the physiological effects of secreted thyroid hormones(3, 5).

1.3. Thyrotoxicosis

Thyrotoxicosis is a disorder having multiple aetiologies, expressions, and potential remedies and result from unsuitably high thyroid hormone activity in tissues, which also arises from elevated thyroid hormone levels in the tissues (6, 7). Thyrotoxicosis usually refer to all conditions in which there is excess thyroid hormone, regardless of the source whilst hyperthyroidism on the other hand, refers to conditions in which thyroid hormone production and secretion are in excess (8, 9).

Hyperthyroidism is a common occurrence with population prevalence in the USA for example at 1.2% (0.5% overt and 0.7% subclinical) (6) whilst in Britain, it is 2% in women and 0.2% in men(7). In the available data from South Africa, Kalk et al (1989) also suggested a lower annual incidence of hyperthyroidism (almost 10-fold) in black population (0.09 per 1000 women and 0.007 per 1000 men) compared to whites (10, 11). In iodine replete communities also, hyperthyroidism prevalence is 10 times higher in women (10). The incidence among women in the USA has been reported as 0.38 per 1000 per year, whilst in Scotland the figures are almost doubled at 0.77 per 1000 women per year with that of men standing at 0.14 per 1000 per year. There is a higher incidence in white population and in iodine-deficient areas and increases with age(7).

Thyrotoxicosis in general, can occur if there is inappropriate stimulation of the thyroid by trophic factors or autonomous release of excess thyroid hormones due to constitutive activation of thyroid hormone synthesis (6, 7). It may also result from excessive release of preformed hormones from thyroid stores due to autoimmune, infective, chemical or mechanical injury (6). Finally, it can arise as a consequence of exposure to extrathyroidal sources of thyroid hormone; either endogenously (metastatic differentiated thyroid cancer, struma ovarii) or exogenously (factitious thyrotoxicosis) (6). Table 1.1 gives a summary of the many different causes of thyrotoxicosis. The commonest cause of thyrotoxicosis is Graves' disease followed by autonomous overproduction of thyroid hormones by one or multiple thyroid nodules (solitary toxic adenoma and toxic multinodular goitre respectively) referred to as Plummer's disease by some authors (6, 7, 9). A brief discussion of features and characteristics of these common causes of hyperthyroidism is given below.

1.3.1. Graves' disease

This is an autoimmune disorder where autoantibodies bind to and stimulate thyroid stimulating hormone (TSH) receptors found on the surface of thyroid follicular cells, resulting in overproduction of

T4 and T3 (6, 7, 12). In areas of sufficient iodine intake, Graves' disease is responsible for about 80% of cases(7).

The etiology of Graves' disease involves immunogenetic, environmental and psychosocial risk factors with smoking an important trigger in several underlying processes. It is thought that interaction between intracellularly processed antigen, MHC class I molecules and CD8+ lymphocytes, as well as MHC class II molecules and CD4+ lymphocytes, is responsible for the development of Graves' disease(12). Subsequent to antigen recognition, CD4- helper T lymphocytes secrete cytokines, amplifying the immune reaction by activation of CD8+ T lymphocytes or autoantibody-producing B cells (12). There is suggestion of a strong genetic influence as almost half of people with Graves' disease have a close relation with some thyroid dysfunction (13). Also, twin concordance studies propose up to 80% of susceptibility being ascribed to genetic factors, while environmental factors may be responsible for the remaining 20% (7, 12).

Table 1.1: Causes of thyrotoxicosis and hyperthyroidism*

	Pathogenic Mechanism
Common causes	
Thyrotoxicosis associated with hyperthyroidism	
Abnormal thyroid stimulator production	
Graves' disease	TSH receptor antibody stimulation
Autonomous Thyroid	
Toxic multinodular goitre	Activating G-proteins or TSH receptor mutations
Solitary toxic adenoma	Benign tumour, autonomous functioning nodule
Thyrotoxicosis not associated with hyperthyroidism	
Inflammatory disease (thyroiditis)	
Silent thyroiditis (plus post-partum)	Autoimmunity, stored hormone release
Subacute thyroiditis	Likely viral infection
Extrathyroidal source of hormone	
Exogenous thyroid hormones	Excess thyroid hormone ingestion (factitious or iatrogenic)
Uncommon causes	

<p>Thyrotoxicosis associated with hyperthyroidism</p> <p>Production of thyroid stimulating hormones</p> <ul style="list-style-type: none"> TSH secreting pituitary adenoma Pituitary resistance to thyroid hormone <ul style="list-style-type: none"> Neonatal Graves' disease Choriocarcinoma Hyperemesis gravidarum <p>Thyroid autonomy</p> <ul style="list-style-type: none"> Congenital hyperthyroidism Struma ovarii Metastatic follicular thyroid carcinoma <p>Drug-induced hyperthyroidism</p> <ul style="list-style-type: none"> Iodine, radiographic contrast agents, drugs containing iodine eg Amiodarone <p>Thyrotoxicosis not associated with hyperthyroidism</p> <p>Inflammatory disease</p> <ul style="list-style-type: none"> Thyroiditis induced by drugs such as lithium, Amiodaron and interferon alpha Acute infectious thyroiditis Radiation thyroiditis Thyroid adenoma infarction <p>Extrathyroidal source of hormone</p> <ul style="list-style-type: none"> "hamburger" thyrotoxicosis 	<ul style="list-style-type: none"> Pituitary adenoma Thyroid hormone receptor-B mutation with better expression in pituitary than in peripheral tissues. Thyroid-stimulating immunoglobulin HCG secretion HCG secretion <ul style="list-style-type: none"> TSH receptor mutation activation Toxic adenoma in an ovarian dermoid tumour Foci of functional autonomy <p>Jod-Basedow phenomenon</p> <ul style="list-style-type: none"> Thyroid follicle destruction, direct effects of toxic drugs Infections in thyroid (eg bacteria, fungal) Cellular destruction by radioactive iodine Stored hormone release ¹ Consumption of contaminated food
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Stimulating antibodies increase hormone secretion, whereas blocking antibodies inhibit various steps in hormone production. Other organs can be affected by the autoimmunogenic process in Graves' disease with thyroid eye disease being the most significant condition and often co-exists with other autoimmune diseases such as rheumatoid arthritis, suggesting possibly a shared pathogenesis (7, 12). Through molecular mimicry of the TSH receptor, Yersinia enterocolitica infections might be involved in the pathogenesis of Graves' disease (7)

*Adapted from Franklyn et al, 2012

1.3.2. Plummer's disease

This is the development of one or more autonomous cell lines that hypersecrete thyroxine and triiodothyronine, having escaped the normal feedback control mechanisms resulting in either a solitary toxic adenoma or toxic multinodular goitre (7, 9, 12). This form of thyrotoxicosis has high prevalence in areas where endemic iodine-deficiency goitre is widespread (7). In screening studies, up to 40 – 50% prevalence of autonomy has been found in iodine-deficient areas. In contrast, in areas without iodine deficiency, prevalence is very low (< 1%) (7, 12). Unlike Graves' disease, which affects the whole thyroid gland autonomy is mainly a focal disease: about 50% are multifocal, 25% unifocal and 25% disseminated forms of autonomy. Somatic mutations of the TSH receptor or substances responsible for receptor information transmission are partly the cause of functional autonomy(12).

1.3.3. Clinical presentation

Excess thyroid hormone affects every physiological system (table 1.2), increasing tissue thermogenesis and basal metabolic rate (BMR) as well as reducing systemic vascular resistance and levels of serum cholesterol (5, 7, 12). Interaction of intracellular T3 with nuclear receptors that regulate transcription of many different genes as well as uptake of T3 by specific membrane transporters such as monocarboxylate transporter are responsible for these effects (5, 7, 8). Triiodothyronine also display some effects that are non-genomic with excess T3 also enhancing beta adrenergic receptor activity (5, 8)

Symptoms and signs of the cardiovascular system usually dominate with tachycardia and supraventricular ectopic activity seen in patients initially with healthy hearts (8). One of the most serious complications of thyrotoxicosis is atrial fibrillation, which is an independent predictor of mortality (7)

Table 1.2: Signs and symptoms of thyrotoxicosis*

	Symptoms	Signs
Central Nervous System	Tiredness, nervousness, anxiety, hyperactivity, poor concentration	Hyperactivity
Hair	hair loss, Thinning	
Eyes, usually in Graves' disease	Pain, grittiness	Stare, eyelid retraction and lag, periorbital oedema, conjunctival injection, ophthalmoplegia
Thyroid	Swelling in the neck	Goiter
Muscle	Tremor, Weakness	Fine tremor, muscle wasting
Skin	Heat intolerance, increased perspiration	Warm, moist skin. Increased perspiration.
Cardiovascular System	Palpitation, shortness of breath	Tachycardia, atrial arrhythmia, systolic hypertension, high output heart failure
Gastrointestinal System	Weight loss, Increased appetite	Loss of weight ²
Peripheral Nervous System		Hyperreflexia
Reproductive System		Oligomenorrhoea, decreased libido and fertility

Graves' disease is distinguished clinically from other forms of hyperthyroidism by the existence of diffuse thyroid enlargement, ophthalmopathy and rarely pretibial myxoedema(14).

Some of the serious complications of untreated hyperthyroidism consist of weight loss, atrial fibrillation, osteoporosis, embolic events, and even cardiovascular collapse and death (6).

*Adapted from Topliss DI, 2010 and Franklyn et al, 2012

In summary, all patients being investigated for hyperthyroidism must have a comprehensive history taken and undergo a thorough physical examination, which comprises among others measurement of body weight, pulse rate, respiratory rate, and blood pressure. Also thyroid size, tenderness, symmetry and nodularity as well as neuromuscular, pulmonary and, cardiac function; and presence of eye signs, peripheral edema, or pretibial myxedema should be assessed (6).

1.3.4. Laboratory diagnosis

Blood TSH measurement has the greatest sensitivity for thyrotoxicosis diagnosis and is the most suitable tool for screening and excluding it. Blood TSH is undetectable (normally reported as <0.01 mIU/L) in sensitive assays due to negative feedback of thyroid hormones on the anterior pituitary (3, 6, 7).

Thyroxin concentration measured at the same time improves diagnostic accuracy(7).

