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2019
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AN ANALYSIS OF THE FACTORS INFLUENCING OUTCOME OF RADIOIODINE THERAPY IN AFRICAN PATIENTS' WITH GRAVES' DISEASE

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A research article submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of MMED: Internal Medicine

Johannesburg, 9th September 2019

Declaration

I, Dr Naeem Motala, declare that this research article is my own work. It is submitted for the degree of MMED: Internal Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University

…….

The 9th day of September, 2019

Acknowledgements

I would like to thank my Lord, Glorious and Exalted is He, without whom this would not have been possible

To my supervisors, thank you for your time, commitment and support

To my wife, Fatima and my children, Ebrahim and Aaisha, none of this would have been possible without the sacrifices you have made

Abstract

Background

Graves' disease is one of the commonest causes of hyperthyroidism worldwide and amongst our African population. Radioiodine ablation is a treatment modality used to treat Graves' disease. Despite its success in treating the disease, there are a number of patients that will require a second or third ablation to adequately control the hyperthyroid state. It is thus important to document this percentage in our setting, and the role that any pre-treatment factors play in determining outcome following radioiodine ablation.

Objectives

To determine the percentage of patients that require a single, second, and third dose of radioiodine. In addition, to identify factors that may predict a poor response to radioiodine ablation.

Methods

Two hundred adult patients that underwent radioiodine ablation for Graves' disease at Chris Hani Baragwanath Hospital until 30 June 2015 were included in the study. Information was obtained from the medical records from the Departments of Endocrinology, and Nuclear Medicine and captured onto a data sheet.

Results

The total sample of 191 African patients were predominantly female (83%) and between the ages of 40 – 60 years old (52%). Ninety-eight percent of the patients had a TSH value that was suppressed at admission. Seventy-eight percent of the patients had a single radioiodine ablation; twenty percent of the patients had two ablations, and two percent of the patients had had three ablations. At twelve months post ablation, seventy-two percent of the patients had a TSH value that was normal or high, with only twenty-two percent having a TSH value that was still suppressed. There was no statistically significant relationship between age, gender, and TSH level with treatment outcome. The level of FT4 at three months was significantly associated with treatment outcome at three months post ablation with a higher FT4 level associated with treatment failure and subclinical hyperthyroidism. This was not seen at six or twelve months. Treatment with anti-thyroid drugs prior to ablation was not significantly associated with treatment outcome.

Conclusion

This study concluded that seventy-eight percent of patients required a single ablation with twenty percent requiring a second ablation and two percent requiring a third ablation. The FT4 level at three months was significantly associated with treatment outcome, but this was not seen at six or twelve months post ablation. There was no statistically significant association between age, gender, TSH level, FT4 level at six and twelve months, thyroid antibodies, Graves' eye disease, thyroid morphology, and the use of anti-thyroid drugs with treatment outcome.

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Chapter 1: Protocol and Extended Literature Review

1.1: Introduction and Background

Thyroid disorders are common amongst patients of different backgrounds and races on the African continent. Iodine deficiency and resultant goitre, hypothyroidism and cretinism is a major issue affecting public health on the continent, but urbanisation and fortification of dietary salt with iodine has changed the profile of thyroid disorders [1]. Hyperthyroidism is a multisystem disorder that can lead to considerable morbidity and mortality, and is closely related to cardiovascular and musculoskeletal complications. It affects women more than men and has a prevalence among women of approximately 0.6 percent [2].

Underdiagnosis of autoimmune thyroid disease is still a problem in parts of the African continent and this leads to difficulty in assessing the true prevalence of this form of thyroid illness amongst our patients. The studies that have been conducted have revealed a prevalence rate of 1.2 – 9.9 percent [3]. Other causes that must be considered in a patient presenting with hyperthyroidism include multinodular goitre, toxic adenoma, papillary and follicular thyroid cancer, and drug induced thyroid disease most often secondary to the use of amiodarone.

1.2: Graves' disease

Graves' disease is the commonest disease causing hyperthyroidism in many countries. It is autoimmune in nature. It affects people of all ages and peaks in young adults between the ages of 30 – 50. It results from the interplay between genetic and environmental factors and is characterized by IgG antibodies against the Thyroid stimulating hormone receptor (TSH-R). This stimulates production of thyroid hormone. There are also antibodies that block the

very same receptor and this interplay between the stimulating and blocking antibodies determines thyroid function. Other antibodies include Anti-thyroid peroxidase and anti-thyroglobulin antibodies [4]. Clinical features of Graves' disease are due to a combination of the effects of the goitre, the hyperthyroidism, sympathetic nervous system activation, and autoimmunity. Most patients complain of weight loss, heat intolerance, excessive sweating and tremor. Patients may also report symptoms related to an enlarging goitre or orbitopathy. In addition, patients may present with cardiac complications such as atrial fibrillation and heart failure amongst others. Orbital signs can range from proptosis and lid retraction to chemosis, inflammation and visual loss.