In almost all cases of overt hyperthyroidism, free T4 concentrations are raised (3, 6). In cases with normal T4 and suppressed TSH, the potential for T3 toxicosis exists, hence free or total T3 concentrations should also be measured (3, 5, 7).

Subclinical hyperthyroidism is defined as a low or undetectable serum TSH with T3 and T4 values within estimates for the normal reference range (6). Typical signs and symptoms may arise from both overt and subclinical disease.

A diagnosis of Graves' hyperthyroidism can be established by measurement of thyroid stimulating hormone receptor (TSHR) antibodies though the test is not widely used. Also autoimmune disease can be differentiated from toxic nodular hyperthyroidism with thyroid peroxidase antibodies (anti-TPO) which are present in about 75% of cases of Graves' hyperthyroidism (7, 9).

1.3.5. Imaging

Radioiodine uptake (RAIU) in the thyroid is a kinetic, non-imaging measurement of the percentage of an administered radioiodine dose incorporated by the thyroid over a standard time period, an individual measurement representing a single point in a dynamic process(9). This gives a useful clinical index of thyroid function and is easily performed. The goals of an uptake tests before RAI treatment are to ensure that the thyroid will take up radioactive iodine and also to help decide how much activity to give during treatment(4, 15). Diagnosis of hyperthyroidism or hypothyroidism is a biochemical diagnosis made solely by measurements of easily serum TSH and/or thyroid hormones hence thyroid uptake studies not useful in such situations; however, it may be useful in differentiating Graves' disease from sub-acute thyroiditis or factitious hyperthyroidism ((4, 9, 15)as demonstrated in figure 1.1 below.

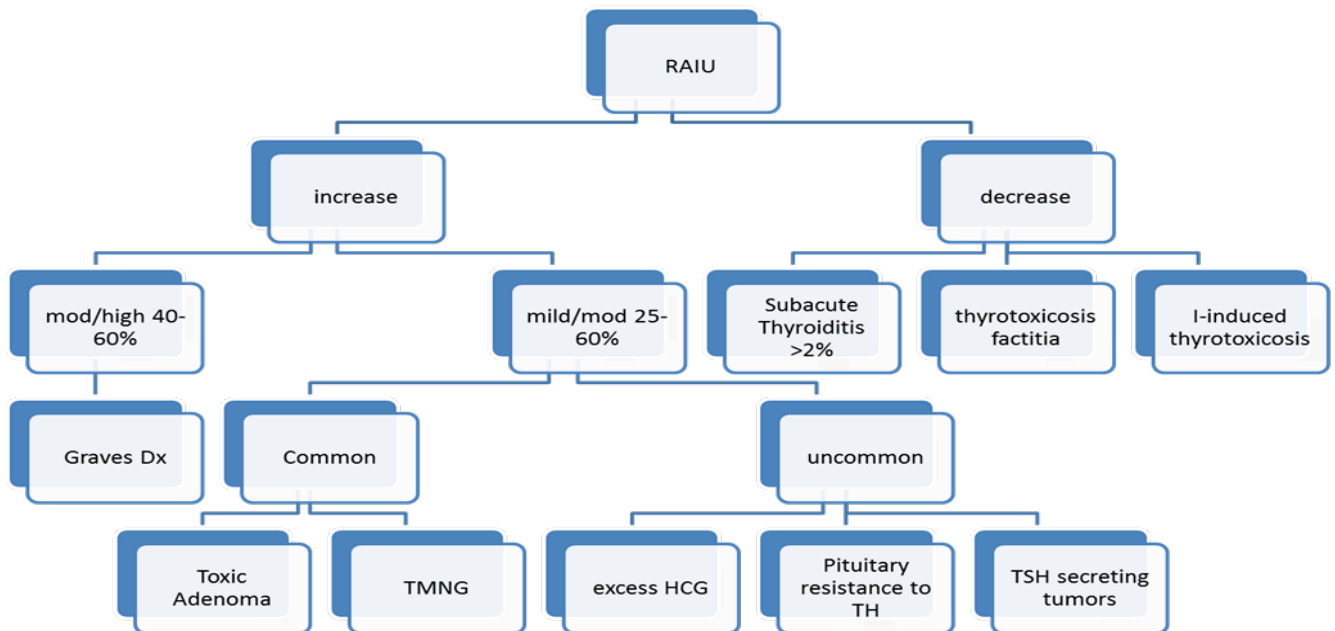


Figure 1.1. Radioactive Iodine uptake (RAIU) for diagnosing the aetiology of thyrotoxicosis.

Scintigraphy is necessary in all patients with nodules of diameter > 1 cm and is indicated also in patients with smaller nodules if there are signs of malignancy or functional disorders(12) Several tracers can be used for scintigraphy of the thyroid gland. Their uptake depends largely on the concentration and activity of the Na^+/I^- symporter (NIS)(12) as the co-transport mechanism with sodium, due to the sodium gradient drives the iodine transport (9). Iodine, and also pertechnetate, which has a comparable molecular size, is transported into the follicular cell via the NIS. Therefore, I-123 and $^{99\text{m}}\text{Tc}$ -pertechnetate can be used for scintigraphy and I-131 for therapy (9, 12).

The indications for thyroid scintigraphy in thyrotoxicosis include:

- Relating the thyroid structure to function, principally in distinguishing Graves' disease from toxic nodular goitre. Hyperthyroidism results in an increased tracer uptake, either iodine or pertechnetate as shown in figure 1.2, in a diffuse pattern (Graves' disease) or a heterogeneous or nodular pattern (toxic multinodular goitre and toxic adenoma). This distinction is important in determining therapeutic radioiodine dose (4, 15, 16) as would be seen later on in this chapter.
- Determination of function in a precise area, e.g. in the assessment of a palpable nodule for functionality (4, 15)
- Location of an ectopic thyroid tissue(4, 15)
- Differentiating thyrotoxicosis aetiology; that is, Graves' from sub-acute, silent or postpartum thyroiditis, or factitious thyrotoxicosis. The latter disorders show symptoms of mild hyperthyroidism with raised serum thyroid hormones, but radioiodine studies reveal low RAI uptake and poor visualization (4, 9, 15, 16).

1.3.6. Treatment

After confirmation of hyperthyroidism, a choice between surgery, radioiodine therapy and antithyroid medications is required (6, 7, 9). Treatment is customised to the individual and the patient's age, the presence of comorbidities, goitre size, likelihood of remission with antithyroid drugs alone, timing of potential future pregnancies and patient preference ought to be considered (6, 9).

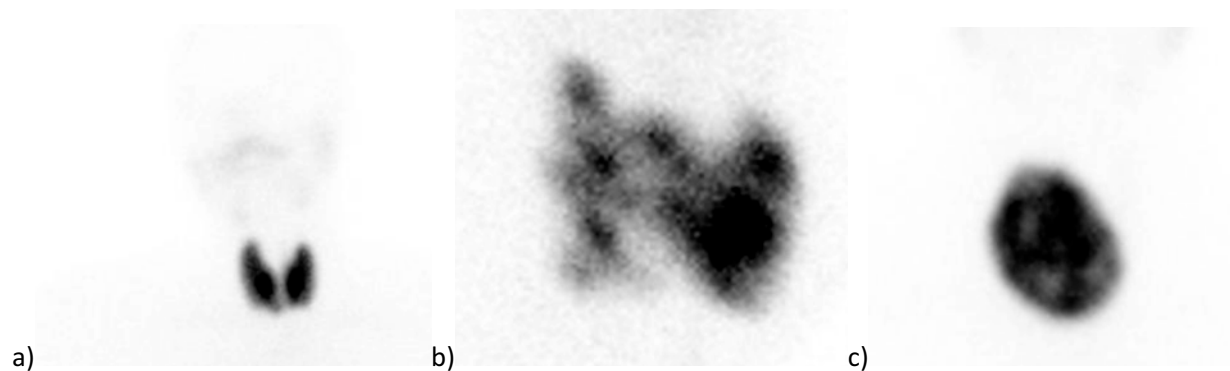


Figure 1.2. Patterns of radioiodine uptake in hyperthyroidism in selected images from our local archive; a) Graves' disease, b) multinodular goitre, c) toxic adenoma.

In a randomised prospective trial comparing treatment outcomes, patient satisfaction between the 3 modalities was 90%, with no difference in time to euthyroidism, and sick leave rates also remained very similar for all modalities (17). Patel et al (2006) also demonstrated similarities in long-term quality of life for all treatment choices, although RAI exhibited lowest cost(18).

1.4. Radioiodine therapy in hyperthyroidism

1.4.1. Physical and radiobiological properties of radioiodine

As discussed earlier, iodine is an essential constituent of thyroid hormones: Thyroid cells extract and concentrate iodide from plasma. Iodine-131 is successfully applied in the therapy of patients with hyperthyroidism and differentiated thyroid cancer. Advantages of iodine include: good tolerability, safety and efficacy of therapy and ease of application (19, 20). Iodine-131 is currently available in

gelatine capsules and drinking solution for oral use as well as in intravenous injections as sodium iodide. At each passage through the gland, about 20% of the circulating iodide is removed (19, 20).

The thyroid gland is the critical organ for iodine which is taken up by the thyroid follicular cells within the gland (19). Iodine retention in the cells depends on the cells' metabolic activity (20). The thyroid takes up 20-30% of ingested iodine in normal subjects, with up to 70% directly excreted in the urine (20). In hyperthyroid patients the fraction absorbed by the thyroid is increased to even more than 90% in extreme cases (4, 19, 20).

I-131, employed in the therapy of thyroid disorders, is reactor produced from the fission of U-235 or neutron irradiation of tellurium(21). It decays to stable Xe-131 by beta emission. The physical properties of I-131(4, 19-21) are given in table 1.3 below. With regard to living organisms, the biological half-life of iodine in the thyroid gland (which is 120 days) should be taken into consideration. Hence the effective half-life in the living body is calculated to be 7.6 days (20).

Iodine-131, as seen in table 1.3, emits two types of radiation; gamma radiation which is used in imaging and beta minus (B-) used in treatment or therapy. For I-131, electron penetration in soft tissue is about 1mm; hence the energy of the electron radiation is absorbed very close to the radiation source. Due to this, the damaging effect of beta radiation is restricted to thyroid cells with adjacent cells not exposed to significant radiation (20). Radiobiological effects of radioactive iodine on tissues are either direct where radiation is deposited inside DNA or indirect, which leads to free radical production that in turn react with essential macromolecules(20)

Table 1.3. Physical characteristics of I-131*

Characteristics	
Physical half-life ($t_{1/2}$)	8.02 days
Gamma energy	Energies ranging between 80 and 723keV 364keV,(82% abundance), most abundant
Beta emissions	
Maximum energy	0.606 MeV (89% abundance)
Average	0.192MeV
Range in soft tissue	
mean	0.8mm
Maximum	3mm

1.4.2. Clinical indications and contraindications in hyperthyroidism

The clinical indications for I-131 radioactive iodine therapy in hyperthyroidism (4, 6, 19, 22) include:

- First line in Graves' dx treatment
- Autonomous functioning nodules
- Relapsed cases of hyperthyroidism
- Persons suffering from comorbidities which worsen surgical risk
- Previously operated individuals or those who previously received radiation to the neck
- Unavailability of a high-volume thyroid surgeon
- Contraindications or allergy to antithyroid drug use
- In patients with malignant ophthalmopathy with inactive eye disease, used for ablation of residual thyroid tissue post-thyroidectomy.

Multiple considerations go into decision on the choice of therapy. Together with the patient, an endocrinologist should carefully appraise the treatment risks and benefits and make a specific

recommendation; with the final decision respecting the patients' preferences (23). Patients electing for I-131 RAI treatment for Graves' disease likely place a relatively higher value on definitive control of their hyperthyroidism, the potential side effects of antithyroid medications and surgery, as well as a relatively lower premium on the need for lifelong thyroid hormone replacement, potential worsening or development of Graves' orbitopathy and the rapid resolution of hyperthyroidism (6, 24).

Absolute contraindications for the RAI therapy (6, 7, 16, 24) include:

1. Pregnancy, postpartum and lactation
2. Small children without appropriate child care
3. Active or progressive ophthalmopathy. Glucocorticoid therapy used to prevent worsening of mild thyroid eye disease after RAI treatment
4. Suspicion of associated thyroid malignancy. Thyroid nodules therefore should be assessed prior to RAI treatment to exclude malignancy
5. Large obstructive goitre
6. Inability to swallow liquids and/or capsules;
7. Inability to comply with radiation precautions and safety guidelines
8. Females planning a pregnancy within 4–6 months
9. Exposure to iodinated CT scan contrast within the prior 6 weeks.

1.4.3. Iodine-131 dose selection

The main aim of RAI treatment is to return the patient to a euthyroidism, with or without T4 treatment (6, 7). In toxic nodular disease, ablation of nodules or reduction in size of goitre is also a desired goal (6, 7, 23). These goals are achieved equally well by either administering a calculated dose based on the size of the thyroid and its ability to trap iodine or a fixed dose of radioactive iodine. Many investigators have

tried several techniques to calculate the radioiodine dose needed to render patient euthyroid and avoid hypothyroidism based on factors such as radioisotope uptake or turnover or thyroid size (6, 7, 23).

However, the use of a calculated dose has been shown to have no advantages over a fixed dose in terms of outcome (22, 23, 25) and apart from being more costly, is also inconvenient because of the need for extra visits and investigations.

1.4.4. Factors affecting I-131 uptake and treatment response

Some factors have been shown to influence the outcome of radioiodine treatment. Individuals with larger-volume thyroid glands and severe hyperthyroidism (13, 26) have demonstrated a greater likelihood of failure to respond to a single dose of RAI (13, 14). In addition to the dose of radioiodine administered, these clinical factors are widely viewed as the most reliable predictors of response to treatment (13).

In an audit of 813 patients treated with radioiodine, Allahabadia et al. demonstrated amongst others, a significantly worse outcome after RAI treatment in males compared to females, despite showing a reduced prevalence of palpable goitre (13).

Antithyroid drug pre-treatment is also known to affect I-131 therapy outcomes (13, 27). Pre-treatment with propylthiouracil has in recent studies demonstrated having adverse effects on cure rate post RAI therapy with this effect appearing to persist even up to 2 months after the drug is stopped prior to RAI administration (13, 27, 28). The thionamides on the other hand appear to have no apparent adverse effect on cure rate, provided the drug is stopped at least a day before radioiodine treatment is given (6, 27, 28) though minimum of 3-5 days usually advised.

Other factors which have been shown to affect I-131 therapy outcomes include the 24 hour radioactive iodine uptake (which gives an indication of the residence time of the radioactive iodine in the thyroid), age

of the patient (greater risk of failed treatment in the young)(29), and the presence or absence of nodules in the goitre (13, 30) as well as other iodine containing medications and preparation (eg. Amiodarone, intravenous contrast) that are used close to therapy (4, 16)

1.5. Lithium and the thyroid

In 1967, at a conference in Denmark, incidence of goitre in patients receiving lithium was cited and these data published in the British Medical Journal in 1968(31). The physiology and clinical effect of lithium on the thyroid since then has been significantly studied.

Lithium a drug used in treatment of psychiatric disorders like manic-depressive psychosis and for prophylaxis of bipolar affective disorders(32). It is also used both in augmenting treatment of depression and in some cases of unipolar depression (33). Through its inhibitory effects on the activity of adenosine triphosphatase (ATPase), cyclic adenosine monophosphate (cAMP) as well as intracellular enzymes, Lithium affects cell function (33, 34). Also, signal transduction is affected by the inhibitory effect of lithium on inositol phospholipid metabolism which partly accounts for some of its action in manic depression (33), i.e., prophylactic prevention of recurrent mania as well as recurrent depression. Lithium is rapidly absorbed from the gastro-intestinal system as a simple cation unbound to tissue proteins or plasma, with almost 95% of a given dose excreted unchanged via the kidneys in 24 hours (34).

Serious side effects from taking lithium are rare however; minor complaints such as diarrhoea, nausea, gastrointestinal discomfort, weight gain, skin eruptions, polyuria, alopecia, and edema are common. Significant nephrotoxicity does not usually occur though urine-concentrating abilities may be decreased (34). Some of the more severe side effects consist of poor concentration and memory, ataxia, tremor, dysarthria, and incoordination (34, 35).

1.5.1. Effect of Lithium on thyroid physiology

Lithium has several effects on the physiology of the thyroid. Contributing to this picture is the receptor mediated mechanism of thyroid hormone activity as well as the autonomous effects of the hypothalamic–pituitary–thyroid axis (33, 36). Though the mechanism of action is still not clear, it is thought that the intracellular disturbances that occur can be explained partly by the inhibition of cyclic AMP-mediated cellular events by lithium and also by the resultant inhibitory actions on the phosphoinositol pathway (33, 36). Lithium also has immunological effect on thyroid antibody levels which leads to a faster inception of thyroid autoimmunity usually characterised by goitre and hypothyroidism but also with the possibility in some situations of hyperthyroidism (33, 36).

The most essential clinically relevant action of lithium especially for purposes of this study is probably the inhibition of the release of thyroid hormones which result in the development of hypothyroidism and goitre (36). There is a surge in TSH concentration due to the earlier inhibition of thyroid hormone release resulting in thyromegaly. 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 cell (33, 36) which further potentiates its hypothyroidal and goitrogenic effect. The inhibition of thyroid hormone release is also linked to the Lithium associated hypothyroidism and may occur in patients with or without a goitre (36). However hyperthyroidism have been reported in significant numbers, despite generally the suppressive actions of lithium on the function of the thyroid (36).

Other thyroidal effects of lithium include impaired iodination of thyroglobulin and peripheral deiodination of T4 (30, 32). Direct inhibitory effects of lithium on the synthesis and secretion of thyroid hormones can result in a compensatory increase in serum TSH.

Lithium is also known to inhibit colloid formation, and involved in blocking organic iodine as well as thyroid hormone release from the thyroid gland without an effect on the radioiodine uptake (30, 32, 35). This directly leads to increased radioiodine retention in the thyroid gland.

Due to its potency as a thyroid hormone inhibitor, it was just a matter of time that attempts were initiated to assess its effectiveness in management of thyrotoxicosis. Early studies (36, 37) showed satisfactory reduction in thyroid hormone levels, however a randomised trial by Kristensen et al (38) failed to demonstrate lithium as better than thionamides in therapy for thyrotoxicosis. Another study established that in individuals who showed poor tolerance or response to thionamides, low dose lithium was a fairly safe and effective substitute in controlling thyrotoxicosis (39). In very severe incidents of thyrotoxicosis, it is particularly useful when add to thionamide therapy (36).

Though the physiologic and clinical actions of lithium on the thyroid suggest its effectiveness as an adjunct to radioiodine therapy, there are however conflicting reports on the ground.

The first to suggest lithium as an adjunct therapy in hyperthyroidism with radioiodine, Turner et al. in 1976, recognised an increased thyroidal retention of I-131 in their patients (40). The Pisa group in Italy, showed in two large randomised trials that lithium improved the efficacy of I-131 therapy by a prompter control of the disease and in patients with large goitres, improving the rate of permanent control (30, 41) This group also showed that adjuvant lithium given at the time of treatment prevented the increase in thyroid hormone concentrations associated with anti-thyroid drug withdrawal and 131I administration(41). Results from a cohort study by this same group on Graves' disease patients in 2010 not only confirmed or supported the above, but also showed a greater cure rate of patients treated with RAI plus lithium (91%) as against RAI alone (85%, $P = 0.030$)after 1 year(35). Martin et al (42) also demonstrated improvement in efficacy of RAI with adjuvant lithium in both Grave's and toxic nodular

goitre by a 9% higher cure rate after a year follow-up, significant reduction in time to achieve cure and significant reduction in T4 (12%) and T3 (17%) concentrations.