1.3: Treatment of Graves' disease

Timely and effective treatment of Graves' disease is important to prevent morbidity and mortality. Spontaneous remission does occur in approximately 30% of patients' with Graves' disease [4].There are three effective treatment modalities available and these are: anti-thyroid drugs, radioiodine ablation, and thyroidectomy. Each modality has its own advantages and disadvantages. The anti-thyroid drugs Carbimazole and Propylthiouracil block thyroid hormone synthesis. This occurs via inhibition of the enzyme, thyroid peroxidase. In addition Propylthiouracil also prevents peripheral conversion of thyroxine to triiodothyronine. The advantages include treatment as an outpatient, no surgical risk, no radiation exposure and a relatively low risk of hypothyroidism. Disadvantages of medical therapy include frequent hospital visits, and a risk of recurrence when treatment is stopped. Adverse effects of the drugs include hepatotoxicity and a risk of agranulocytosis, although these occur infrequently. Beta adrenergic blockers are used to control the symptoms related to activation of the sympathetic nervous system and do not alter the outcome of the

disease. Allanic et al. proved that a longer duration (18 months vs 6 months) of anti-thyroid drugs improved the remission rate in patients' with Graves' disease [5].

Surgery as a primary treatment modality of choice for Graves' disease has been somewhat overtaken by the use of anti-thyroid drugs and radioiodine ablation. However, it does offer the patient the advantage of definitive therapy and may be more suitable for large goitres that are cosmetically unacceptable or that cause compressive symptoms. In addition, surgical outcomes have improved with the use of drug therapy pre-operatively and modern surgical techniques. A large meta-analysis performed in 1999 involving 7241 patients assessed the effectiveness of surgery for Graves' disease. The outcomes showed that total or subtotal thyroidectomy successfully treated the disease in 92 percent of patients. Outcomes were better with total thyroidectomy compared to subtotal thyroidectomy. Injury to the recurrent laryngeal nerve occurred in 0.9 percent of patients undergoing total thyroidectomy and 0.7 percent of patients undergoing subtotal thyroidectomy. Hypoparathyroidism occurred in 1.6 percent and 1 percent of patients respectively [6]. Patients should be treated with anti-thyroid drugs pre-operatively and ideally should be rendered euthyroid prior to surgery. Surgery has no effect on the course of the opthalmopathy associated with the disease [4].

1.4: Radioiodine Ablation

Radioiodine ablation of the thyroid gland is a simple, inexpensive and effective mode of therapy that has been used to manage Graves' disease since the 1940's [2]. It allows for resolution and control of hyperthyroidism with few side effects. Despite its benefits, there is a lack of large prospective trials evaluating aspects related to its use in thyroid disease [7]. Iodine is a component of triiodothyronine (T3) and thyroxine (T4). These are hormones

produced by the thyroid gland, which avidly takes up iodine. Radioiodine affects DNA within the thyroid cell that eventually leads to destruction of the gland and hence the desired clinical outcome. Radioiodine therapy and Graves' disease has been evaluated during the last 4 decades with the results showing that between 50 – 90 percent of patients experience control of the hyperthyroidism 3 – 12 months after radioiodine therapy [7]. Radioiodine therapy often results in hypothyroidism which is then managed with levothyroxine therapy. This was initially thought to be due to overtreatment with radioiodine, however it is now recognized as an outcome that is seen in up to 50 percent of patients treated in the first year, with an annual incidence of 3 – 5 percent thereafter [8]. In fact, guidelines published by the American Thyroid Association and American Association of Clinical Endocrinologists on management of hyperthyroidism recommend using a dose of radioiodine that will render the patient hypothyroid [9].

An elevation of thyroid hormone may occur transiently in the period following radioiodine ablation and is due to the release of stored hormone. Most patients are asymptomatic, although there have been a few cases of thyroid storm [10]. To avoid this, most patients are treated with anti-thyroid drugs pre ablation. Patients may experience adverse effects related to the salivary gland and these may include dry mouth, an alteration in taste, pain, salivary gland swelling and reduced salivary secretion. These symptoms are usually transient and persist in a small percentage of patients [11]. The concern regarding an increase in cancer amongst patients receiving radioiodine therapy has been addressed in numerous studies. Long term studies have shown no increase in the risk of death from malignancy in patients treated with radioiodine therapy [12, 13]. Pregnancy or planned pregnancy within the next 6 months, lactation, a suspicious thyroid nodule or thyroid cancer, and those individuals that are not able to comply with radiation safety guidelines are contraindications to radioiodine

therapy. Moderate to severe thyroid opthalmopathy at presentation is a relative contraindication to therapy as the eye disease may worsen following radioiodine exposure. Corticosteroids can be used to dampen the inflammatory response but there has been no agreement on the initiating dose and length of treatment. In addition, there is a paucity of prospective randomized trials to evaluate this issue [14, 15].

1.5: Treatment Strategy

Decision on treatment choice for Graves' disease can be challenging for both the patient and the treating physician. In addition, there is no consensus amongst physicians as to the best treatment strategy to treat these patients[16]. A survey performed in the United States, Europe and Japan revealed these differences. Radioiodine ablation is used as the first line of therapy for Graves' disease amongst 69 percent of North American physicians; in Europe this figure is much lower at 22 percent, and in Japan, even lower at 11 percent. Anti-thyroid drugs were used as first line therapy amongst 88 percent of physicians in Japan and 77 percent of those in Europe [16].