However in another randomised controlled study involving 350 hyperthyroid patients (43), no statistically significant difference was observed in response between those receiving RAI alone and RAI with adjuvant Lithium. Even in patients with glands that are discharging rapidly or have large goitre, no statistically significant difference was observed in RAI treatment outcome between the 2 groups(43). Though Zha et al (44) showed cure of hyperthyroidism was achieved in 72% of patients treated with I-131 alone and in 76% patients treated with I-131 plus lithium; this did not differ significantly at the end of the study ($p > 0.05$). While lithium may not affect the outcome of radioiodine therapy in the long term, it may be beneficial in therapy in patients with a very short effective half-life of the isotope to reduce the activity required and the whole-body radiation dose (44, 45). Using lithium as adjunct to radioiodine therapy improves the radiation dose delivered to the thyroid by 39% on average and nearly 30% of radioiodine activity can be saved in these patients(45). It may also be employed in the radioiodine treatment of multi-nodular goitre where it has been shown to reduce radioiodine-induced hyperthyroidism, thus making iodine-131 therapy safer in the elderly patient who may have cardiovascular disease (46).

1.6. Problem statement

On the average 30 to 40 patients are treated every month with RAI for hyperthyroidism at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH). This includes patients who are reporting for second dose of RAI following an unsuccessful previous treatment.

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 (47). Generally, literature reports between 10 and 20% treatment failure (35, 48). 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(49). Also, retreatment with radioiodine was necessary in 10 – 30% of patients with toxic adenoma and 6 to 18% of those with toxic multinodular goitre (23).This has therefore led to the quest for cheaper and more effective ways of improving efficacy of RAI.

The effects of lithium on the thyroid gland as stated earlier in this text, as well as other studies carried out led to the postulation of the problem statement: Does Lithium administered as an adjuvant therapy to radioactive iodine improve its efficacy in hyperthyroid patients?

1.7. Aim

To compare the effect of adjuvant lithium therapy on the efficacy of radioactive iodine therapy in hyperthyroidism.

1.8. Study objectives

The objectives of this study include:

- a. To compare the effectiveness of radioactive iodine combined with lithium versus radioactive iodine alone in the treatment of hyperthyroidism.
- b. Establish whether there is significant difference in results obtained for the two groups.
- c. To modify whenever possible current management protocol for patients receiving RAI locally.

2. Subjects and methods

2.1. Study design

This was a prospective simple randomised comparative, experimental cohort study of hyperthyroid patients for radioactive ablation therapy.

2.2. Study population

The study included 185 hyperthyroid patients referred to the Departments of Nuclear Medicine and Molecular Imaging of both the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) between February 2014 and September 2015.

2.2.1. Inclusion criteria

Hyperthyroid patients, both Graves' disease and Plummer's disease patients referred for Radioactive Iodine 131 ablation.

2.2.2. Exclusion criteria

The following patients were excluded from the study.

1. Patients who decline the request to participate in the study
2. Patients with active ophthalmopathy
3. Psychiatric patients and those already on lithium treatment
4. Patients with contraindications to lithium therapy such as;
 - a. Lithium allergy
 - b. Renal dysfunction
 - c. Cardiac dysfunction
 - d. Prolonged QT intervals

2.3. Methods

Hyperthyroid patients referred for radioactive iodine ablation were approached to enter the study. After thorough explanation of the study, those who volunteered to take part were made to sign 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.

2.3.1. Treatment

Some patients were pretreated with neomercazole. This was withdrawn at least 5 – 7 days before the RAI treatment. The patients who met the eligibility criteria were put into two parallel groups on the day of treatment;

1. The first group was the control group which received fixed dose of radioactive iodine-131 only
2. The second group receiving fixed dose of radioactive iodine-131 plus Lithium carbonate (800mg) daily for 7 days, starting from day of RAI administration. The lithium was started on the day of radioactive iodine administration firstly to reduce the number of hospital visits and also for convenience of patients as some of the patients were referred from outlying hospitals

Dose of radioactive iodine given was 10mCi for Graves' disease, 20mCi in two weekly fractionated doses for toxic adenoma and 30mCi in three weekly fractionated doses for toxic multinodular goitre.

2.3.2. Follow-up

All patients were followed up for three months (12 weeks) from date RAI was administered, which was selected as the first day. The end point of 3 months was based on findings that hyperthyroid patients who fail to respond to RAI therapy after 3 months can be retreated as treatment failure can be assumed

in such circumstances (6, 50, 51) 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 assessed through their database.

2.3.3. 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 NHLS which are given below:

1. TSH normal range: 0.35 – 5.50mIU/L. Patient is hyperthyroid when TSH is less than 0.35mIU/L and hypothyroid when TSH is greater than 5.50mIU/L
2. Free T4 normal range: 11.5 – 22.0 pmol/L
3. T3 normal range: 3.1 – 6.6 pmol/L

2.4. Data collection

Data on the patients were collected and displayed on the data collection sheet shown in appendix A.

All the information inputted into the data collection sheet was obtained from history taken from the patient, patient's hospital records and results from the NHLS trackcare system.

2.5. Bias

All patients involved in the study were known to be hyperthyroid and the type of hyperthyroidism (Graves' disease or Plummer's' disease) was known. Selection of patients into the different arms of the study was done by simple randomisation. On day of treatment every other patient received RAI with

adjuvant lithium. The doctor administering the capsules on the day decides 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 enters which arm of the study eliminating all possible biases in patient selection.

2.6. Statistical analysis

Data was analysed using SPSS. Results were presented as mean \pm 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 \pm SD. The baseline characteristics of the two groups (RAI only and RAI with adjuvant Lithium) were compared by nonparametric Mann-Witney 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 were compared using the Wilcoxon Signed rank test and the Freidman test.

2.7. Ethics

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, clearance certificate number M130846. This certificate is attached as Appendix B.

2.8. Data safety

Patient's anonymity was ensured using assigned study numbers or codes. The key to decipher the number codes were kept in a secure location known only to the primary investigator. Several back-up versions of the data were kept at all times to prevent loss of information due to data corruption and these were kept in on storage devices with password protection.

3. Results

A total of 185 patients were recruited to be part of this study. Out of this number;

- 163 patients met the inclusion criteria and had reached the end point at the time of data analysis.
- 1 patient was dropped from the study due to symptoms suggestive of lithium side effects.
- Another 2 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 3 months
- 9 patients recruited had not reached endpoint at the time of data analysis.

3.1. Demographics

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 shown in table 3.1. Generally, the two treatment groups did not differ in their main clinical and biochemical features.

Table3.1. 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
Mean age +/- SD	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

Mean T4 at V1 (pmol/l)	33.72 +/- 20.50	34.83 +/-24.55	0.637
Mean TSH (mIU/l)	0.04	0.05	0.253

3.2. Cure rate

Table 3.2 demonstrates the distribution of patients according to those who got cured and those who remained hyperthyroid at the endpoint of the study in the two main groups (RAI only and RAI and Lithium). Out of the total 163 patients enrolled, 111 (68.1%) got cured (i.e.euthyroid or hypothyroid) 3 months post RAI therapy which was the end point of the study whilst 52 (39.1%) remained hyperthyroid.

For the patients who received RAI only, 42 making 56% were cured whilst 33 patients (44%) remained hyperthyroid after 3 months. In the patients who received RAI with adjuvant Lithium therapy however, 78.4% (69 patients) got cured whilst only 21.6% (19 patients) remained hyperthyroid at the endpoint of the study. This represents a significant 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 ($p = 0.002$).

Table 3.2. Number/proportion of patients cured at 3 months post-RAI therapy.

	No Cure (Hyperthyroid)	Cured (Euthyroid+hypothyroid)	Total
RAI Only	33 44%	42 56%	75 100%
RAI + Lithium	19 21.6%%	69 78.4%	88 100%
Total	52 39.1%	111 68.1%	163 100%

At 1 month post RAI therapy, 27.4% of patients who received RAI with adjuvant therapy were cured compared to just 14.5% cure rate in those who received RAI alone as seen in figure 3.1. This 12.9% difference in cure rates however showed a trend of being statistically significant ($p = 0.08$).

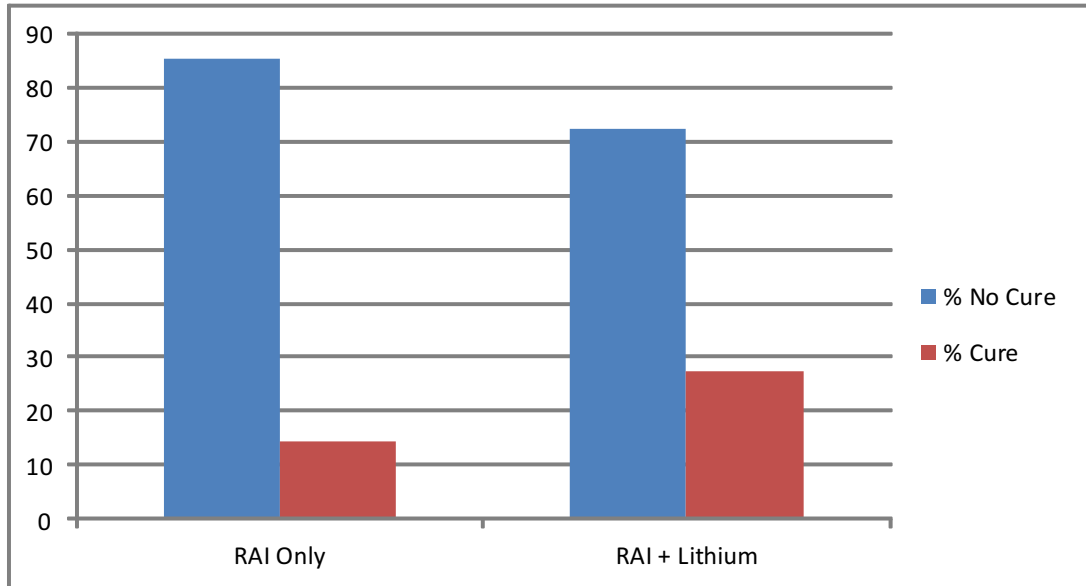


Figure 3.1. Graph showing percentage of patients who were cured and those who remained hyperthyroid (no cure) 1 month post-ablation.

Table 3.3 gives a breakdown of the number of patients who were cured after RAI only or RAI with adjuvant lithium therapy at 3 months according to diagnosis.

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 ($p = 0.012$) as illustrated in figure 3.2. 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 (table 3.3, figure 3.3), 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 ($p = 0.151$).