1.6: Treatment Failure: Age and gender

Although radioiodine ablation usually renders the patient hypothyroid, up to 30 percent of patients experience treatment failure. This is defined as persistent clinical and/or biochemical evidence of hyperthyroidism following 3 months to one year post radioiodine therapy [17]. These patients will require a second and/or third dose of radioiodine to successfully control the hyperthyroidism. It is thus important to identify and document the percentage of patients that experience treatment failure, and investigate if there are any

factors that may be associated with treatment failure. Studies have revealed that there is no correlation between gender and treatment outcome [17, 18]. The effect of age on treatment outcome has been evaluated in numerous studies with conflicting results. This may reflect the fact that at the extreme of ages, patients often exhibit differences in other aspects of the disease that may influence treatment outcome. Younger age at presentation (<40) was associated with an increased risk of treatment failure in large retrospective studies examining patients treated over a 6 – 10 year period [18, 19, 20]. However, the study conducted by Isgoren et al conducted over a period of four years showed no correlation between age and treatment failure [17].

1.7: Treatment Failure: Thyroid Morphology

The normal thyroid gland weighs approximately 20 grams or less [20, 21]. Studies evaluating the effects of thyroid gland size and outcome following radioiodine ablation have yielded differing results. This may be due to the fact that most studies use a fixed iodine dose independent of thyroid gland size. Another factor that may play a role is that thyroid size is often assessed clinically or via an uptake scan. Both these methods are inferior to actual thyroid gland size measurement via ultrasonography or CT scan [7]. Larger thyroid gland size has been shown to be associated with a poorer outcome following radioiodine ablation in numerous studies [20, 22, 23]. However, other studies have failed to prove this association [24, 25]. Thus, the effect that thyroid gland size may have on treatment outcome has still not been resolved. Thyroid glands with an increased avidity for iodine as reflected by an increased 24 hour radioiodine uptake had a higher chance of relapse [17, 20]. The half-life of radioiodine is shortened as the iodine is rapidly removed from the thyroid gland and this contributes to

the increased risk of relapse [17]. In addition, the dose used may not factor in the half-life of Iodine and may be less than is actually needed [7].

1.8: Treatment Failure: Thyroid Hormones

Numerous studies have shown an association between higher FT3 and FT4 levels at presentation and an increased risk of treatment failure following radioiodine ablation. These patients have severe thyrotoxicosis at presentation which in itself is a risk factor for treatment failure following radioiodine ablation [20, 21]. Most of the studies evaluating this aspect focus on the FT3 and FT4 levels at diagnosis. It may be that the level of the hormones immediately prior to radioiodine ablation is more important than at diagnosis and further studies are needed in this regard. Some studies have shown that the level of TSH prior to radioiodine therapy is associated directly with the outcome of therapy [26, 27, 28]. However, serum TSH will be supressed in patients with hyperthyroidism and elevated TSH values will be seen in patients treated with anti-thyroid drugs. A higher TSH value may also be seen in patients that do not have severe disease and may reflect a more sensitive thyroid gland.

1.9: Treatment Failure: Thyroid Antibodies

The role of TSH-Receptor/thyroid stimulating antibodies (TSab), TSH-blocking antibodies (TSHBAb) and thyroid peroxidase antibodies (TPOab) in treatment outcomes is controversial. TSab are measured as a percentage of basal cyclic-AMP production with a value of > 130 percent considered a positive TSab result. Chiovato et al studied the outcome of patients with Graves' disease treated with radioiodine ablation and concluded that a higher titre of TSab (>600 percent of basal cyclic-AMP production) prior to therapy was associated with a poorer outcome [22]. Other studies have shown an inverse relationship between TSab levels and cure rate [27, 29]. The relationship, however, is not absolute as some

studies have not found any relationship between TSab and outcome [30, 31]. TPOab was associated with hypothyroidism following treatment [32]. However, the effect has not been proven consistently enough.

1.10: Treatment Failure: Anti-thyroid drugs

The use of anti-thyroid drugs prior to radioiodine ablation and its effects on treatment outcome has been debated for decades. The intention of using anti-thyroid drugs before radioiodine ablation is to prevent the development of a worsening hyperthyroid state and potentially a thyroid storm. Most studies evaluating this aspect of the disease have shown that the use of anti-thyroid drugs increases the risk of treatment failure with radioiodine ablation [19, 20, 33]. Of note is a large meta-analysis published in the British Medical Journal in 2007 which evaluated all randomised controlled trials on this issue over a period of 54 years from 1952 – 2006. They concluded that treatment with anti-thyroid drugs increased the risk of treatment failure if given before, with, or after radioiodine [34]. Weaknesses in this meta-analysis include differences in the trial designs, inclusion and exclusion criteria, doses of anti-thyroid drugs used and the interplay between the radioactive iodine and the anti-thyroid drugs.

1.11: Treatment Failure: Other mechanisms

Other mechanisms that have been proposed to play a role in treatment outcome include the effect of dietary iodine. Radioiodine uptake of the thyroid gland changes with dietary iodine intake. Dietary iodine restriction prior to radioiodine therapy has been advised as per nuclear medicine guidelines. However, this is mainly of use in patients with thyroid cancer or goitre. Other therapies that have been used include Lithium and diuretics but neither has been used consistently enough in patients with Graves' disease.

Radioiodine ablation of the thyroid gland is an important and effective treatment modality to control hyperthyroidism caused by Graves' disease [2]. There are various factors that may influence the outcome of radioactive iodine ablation. These have not been studied in a South African population before, specifically amongst African patients. It is thus important to document the percentage of patients that experience treatment failure and the factors that may play a role in contributing to this. This may allow us in the future to identify patients that will benefit most from this treatment modality, and to tailor the treatment approach in this regard.

1.12: Objectives

The primary objective is to identify treatment outcomes in African patients who undergo radioiodine ablation for Graves' disease. To determine the percentage of patients that require a single ablation, and the percentage that require a second or third ablation. The study also proposes to identify factors that may predict a poor response to radioiodine ablation. The study assesses the effect of age, gender, thyroid hormone levels, thyroid antibodies and the use of anti-thyroid drugs on treatment outcome

1.13: Methods

1.13.1: Study design and setting

This was a single centre, retrospective, observational study that was conducted jointly at the Division of Endocrinology and Metabolism, Department of Internal Medicine and at the Department of Nuclear Medicine at Chris Hani Baragwanath Academic Hospital in Soweto, Johannesburg. This is a tertiary level academic hospital situated in Gauteng, South Africa.

1.13.2: Study sample and data collection

The study sample included all adult patients with hyperthyroidism secondary to Graves' disease that underwent radioiodine ablation from 01 August 2010 until 30 June 2015 at Chris Hani Baragwanath Hospital. Exclusion criteria included patients with less than 3 months follow up, patients with incomplete records, and patients that were lost to follow up. Data was collected from the patient records from the Division of Endocrinology and from the Department of Nuclear Medicine's patient database. This database included all patients that received radioiodine ablation for various medical and/or surgical indications. The records of patients that underwent ablation for thyroid related illnesses were then screened and the patients with Graves' disease were included. This was then matched to data records of patients with Graves' disease from the Division of Endocrinology. Data was collected retrospectively from patients that received radioiodine ablation from 30 June 2015 until two hundred patients were obtained.

Demographic data including age and gender was collected. Age was divided into less than 20 years; between 20 – 40 years; between 40 – 60 years; greater than 60 years; and a category for unknown age. Gender was divided into male or female. Biochemical data was divided into categories for levels of Thyroid Stimulating Hormone (TSH), FT4 and FT3; and the presence or absence of TSH Receptor Antibody (TSHRab), Antithyroid Peroxidase Antibody, and Antithyrogobulin Antibody. Values were collected for the levels of TSH, FT4 and FT3 at admission, and at 3 months, 6 months, and 12 months post radioiodine ablation. TSH was measured in Milli-International Units per Litre (mIu/L) and was divided into less than 0.27mIu/L, between 0.27 and 4.20, greater than 4.20, and a category for unknown value. FT4 was measured in picomole per litre (pmol/l) and was divided into less than 12pmol/l, between 12 and 22, between 22 and 50, greater than 50 and a category for unknown value. FT3 was also measured in pmol/l and was divided into less than 3.5 pmol/l, between 3.5 and

6.5, greater than 6.5 and a category for unknown value. Thyroid antibodies were divided into positive, negative or not done. Thyroid gland morphology was subdivided into the presence of a smooth diffuse goitre on clinical examination or the presence or absence of thyroid nodules. This was then confirmed via nuclear medicine uptake scan into smooth and diffuse uptake of the iodine tracer, or the presence of a hot or cold nodule. Thyroid eye disease was recorded as present, absent, or not recorded. Data was then collected regarding treatment of the Graves' disease. This included information regarding the use of anti-thyroid drugs and beta-blocking agents prior to radioiodine ablation, and number of radioiodine therapies undertaken previously. Data was then collected regarding the addition of thyroid hormone and treatment outcome at three, six and 12 months post radioiodine therapy. Treatment outcome was then assessed at three, six, and 12 months post ablation and treatment success was defined as euthyroidism, hypothyroidism, or the addition of thyroxine replacement therapy. Treatment failure was defined as persistent hyperthyroidism at least 12 months post radioiodine ablation.

1.13.3: Data analysis

The data was captured in Microsoft Excel and exported into the statistical programme Statistical Product and Service Solutions where the analysis was conducted. Descriptive statistics such as the frequency distribution, mean and standard deviation were conducted to analyse the data. Pie charts and bar graphs were used to graphically demonstrate the data. The Chi square test of association was used to assess whether there was an association between two categorical variables such as gender and treatment outcomes. A p-value of less than 0.05 indicated a significant association between two variables and a p-value of greater than 0.05 indicated no significant association between the variables.

1.14: Study Limitations

As the study is retrospective and data will be obtained entirely from patient records, poor record keeping will hinder the study. In addition, the study is limited by the possibility that there are factors not under investigation in this study that may contribute to treatment failure.

1.15: Ethics

Patients' confidentialty was maintained at all times during the study. Permission to conduct the study was obtained from the Ethics Committee at the University of the Witwatersrand and from Management at Chris Hani Baragwanath Hospital.

1.16: Funding

The study did not require any funding.

1.17 Timing

	Jan	Feb	March	April	May	June	July	August	Sept	Oct	Nov	Dec
Literature review												
Preparing Protocol												
Protocol Assessment												
Ethics Approval												
Data Collection												
Data Analysis												
Writing up thesis												

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Chapter 2: Submissible Article

TITLE: AN ANALYSIS OF THE FACTORS INFLUENCING OUTCOME OF RADIOIODINE THERAPY IN AFRICAN PATIENTS' WITH GRAVES DISEASE

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Short Title:

Factors Influencing Outcome of Radioiodine Therapy in African Patients' with Graves' disease

Conflict of Interest:

Nil

Keywords:

Outcome; Radioiodine therapy; Graves' disease

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Total word count: 3237 words

Abstract word count: 407 words

Abstract

Background

Graves' disease is one of the commonest causes of hyperthyroidism worldwide and amongst our African population. Radioiodine ablation is a treatment modality used to treat Graves' disease. Despite its success in treating the disease, there are a number of patients that will require a second or third ablation to adequately control the hyperthyroid state. It is thus important to document this percentage in our setting, and the role that any pre-treatment factors play in determining outcome following radioiodine ablation.