Table 3.3. Proportion of patients cured at end of study grouped by diagnosis

Diagnosis	Treatment	No cure	Cure	Total
Graves' disease	RAI only	27 44.3%	34 55.7%	61 100%
	RAI + Lithium	16 22.2%	56 77.8%	72 100%
	Total	43 32.3%	90 67.7%	133 100%
Nodular disease	RAI only	6 42.9%	8 57.1%	14 100%
	RAI+ Lithium	3 18.2%	13 81.2%	16 100%
	Total	9 30.0%	21 70.0%	30 100%

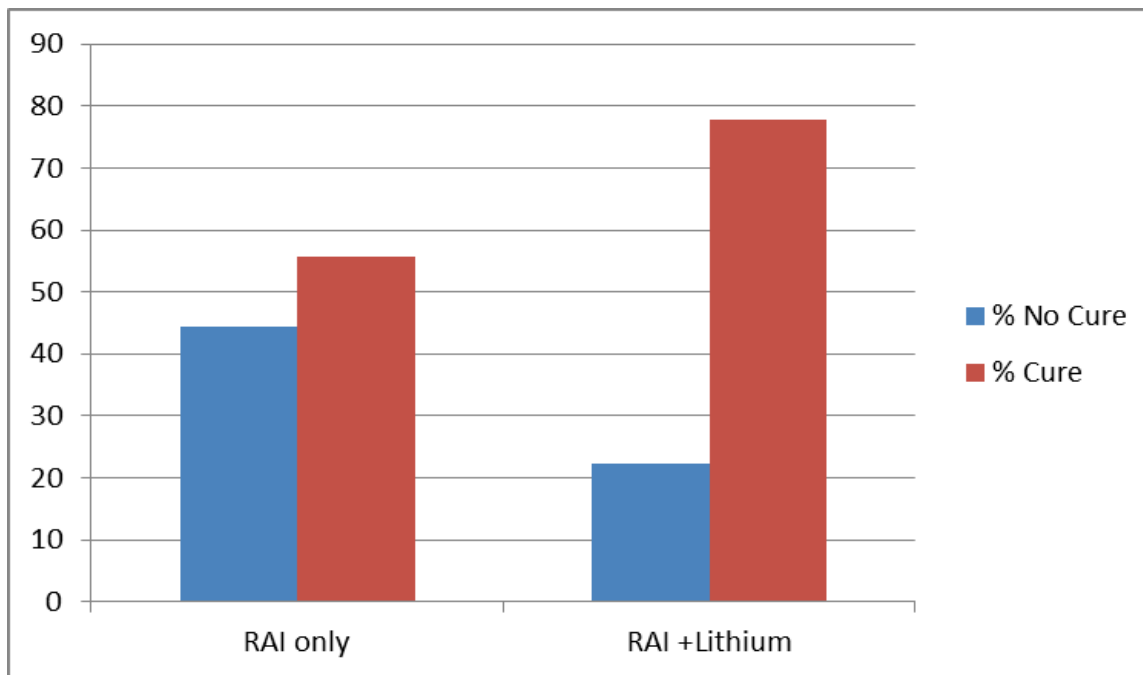


Figure 3.2. Graph showing response to therapy at 3 months for patients with Graves' disease.

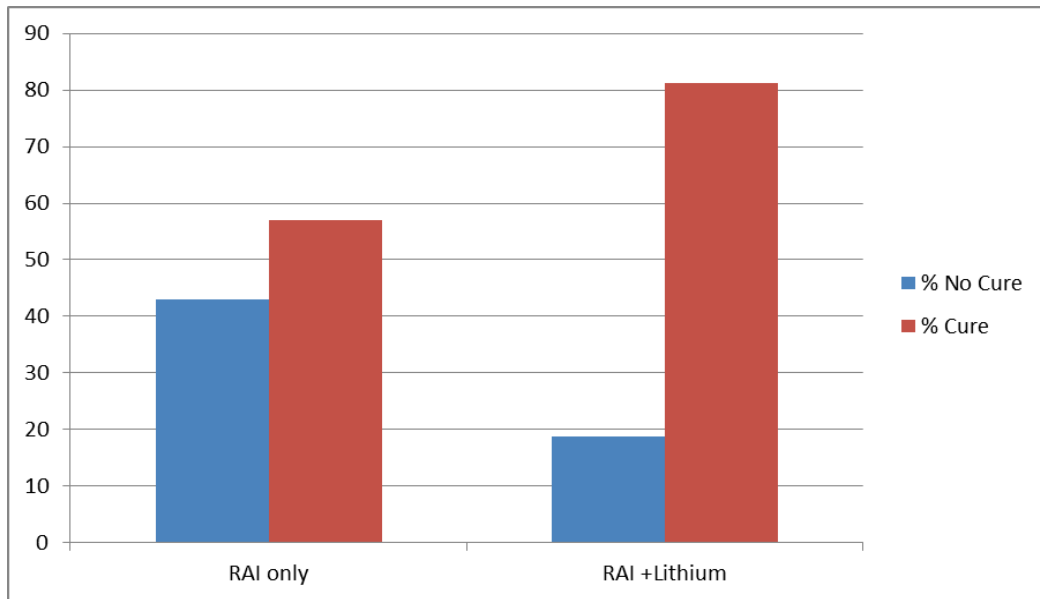


Figure 3.3. Graph showing response to therapy at 3 months for patients with nodular disease.

Table 3.4 illustrates the distribution of patients post RAI only and RAI with adjuvant Lithium grouped by gender 3 months post-therapy.

Female patients who received RAI with adjuvant Lithium therapy had significantly higher cure rates (78.5%) compared with those who received RAI alone (53.1%) ($p = 0.001$). The 25.4% increase in patients cured who received adjuvant lithium highlights the association (with a small effect size) of adjuvant Lithium and female sex with higher cure post RAI therapy ($\Phi = 0.268$, $p = 0.001$).

There was no statistically significant difference in cure rates between male patient who received RAI with adjuvant Lithium (77.8 %) and those who received RAI alone (72.7%) ($p = 0.795$)

Table 3.4. Proportion of patients cured at end of study grouped by gender

Gender	Treatment	No cure	Cure	Total
Female	RAI only	30 46.9%	34 53.1%	64 100%
	RAI + Lithium	17 21.5%	62 78.5%	79 100%
	Total	47 32.9%	96 67.1%	143 100%
Male	RAI only	3 27.3%	8 72.7%	11 100%
	RAI+ Lithium	2 22.2%	7 77.8%	9 100%
	Total	5 25%	15 75.0%	20 100%

3.3. Thyroid hormone concentration

Figure 3.4 shows serum free T4 concentrations in patients who received RAI only and those who received RAI with lithium at baseline (V1), 1 month (V2) and 3 months (V3) post treatment.

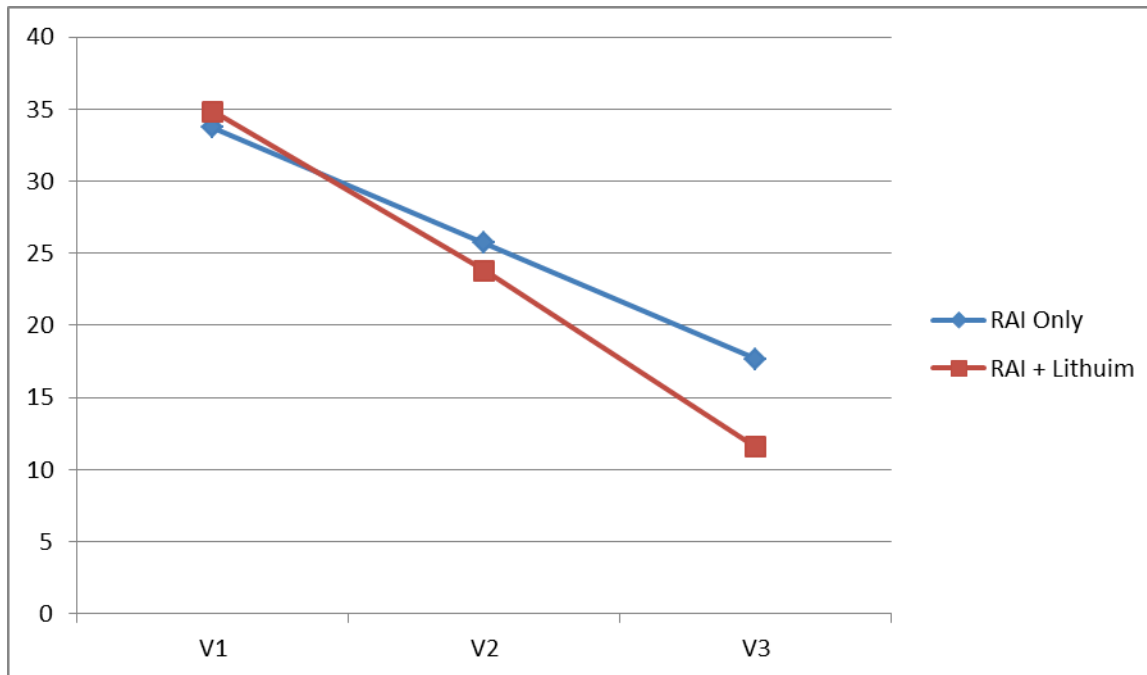


Figure 3.4. Mean T4 concentration between the RAI only and RAI with Lithium groups over the 3 visits.

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 1month post-treatment (U = 1611.5, Z = -1.282, p = 0.200, r =0.01). However, difference in mean T4 concentration at 3 months between RAI only (17.67pmol/l) and RAI with Lithium (11.55pmol/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 3 months visit in the two groups were significant (p = 0.000 in both groups). In patients treated with RAI only, this significant decrease was observed from between the 2nd and 3rd visits with moderate effect (p= 0.000, r =0.341) and the baseline and 3rd visits also with moderate effect size (p = 0.000, r = 0.428). For patients who received both RAI and lithium, significant drop in T4 concentrations were observed between the baseline and 1 month visit with small effect size (p = 0.001, r = 0.287), 2nd and 3rd visits also with small effect size (p = 0.000, r = 0.455) and the baseline and 3rd visits which showed a large effect size (p = 0.000, r = 0.579).

3.3.1. T4 concentration and Diagnosis

Graves' disease

Figure 3.5 is a plot of free T4 concentrations over time for patients with Graves' disease who were treated with RAI only and RAI with lithium.