Objectives

To determine the percentage of patients that require a single, second, and third dose of radioiodine. In addition, to identify factors that may predict a poor response to radioiodine ablation.

Methods

Two hundred adult patients that underwent radioiodine ablation for Graves' disease at Chris Hani Baragwanath Hospital until 30 June 2015 were included in the study. Information was obtained from the medical records from the Departments of Endocrinology, and Nuclear Medicine and plotted onto a data sheet.

Results

The total sample of 191 African patients were predominantly female (83%) and between the ages of 40 – 60 years old (52%). Ninety-eight percent of the patients had a TSH value that was suppressed at admission. Seventy-eight percent of the patients had a single radioiodine ablation; twenty percent of the patients had two ablations, and two percent of the patients had had three ablations. At twelve months post ablation, seventy-two percent of the patients had a TSH value that was normal or high, with only twenty-two percent having a TSH value that was still suppressed. There was no statistically significant relationship between age, gender, and TSH level with treatment outcome. The level of FT4 at three months was significantly associated with treatment outcome at three months post ablation with a higher FT4 level associated with treatment failure and subclinical hyperthyroidism. This was not seen at six or twelve months. Treatment with anti-thyroid drugs prior to ablation was not significantly associated with treatment outcome.

Conclusion

This study concluded that seventy-eight percent of patients required a single ablation with twenty percent requiring a second ablation and two percent requiring a third ablation. The FT4 level at three months was significantly associated with treatment outcome, but this was not seen at six or twelve months post ablation. There was no statistically significant association between age, gender, TSH level, FT4 level at six and twelve months, thyroid antibodies, Graves' eye disease, thyroid morphology, and the use of anti-thyroid drugs with treatment outcome.

Introduction:

Thyroid disorders are common amongst patients of different backgrounds and races on the African continent. Iodine deficiency and resultant goitre, hypothyroidism and cretinism is a major issue affecting public health on the continent but urbanisation and fortification of dietary salt with iodine has changed the profile of thyroid disorders [1]. Hyperthyroidism is a multisystem disorder that can lead to considerable morbidity and mortality, and is closely related to cardiovascular and musculoskeletal complications. It affects women more than men and has a prevalence among women of approximately 0.6 percent [2].

Graves' disease is the commonest autoimmune disease that affects the thyroid gland and is the commonest cause of hyperthyroidism in many countries. It affects people of all ages and peaks in young adults between the ages of 30 – 50. It is characterized by antibodies that stimulate the TSH receptor resulting in the production of thyroid hormone. Anti-thyroid peroxidase and anti-thyroglobulin antibodies also occur in patients with Graves' disease [3].

Timely and effective treatment of Graves' disease is important to prevent morbidity and mortality. Spontaneous remission does occur in a subset of patients' with Graves' disease [3]. There are three effective treatment modalities available and these are: anti-thyroid drugs, radioiodine ablation, and thyroidectomy. The long term quality of life was found to be similar amongst patients randomly assigned to one of the above therapies [4].Surgery is definitive therapy and more suitable for larger goitres; however it runs the risk of hypoparathyroidism, damage to the recurrent laryngeal nerve and post-operative bleeding [5]. The anti-thyroid drugs Carbimazole and Propylthiouracil block thyroid hormone synthesis via inhibition of the thyroid peroxidase enzyme. In addition Propylthiouracil also prevents peripheral conversion of thyroxine to triiodothyronine. Advantages of medical therapy

include treatment as an outpatient, no surgical risk or radiation exposure, and a low risk of hypothyroidism. Adverse effects include the risk of hepatotoxicity, agranulocytosis, and a risk of recurrence if treatment is stopped. There is no consensus amongst physicians as to the optimal treatment strategy for patients with Graves' disease [6]. A survey performed amongst members of thyroid associations in the United States, Europe and Japan revealed these differences. Radioiodine ablation is used as the first line of therapy for Graves' disease amongst 69% of North American physicians; whereas it is used by only 22% of physicians in Europe and 11% of physicians in Japan as first line therapy. Anti-thyroid drugs were used as first line therapy amongst 88% of physicians in Japan and 77% of those in Europe [6].

Radioiodine ablation of the thyroid gland is a simple, inexpensive and effective mode of therapy that has been used to manage Graves' disease since the 1940's [2]. It allows for resolution and control of hyperthyroidism with few adverse effects. Contraindications to the use of radioactive iodine include pregnancy or planned pregnancy within the next six months, lactation, a suspicious thyroid nodule, thyroid cancer, and those individuals that are not able to comply with radiation safety guidelines. Long term follow up studies have shown no increase in the risk of death from cancer in patients treated with radioiodine therapy [7, 8]. The goal of therapy is complete ablation of the thyroid gland. If successful, this results in hypothyroidism which is then managed with levothyroxine therapy. As many as 30 percent of patients treated with radioiodine ablation experience treatment failure. This is defined as persistent clinical and/or biochemical evidence of hyperthyroidism following at least 3 months to one year post radioiodine therapy [9]. These patients will require a second and/or third dose of radioiodine to successfully control the hyperthyroidism. It is thus important to identify and document the percentage of patients that experience treatment failure and any factors that may be associated with this. Factors that were assessed in this study included

the effect of age, gender, thyroid hormone levels, thyroid antibodies, thyroid morphology, Graves' eye disease, and the use of anti-thyroid drugs on treatment outcome.