For the patient's diagnosed with graves' disease, there was no significant difference in freeT4 concentration between the two groups at baseline and 1 month post therapy. The difference in T4 concentrations at 3 months between the RAI only and RAI with adjuvant Lithium groups was significant (p = 0.032, r =0.189).

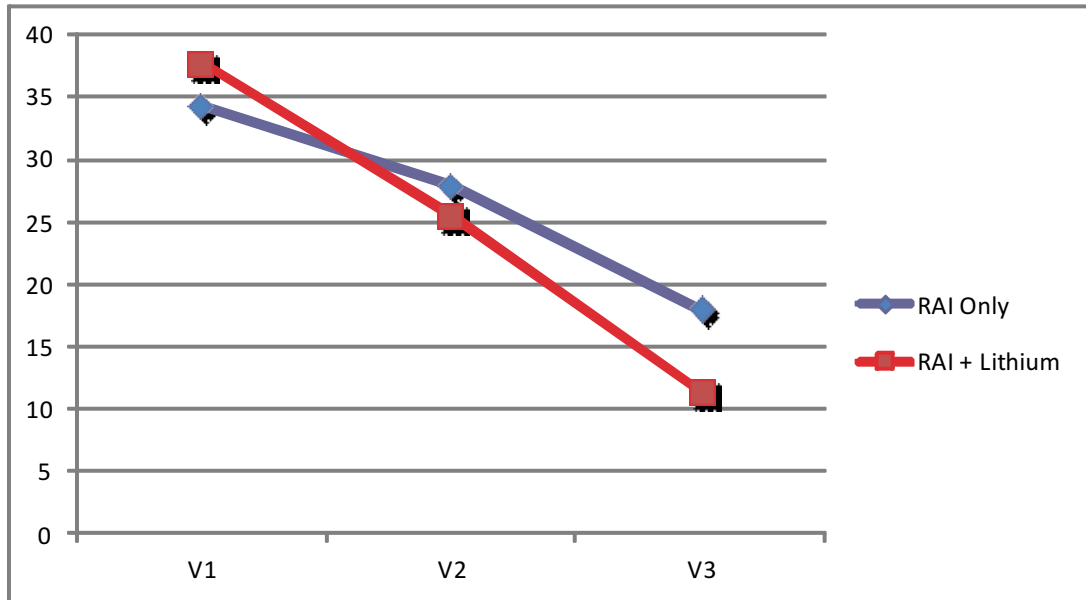


Figure 3.5. Mean T4 concentration across the 3 visits in patients diagnosed with Graves' disease.

The decrease in T4 concentration across the 3 visits was found to be significant in the two groups (RAI only $p = 0.000$, RAI with lithium, $p = 0.000$). For those who received RAI only, the significant decrease was noted between the 1 month and 3 months visits with a moderate size effect ($p = 0.001$, $r = 0.365$) and between the baseline and 3 months visits also with moderate size effect (0.001 , $r = 0.427$). For patients who received adjuvant lithium, significant decrease in T4 concentration was noted as early as between baseline and 1 month visit with moderate effect size ($p = 0.003$, $r = 0.283$) and also between 1 month and 3 months visits ($p = 0.000$, $r = 0.464$). There was a significant decrease with a large size effect when we considered the change from baseline (37.657 pmol/l) to 3 months concentrations (11.451 pmol/l) ($p = 0.000$, $r = 0.597$).

Nodular disease

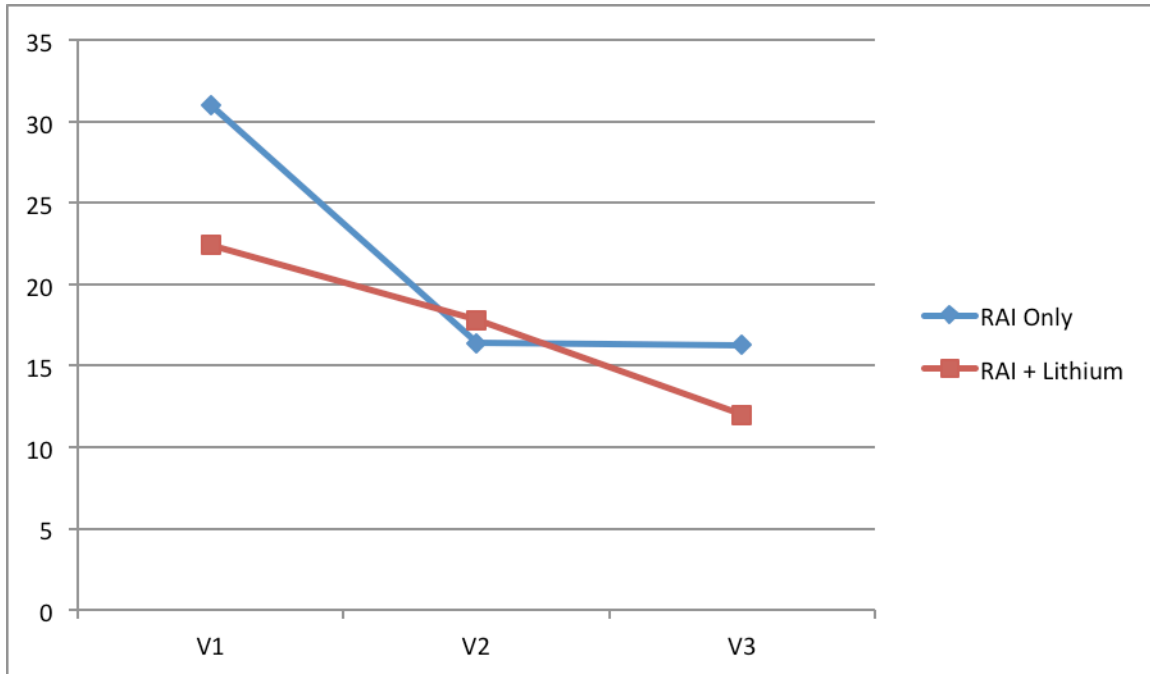


Figure 3.6. Mean T4 concentration across the 3 visits in patients diagnosed with nodular disease.

There is no statistically significant difference in T4 values at baseline, 1 month or 3 months between patients who took RAI with adjuvant lithium and those who had RAI only (baseline $p = 0.645$, 1 month $p = 0.471$, 3 months $p = 0.149$).

Across the 3 visits, there was no significant difference in T4 concentration in patients treated with RAI only ($p = 0.607$). However, for patients who received adjuvant Lithium with RAI therapy, there was a statistically significant difference in mean T4 concentration across the 3 visits ($p = 0.001$); seen as decrease in mean T4 concentration from baseline of 22.060 pmol/l, through 1 month visit (17.807 pmol/l) to 3 months (11.013 pmol/l). This decrease is seen between the 1 month and 3 months visits with moderate size effect ($p = 0.18$, $r = 0.4305$) and baseline and 3 months visits with a large size effect ($p = 0.006$, $r = 0.500$).

3.3.2. Neomercazole Pretreatment and lithium

Table 3.5. Mean T4 concentration across the 3 visits for patients who received Neormecazole pretreatment and those who did not.

		RAI Only	RAI +Lithium
No Pretreatment	V1	27.7146	34.1042
	V2	29.527	20.690
	V3	15.769	10.384
Neomercazole pretreatment	V1	33.377	23.800
	V2	24.498	18.480
	V3	18.480	12.297

Table 3.5 shows the mean T4 concentration during each of the 3 visits for patients who received Neomercazole pre-treatment and those who had no pre-treatment. The effects of pre-treatment and lithium on T4 concentration are discussed below.

No pretreatment

There was no significant difference in mean T4 concentration between those who had RAI only and those who had RAI with adjuvant lithium at baseline ($p = 0.750$) and at 1 month ($p = 0.099$). There was however a significant difference in mean T4 concentration between the two groups at 3 months with a moderate effect size ($p = 0.048$, $r = 0.320$).

For the patients who received RAI only, there was no significant difference in mean T4 concentration across the 3 visits ($p = 0.06$) in contrast to those who received RAI with adjuvant lithium who showed a significant difference ($p = 0.000$). This difference is seen as a decrease in mean T4 concentration from baseline to 1 month visit ($p = 0.022$, $r = 0.363$), 1month to 3 months ($p = 0.000$, $r = 0.590$) and from baseline to 3 months ($p = 0.000$, $r = 0.598$).

Neomercazole pretreatment.

There was no significant difference in mean T4 concentration between the RAI only and RAI with adjuvant Lithium groups during all 3 visits in patients pre-treated with Neomercazole ($p = 0.910$, 0.0702 and 0.083 respectively).

Both groups however showed significant decrease in mean T4 concentration across the visits (RAI only $p = 0.002$; RAI with Lithium $p = 0.000$). In both groups, the differences are noted from the 1 month to 3 months visits and also the baseline to 3 months visit with moderate size effect in patients who received RAI only ($p = 0.021$, $r = 0.265$; $p = 0.000$, $r = 0.473$ respectively) and large effect size in patients who received RAI with adjuvant Lithium therapy ($p = 0.000$, $r = 0.573$ and $p = 0.000$, $r = 0.599$ respectively).

3.3.3. Gender and lithium

Table 3.6 and figure 3.7 illustrate mean T4 concentrations of males and females over the 3 visits for patients who received RAI only and for patients who received RAI with adjuvant lithium therapy.

Females

Whilst the difference in mean T4 concentration at baseline and 1 month between the RAI only and RAI with adjuvant lithium groups remained insignificant (baseline $p = 0.8291$, 1 month $p = 0.8255$), the difference at 3 months however was significant ($p = 0.0067$) with T4 concentrations being lower in patients who received adjuvant lithium (11.398 pmol/l) compared with RAI only (18.439 pmol/l).

For both groups of patients (i.e. RAI only and RAI with adjuvant lithium), the observed drop in T4 concentration from baseline through to the 3 months visits were significant (RAI only, $p = 0.000$, RAI and lithium = 0.0000). For patients who received RAI only, these were observed between the 1 month and 3 months visit with a moderate effect size ($p = 0.3105$, $r = 0.3105$) and between baseline and 3 months also with a moderate effect size ($p = 0.000$, $r = 0.427$). In the patients who received adjuvant lithium

however, significant differences were noted as early as between baseline and 1 month visits with moderate size effect ($p = 0.002$, $r = 0.275$) as well as between 1 month and 3 months visits ($p = 0.000$, $r = 0.470$) and baseline and 3 months visits ($p = 0.000$, $r = 0.592$) with moderate and large effect sizes respectively.