Radioiodine ablation of the thyroid gland is an important and effective treatment modality to control hyperthyroidism caused by Graves' disease [2]. There are various factors that may influence the outcome of radioactive iodine ablation. These have not been studied in a South African population before, specifically amongst African patients. It is thus important to assess the local data regarding this aspect of Graves' disease in order to facilitate further study in this regard with the hope of identifying patients that may most benefit from this form of therapy.

Methods:

This was a single centre, retrospective, observational study that was conducted at a single tertiary academic hospital in Soweto, Johannesburg. The study sample included all adult patients with hyperthyroidism secondary to Graves' disease that underwent radioiodine ablation from 01 August 2010 until 30 June 2015 at Chris Hani Baragwanath Hospital. Exclusion criteria included patients with less than 3 months follow up, patients with incomplete records, and patients that were lost to follow up. Data was collected from the patient records from the Division of Endocrinology and from the Department of Nuclear Medicine's patient database. Patients that underwent ablation for Graves' disease were then included in the study. Data was collected retrospectively from patients that received radioiodine ablation from 30 June 2015 until two hundred patients were obtained.

Results

A total of 200 patients were assessed of which 191 were black and were included in the study. The majority of the patients were between the ages of 40 and 60 years old (52%);

37% of the patients were between the ages of 20 and 40 years old and 9% were older than 60 years old. Most of the patients were female (83%) with males comprising 17% of the study.

98% of the patients had an admission TSH that was supressed with 94% of the patients having a value of <0.27mIu/L. At three months post ablation, 34% of the patients had a TSH that was normal or high and 30% of the patients had a TSH that was still supressed. These values were influenced by the fact that 36% of the patients did not have a TSH at three months. At six months post ablation, 50% of the patients had a TSH that was normal or high. At one year post ablation, 72% of the patients had a TSH that was normal or high with only 22% having a TSH value that was still supressed.

At admission, 79% of the patients had a FT4 of >22pmol/L with 42% having a value between 22 and 50pmol/L and 37% having a value of >50pmol/L. At 12 months post ablation, 78% of the patients had an FT4 value that was normal or supressed. The majority of the patients did not have an FT3 or a TSH-R antibody done during the course of their care. 7% of the patients had a positive Anti-thyroid peroxidase antibody test and one percent of the patients had a positive Anti-thyroglobulin antibody test.

With regards to thyroid morphology, 81% of the patients had a smooth diffuse goitre and there was no goitre in 13% of the patients. Thyroid nodules were recorded as palpable in only 3% of the patients analysed. Graves' eye disease was present in 16% and absent in 78% of the patients analysed.

The majority of the patients (97%) were treated with anti-thyroid drugs prior to ablation and 35% of the patients had received beta blockers. Regarding radioiodine ablation, 78% of the

patients had had a single ablation, 20% had had two ablations and only 2% of the patients had had three ablations.

At six months post ablation, 43% of the patients had thyroxine replacement and this figure increased to 66% at twelve months post ablation. Treatment success at three months post ablation was 38%; this increased to 53% at six months and 73% at twelve months post ablation. At twelve months post ablation, 13% of patients had subclinical hyperthyroidism and 8% had treatment failure. (Table 3)

There was no statistically significant relationship between age and treatment outcome at 3, 6, and 12 months (p=0.276; p=0.500; p=0.928 respectively). There was no statistically significant relationship between gender and treatment outcome (p=0.717; p=0.997; p=0.315). TSH was also not associated with treatment outcome at 3, 6, and 12 months (p=0.753; p=0.604; p=0.199). The level of FT4 at 3 months was significantly associated with treatment outcome at 3 months post ablation (p=0.011) with a higher level of FT4 being associated with treatment failure and subclinical hyperthyroidism. However, this significance was not seen at 6 months and 12 months post ablation. The presence of thyroid antibodies was not significantly associated with treatment outcome at 3, 6 and 12 months post ablation. The presence of a smooth diffuse goitre or of thyroid nodules and the presence of eye signs were not significantly associated with treatment outcome at 3, 6 and 12 months post ablation. Treatment with anti-thyroid drugs prior to ablation was not significantly associated with treatment outcome.