Table 3.6. Mean T4 concentration across the 3 visits for males and females.

		RAI Only	RAI +Lithium
Female	V1	34.98499	35.0149
	V2	24.739	23.913
	V3	18.439	11.395
Male	V1	27.2273	33.2111
	V2	31.363	22.863
	V3	12.850	13.063

Males

There is no significant difference in T4 concentration across the 3 visits in both the RAI only and RAI with adjuvant lithium groups in male patients ($p = 0.66$ in RAI only, $p = 0.72$ in RAI with lithium).

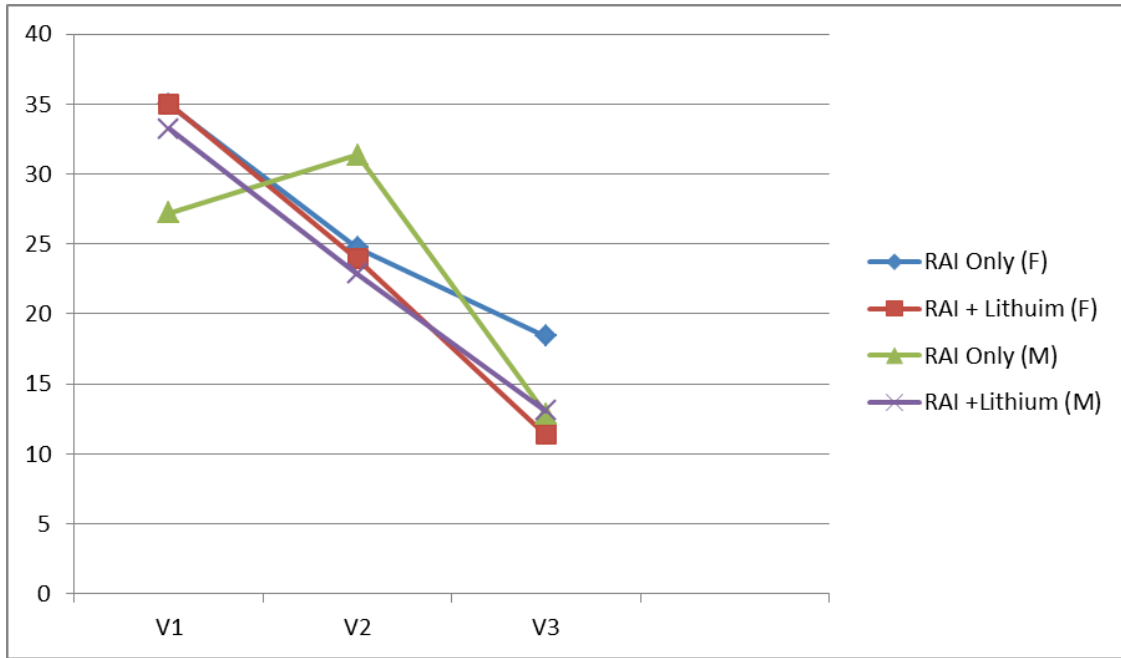


Figure 3.7. Mean T4 concentration across the 3 visits for males (M) and females (F).

4. Discussion

4.1. Introduction

Radioactive iodine therapy has been shown to be very effective in hyperthyroidism treatment. The goal of radioiodine therapy as earlier discussed is the return of patients to euthyroidism either with or without T4 replacement. Advantages of radioactive iodine therapy include good tolerability, ease of application, safety and efficacy of therapy (19, 20). There are however reports of poor response to RAI therapy in some patient. Generally, different literature reports between 10 and 25% treatment failure between Six to twelve months post RAI administration (35, 48, 49). We set out in this study to increase the efficacy of RAI treatment and thus reducing incidence of treatment failure by adding adjuvant Lithium to the RAI therapy.

4.2. Cure rate

The results from this study clearly show that addition of adjuvant lithium to RAI therapy is beneficial in the treatment of hyperthyroidism. It clearly demonstrated that a higher proportion of patients (78.4%) who received adjuvant lithium were cured at the end point of the study (three months after RAI administration) compared to those who received RAI only (56%). Lithium treatment resulted in an additional 22.4% increase in cure rate 3 months post RAI therapy. Our findings are comparable to those from Martin et al, the Pisa group and Zha et al (30, 35, 42, 44). The lower proportions of cure rate observed in our study compared to those from Martin et al and the 2 studies from the Pisa group can be attributed to the shorter end point of 3 months in our study compared to at least 1 year in the others. It is worthy of note that our findings contrasted that of Bal et al who found no difference between the RAI only group and RAI with adjuvant lithium group (43) 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 (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 (42). 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 to Graves' patients (6).

Just like in Graves' patients, our female patients also showed a positive association with increased cure rates with adjuvant lithium therapy. This was seen in the 25.4% increase in cure rate over females who received RAI only. In the male patients however, we failed to demonstrate any positive association of lithium therapy with cure 3 months post therapy. Though a slightly higher percentage of patients who received adjuvant lithium got cured (77.5%) compared to those who received RAI alone (72.7%), this was not statistically significant. The lack of significance, just like in the patients with nodular disease could be related to the small number of male patients involved in the study (20 patients in total).

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 to those achieved in similar studies, which had cure rates greater than 80% (30, 35, 42, 44). This however can be explained by the fact that our study

had a shorter endpoint of 3 months post RAI therapy in comparison to 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 lags 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 3 months seen in Graves' patients (35) or the 55% cure rate at 3 months in toxic multinodular disease (6).

4.3. Time to cure

Our study showed that 12.9% more of patients who had adjuvant Lithium therapy received cure 1 month post RAI therapy compared to those who received RAI only. This trend towards statistical significance showed by this finding, together with the fact that at 3 months, 78.4% of patients who received adjuvant lithium compared to 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 significant reduction in time to cure in their studies (30, 42). 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 2 months compared to RAI only group who had 50% cured in 3 months (35).

This prompter control of hyperthyroidism is likely due to the fact that release of organic iodine as well as thyroid hormones are blocked by Lithium without affecting RAIU by the gland (30, 44). 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 (52). 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 (44). Adjunct lithium can increase radiation dose

to the thyroid by an average of 39% (45). 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 (45)

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.

4.4. T4 concentration

According to the American Thyroid Association (ATA) guidelines (2011) on management of hyperthyroidism, RAI therapy is repeated if hyperthyroidism continues 6 months after initial RAI or there is minimal response 3 months after the initial RAI (6). 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 2 groups at 3 months post therapy as illustrated in figure 3.4 in the previous chapter, 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 3 months for patients who received adjuvant lithium, but also showed a significant decrease from baseline T4 concentration 1 month post RAI therapy albeit with a small effect size. This

however 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 3 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 above goes to reiterate the fact that adjuvant Lithium significantly reduces serum T4 concentration throughout the study. This is achieved by inhibition of T4 release from the thyroid. Lithium also is known to prevent deiodination whilst optimising thyroidal iodine uptake(36). These findings, especially that of a significant drop in T4 concentration 1 month post therapy is very essential in the elderly and patients with cardiovascular disease as discussed earlier. These will help prevent 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.

We have discussed earlier in our literature review some of the several factors which influence early hypothyroidism, or put in another way, affect persistence of hyperthyroidism after RAI therapy. These include the diagnosis or cause of hyperthyroidism, gender, pre-treatment with antithyroid drugs (ATDs), dose of RAI used, age, RAIU and others. We tried to observe changes in serum T4 concentration with adjuvant lithium in the presence of some of these factors. Our findings are discussed below.

4.4.1. T4 and Diagnosis

Our findings in Graves' patients were generally a mirror of the response of T4 concentration to adjuvant lithium as discussed earlier above. Patients who received adjuvant lithium therapy had a significantly lower mean T4 concentration 3 months post therapy compared to the RAI only group. Also, though both groups showed a significant drop in T4 concentrations at 3months from the baseline values, we showed that this decrease was large in the adjuvant lithium group compared to the RAI only group which

showed a moderate decrease. Even of greater importance was the fact that at 1 month post RAI therapy, the adjuvant lithium group showed a significant decrease in T4 concentration which was of moderate effect size.

The above findings hence goes to support the concept that adjuvant Lithium in Graves' disease patients is associated with increased cure rate and also prompter response to RAI treatment.

In the patients with nodular disease, we found no significant difference in the mean T4 concentrations between the two study groups neither at 1 month nor 3 months. However, there was a significant drop in T4 concentration at 3 months from baseline values in the patients who received adjuvant lithium. This was not observed in the RAI only group.

Our findings may suggest that adjuvant lithium therapy potentiates effects of RAI therapy in hyperthyroid patients with nodular disease. This can be explained with our earlier finding of higher cure rates (albeit an insignificant finding) in nodular disease patients who received adjuvant Lithium and our current discussion on the effects of adjuvant Lithium on mean T4 concentration as we had observed .

When both observations are considered together, we can deduce that much more nodular patients may have resolution of hyperthyroidism without the need for repeat RAI treatment if patients were allowed more time for TSH levels which always lag behind changes in T4 concentration, to respond and rise. Hence it is more beneficial monitoring such patients with their serum T4 rather than TSH concentration.

4.4.2. T4 Concentration and antithyroid drug pretreatment

It is common to have patients pre-treated with antithyroid medications prior to RAI therapy. Even in patients who RAI therapy has been decided on as the definitive treatment, antithyroid drugs may be initiated especially when T4 values are high and patient shows signs and symptoms of thyrotoxicosis to reduce thyroid hormone toxicity before RAI therapy. Thionamides which includes Neomercazole

(carbimazole) the preferred drug of choice in our institution, and Propylthiouracil are the main antithyroid drugs in use.

Earlier treatment with some antithyroid drugs like Propylthiouracil may be linked with a higher rates of treatment failure but Andrade et al came to the conclusion that methimazole (a thionamide) pre-treatment did not interfere with the final outcome (41, 53). It has been proposed that the radio-resistance associated with propylthiouracil and thioureas in general is as a result of the presence of a sulfhydryl group, which is absent in the thionamides (methimazole and carbimazole) (53). This may explain the lack of interference of RAI with thionamide pre-treatment. Therefore these drugs are usually withdrawn before RAI therapy; 4 – 7 days for thionamides and at least 2 weeks for propylthiouracil.