Discussion

This retrospective study of African patients with Graves' disease was aimed at assessing the outcomes of radioiodine ablation in this patient population. The principal aim was

identifying the percentage of patients that required a single dose of radioiodine ablation, and the percentage that required more than one dose. It also aimed to identify pre-treatment factors that may contribute to treatment failure in this population group. The majority of the patients in the study were between the ages of 40 – 60, and most of the participants were female. Regarding radioiodine ablation, 77% of the patients had a single ablation; 20% had two ablations and only 2% of the patients had 3 or more ablations. There is limited local data available looking at this precise aspect in the outcome of radioiodine ablation for Graves' disease. A poster presentation on a retrospective study looking at local data from Kwa-Zulu Natal that was presented at the Society for Endocrinology, Diabetes and Metabolism of South Africa meeting in 2012 found that 88.8% of their patients treated with radioiodine ablation were euthyroid or hypothyroid at 2 years follow up [10]. A study conducted in Oman amongst 366 patients found that 88% required a single ablation and 11.2% required a second dose [11]. Ninety-four percent of our patients had a pre-treatment TSH level of <0.2. Forty-two percent of the study sample patients had an FT4 level of 22 – 50 umol/L, and 37% had an FT4 level of >50 umol/L. The results of the study indicated that twelve months post ablation, only 22% of the patients had a TSH that was still supressed, with 78% having an FT4 that was normal or low. However, there is a large percentage of patients that did not have regular TSH/FT4 levels assessed during the period post ablation. There is thus a need to develop a standardized protocol to assess the TSH/FT4 levels at fixed periods in the post ablation period. The majority of the patients' in the study had thyroid morphology in keeping with Graves' disease and most did not have thyroid eye disease. Ninety-seven percent of the patients in the study were treated with anti-thyroid drugs prior to radioiodine ablation.

Regarding pre-treatment factors that may be associated with treatment failure, only the FT4 level at three months was associated with treatment failure in this study. However, this effect was not seen at six and twelve months. The rest of the pre-treatment variables that were analysed did not have any significant effect on treatment outcome following radioiodine ablation. There are many studies in the literature that focus on the dose of radioactive iodine used and its effect on treatment outcome, however, this was not the focus of my study.

The strengths of this study is that it is the first such local study assessing treatment outcomes amongst African patients with Graves' disease. The weaknesses are that it is a retrospective study and that the data analysed was dependant on the information obtained from patient records. This study implores scientists to analyse in a prospective manner and in greater detail treatment factors that may influence outcome amongst patients of all races with radioiodine ablation. In this way, we may be able to select treatment options tailored to the individual patient. The issues surrounding dose of radioiodine ablation, the use of anti-thyroid drugs and the appropriateness of radioiodine ablation in patients with Graves' opthalmopathy remain unanswered.

Conclusion

This study concluded that amongst African patients with Graves' disease, 78% required a single ablation; 20% required a second ablation and 2% required three or more ablations. The FT4 level at three months was associated with treatment outcome at this stage. There was no statistically significant association between age, gender, TSH, FT4 at six and twelve

months, thyroid antibodies, Graves's eye disease, thyroid morphology, and the use of anti-thyroid drugs and treatment outcome.