We attempted to find out if pretreatment with neomercazole had any effect of T4 concentrations in our study.

We discovered that there was no difference between mean T4 concentrations amongst the two groups at 3 months in patients pre-treated with Neomercazole. Both groups however showed significant decrease in T4 concentration at 3 months compared to baseline. These decreases were shown to be of a large effect in the adjuvant Lithium group in comparison to the RAI only group which showed moderate effect size. This shows that adjuvant lithium may have an effect on T4 concentrations in patients pre-treated with Neomercazole. This effect likely due to the inhibition of the increased T4 release that results from the Neomercazole withdrawal both before and after RAI therapy (41).

For the patients who had no pretreatment, we observed that the adjuvant Lithium group showed significantly lower T4 concentrations than the RAI only group at 3 months. There was also a significant reduction in mean T4 concentration at 1 month and also at 3 months from baseline in patients who received adjuvant Lithium. This observation however was absent in the RAI only group.

Our observations show that adjuvant Lithium therapy had the greatest effect of lowering mean T4 concentration in patients who did not receive pretreatment with Neomercazole. We also observed that in general, T4 concentration in patients who did not receive pretreatment with neomercazole showed better response to RAI therapy with greater reduction from baseline levels compared to patients who received Neomercazole.

4.4.3. T4 Concentration and gender

As expected, we found that females who had RAI with adjuvant Lithium had significantly lower T4 concentrations at the end of the study compared to those who had RAI alone and also showed a significant decrease from baseline values as early as 1 month post therapy. Though both groups showed decreases at 3 months from baseline, the decrease amongst the adjuvant Lithium group was of larger effect. The above strengthens our earlier finding of a strong association between females receiving adjuvant Lithium therapy and increased cure rates post RAI therapy. It also supports the position of prompter response to RAI therapy with adjuvant lithium therapy and hence earlier resolution of hyperthyroidism, considering the significant decrease in T4 from baseline values observed at 1 month post therapy.

The male patients on the other hand, showed no significant differences in T4 concentration between the 2 groups at the end of the study. There was also no significant decrease in T4 concentration from baseline at the end of the study. As was pointed out earlier whilst discussing the cure rates in males, this lack of difference observed may be due to the smaller numbers of male patients involved in the study. This makes it very difficult to make any meaningful statistical deductions from the study with this group. Also, some studies have suggested male gender as a factor affecting poor response to RAI therapy (13). Allahabadia et al found that males had a significantly lower cure rate, after one dose of radioiodine, than

females (13). However, there are others who found no significant difference in outcomes between males and females post RAI therapy (29).

4.5. Lithium adverse effects

In our study, patients received 800mg of Lithium per day for 7 days starting on the day of RAI therapy. 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 into 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 to previous studies (35, 43). Even in the a previous study where 900mg of adjuvant lithium per day was given for 12 days, occurrence of side effects were insignificant to limit its usage(35). Hence with our lower dose, it is safe to assume that these patients should remain free of adverse effects.

4.6. Loss to Follow-up

Of worry was the number of patients who were lost to follow-up. About 5% (10 out of 185) of the initial patients recruited were lost to follow-up. What made this even more worrying was the fact that we made it a duty to call all patients and remind them of their laboratory appointments the week they were due, after we fail to locate any results for them on the NHLS Trackcare system. This shows that a lot more patients could have ended up defaulting if not for the calls we placed to them. These patients would be at risk of severe complication especially those who become hypothyroidal and those who remain hyperthyroidal as a consequence of treatment failure.

4.7. Limitations of study

The study did not evaluate serum free T3 concentration. This was because 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. These patients we would have failed to detect.

Problems with supply of ¹³¹I for long periods during the study as well as other logistical problems beyond the power of us the investigators led to prolongation of the projected timelines and as a result, delay in the completion of the study. This also prevented us from reaching the projected mark of 200 patients for the study as was initially planned.

4.8. Application of Knowledge

The fact that low dose short course adjuvant lithium therapy has minimal side effect but significantly improves the efficacy of RAI therapy in hyperthyroid patients compels us to advocate for its inclusion in the management of hyperthyroid patients, especially those with serious risk of increased complications from hyperthyroidism such as the elderly and patients with pre-existing cardiac problems.

We also showed that T4 concentration in patients who did not receive antithyroid drug pretreatment responded better to RAI therapy. We therefore suggest patients in whom RAI therapy has been decided as 1st line especially to be sent for their dose of RAI early and avoid Neomercazole pretreatment if possible so as to improve cure rates.

4.9. Future research

Further research needs to be carried out in male patients and patients with nodular disease with a larger sample size, so as to get more robust data on these two groups of patients. Our group also may request

an extension of the Ethics permission to assess the status of all the study participants at 12 month's period from the time of RAI administration.

5. Conclusion

A summary of our major findings are highlighted below.

1. Adjuvant lithium therapy increases efficacy of radioactive iodine treatment in hyperthyroidism by increasing overall cure rate and also shortening the time to cure.
2. 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.
3. Though there was a statistically insignificant increase in cure rate in patients with nodular disease who received adjuvant lithium, the clinically significant drop in T4 concentration at the end of the study from baseline values suggests adjuvant Lithium potentiates the effect of RAI therapy in this group of patients.
4. There was a positive association of adjuvant lithium with increased cure in female hyperthyroidal patients. This observation however was not present in male patients.
5. Adjuvant lithium was also shown to significantly reduce serum free T4 concentration following RAI therapy.
6. Reduction in serum free T4 concentration post RAI therapy from baseline values were higher in patients who were not pre-treated with Neomercazole than those who received pretreatment. Also, adjuvant Lithium therapy was shown to further reduce T4 concentration post RAI in those patients who did not receive pretreatment.
7. Low dose short course Lithium therapy resulted in very minimal side effects and therefore safe to use as an adjunct to RAI therapy.

5.1. Recommendations

From our findings, we recommend:

- Addition of adjuvant lithium to RAI treatment, especially in those patients with Grave's disease and at risk of increased cardiac complications and the elderly.
- Decision to treat patients with RAI should be made as early as possible after diagnosis to minimise the impact of antithyroid medications.

Appendix A: Data collection sheet

Patient code	Hosp. Number	Age	Sex	Diagnosis	Previous RAI TXT	Neomercazole Pretreatnebt	Lithium	Initial Bloods			4-6 weeks			3 months			
								TSH	T4	T3	TSH	T4	T3	TSH	T4	T3	

Appendix B: Ethics Clearance Certificate



R14/49 Dr Emmanuel Nii Boye Hammond

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130846

NAME: Dr Emmanuel Nii Boye Hammond
(Principal Investigator)

DEPARTMENT: Radiation Sciences (Nuclear Medicine)
Charlotte Maxeke Johannesburg Academic Hospital
Chris Hani Baragwanath Academic Hospital


PROJECT TITLE: Comparing the Effect of Adjuvant Lithium Therapy on the Efficacy of Radioactive Iodine Therapy in Hyperthyroidism

DATE CONSIDERED: 30/08/2013

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof MDTHW Vangu

APPROVED BY: 
Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 25/10/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature _____

Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Patient information and consent form

Comparing the effect of adjuvant lithium therapy on the efficacy of radioactive iodine therapy in hyperthyroidism.

Good day

My name is Dr E. Nii Boye Hammond of the Nuclear Medicine Department of Charlotte Maxeke Johannesburg Academic and Chris Hani Baragwanath Academic hospitals. I am conducting a research comparing the effect of adjuvant lithium therapy on the efficacy of radioactive iodine therapy in hyperthyroidism. Research is just the process to learn the answer to a question. In this study we want to learn if giving patients Lithium, in addition to radioactive iodine therapy can help improve cure rates and prevent further treatment of their hyperthyroidism.

I am inviting you to take part in this research study.

What is involved in the study:

In addition to the radioactive iodine treatment you have been referred for, you would be receiving lithium carbonate tablets which you would be taking orally 800mg daily. Routine follow-up and laboratory tests would be done as per the normal clinical protocol.

Study procedure:

Patients in this study will be randomly selected and put into two parallel groups; one receiving fixed dose of 10mCi radioactive iodine-131 only (with no additional treatment) and the other group receiving fixed dose of 10mCi radioactive iodine-131 plus Lithium carbonate (800mg) daily for 7 days, starting from day of RAI administration.

Risks of being involved in this study:

Though very rare, there are few side effects associated with lithium administration which includes gastrointestinal discomfort, nausea, diarrhea, polyuria, weight gain; skin eruptions, alopecia, and edema are common. More rare side effects are tremor, poor concentration and memory, ataxia, dysarthria, and incoordination. However, the dose of lithium we are administering for the study is below the normal therapeutic levels, and also for a very short period (7 days), therefore we do not anticipate any significant effects.

Benefits of being in the study:

Your participation will help us to find out how effective this treatment regime is and also decide if future patients should be made to follow this treatment protocol.

Your participation is voluntary.

Should you choose not to participate, this will not change the way we treat you in any manner.

Confidentiality:

Efforts will be made to keep personal information confidential.

Contact details of researcher:

For further information, please do not hesitate to contact me, Dr E. Nii Boye Hammond on, on 011 488 3559 or 011 9338502

In case you have any concerns, you may contact the Ethics Committee at 011 717 1234

I have read the information provided for the as described above. My questions have been answered to my satisfaction, and I agree to participate in this study. I have been given a copy of this form.

Tel No:

Name of Participant (please print)

Signature of Participant or Legal Representative

Date

SIGNATURE OF WITNESS

Name of Witness (please print)

Signature of Witness

Date

Appendix D: "Turnit in" report

Submission Info

SUBMISSION ID	607217200
SUBMISSION DATE	30-Nov-2015 08:06AM
SUBMISSION COUNT	1
FILE NAME	Emmanuel_Hammond_...
FILE SIZE	1.18M
CHARACTER COUNT	69228
WORD COUNT	12827
PAGE COUNT	60
ORIGINALITY	
OVERALL	15%
INTERNET	6%
PUBLICATIONS	14%
STUDENT PAPERS	3%

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