Appendix

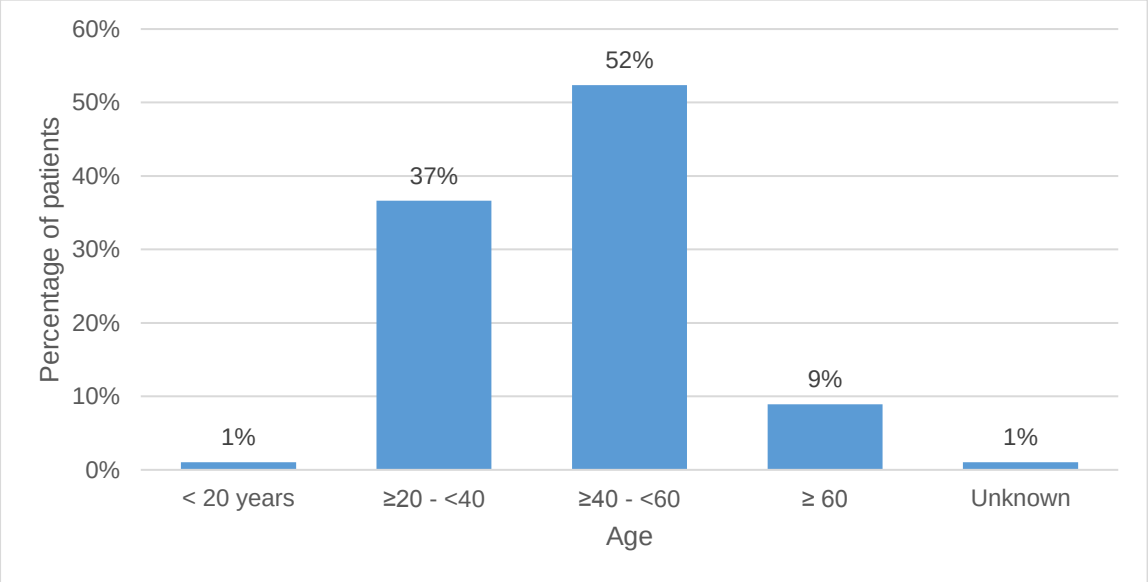


Figure 1 – Characteristics of patients age in the study

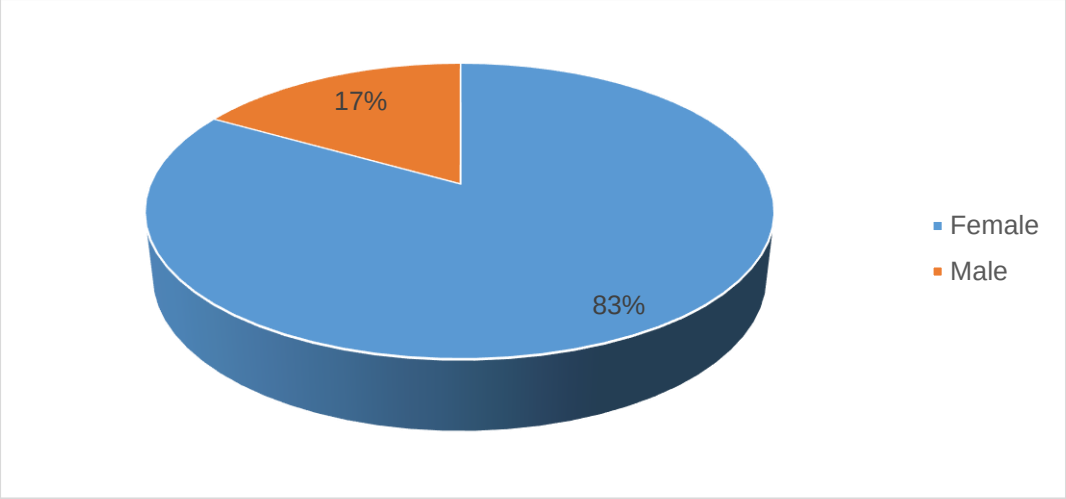


Figure 2 – Characteristics of patients gender

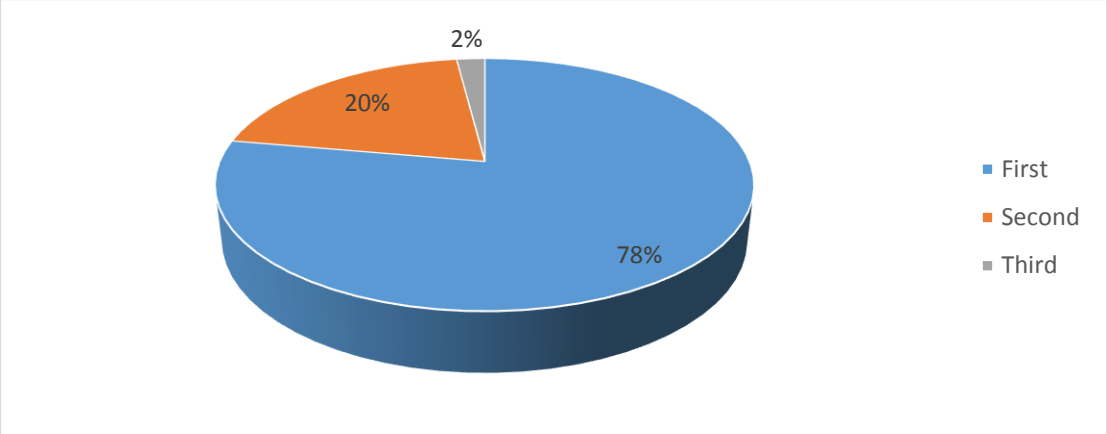


Figure 3 – Number of Radioiodine Therapy

Table 1 – Thyroid Stimulating Hormone at various stages post admission

	Admission	3 months	6 months	12 months
<0.27	94%	30%	20%	22%
≥ 0.27 - <4.20	4%	11%	15%	30%
≥ 4.20	1%	23%	35%	42%
Not done	1%	36%	30%	6%

Table 2 – Free Thyroxine (FT4) at various stages post admission

	Admission	3 months	6 months	12 months
<12.0	1%	33%	35%	30%
≥ 12.0 - <22	16%	17%	26%	48%
≥ 22 - <50	42%	10%	7%	7%
≥ 50	37%	1%	1%	1%
Not done	3%	38%	32%	15%

Table 3 – Treatment outcome at various stages post radioiodine therapy

	Treatment outcome at 3/12	Treatment outcome at 6/12	Treatment outcome at 12/12
Success	38%	53%	73%
Failure	12%	7%	8%
Not assessed	35%	29%	4%
Subclinical hyperthyroidism	14%	10%	13%
Unclear	0%	0%	2%
No records	2%	1%	1%

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Data Collection Sheet

Patient Demographics:

Study Number		
Age		
Gender	**Female**	**Male**

Biochemistry:

	Admission	**3 Months**	**6 Months**	**12 Months**
TSH				
FT4				
FT3				
TSH Receptor Antibody				
Antithyroid Peroxidase Antibody				
Antithyroglobulin Antibody				

Morphology:

Goitre		**Smooth diffuse**	**Nodules**	**Nil**
Uptake scan	**Date**	**Diffuse Uptake**	**Hot nodule/Cold Nodule**	
Opthalmopathy		**Yes**	**No**	

Treatment:

Anti-thyroid Drugs	**Yes**		**No**
Beta-blocker	**Yes**		**No**
Radioiodine Treatment	**First**	**Second**	**Third**
Addition of thyroid hormone at 3 months	**Yes**		**No**
Addition of thyroid hormone at 6 months	**Yes**		**No**
Addition of thyroid hormone at 12 months	**Yes**		**No**
Treatment outcome at 3 months	**Treatment success**		**Treatment failure**
Treatment outcome at 6 months	**Treatment success**		**Treatment failure**

Treatment outcome at 12 months	Treatment success	Treatment failure

R14/49 Dr Naeem Motala

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160528

NAME: (Principal Investigator)	Dr Naeem Motala
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	An Analysis of the Factors Influencing Outcome of Radioiodine Therapy in African Patients' with Graves' Disease
DATE CONSIDERED:	27/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr S Bhana and Dr K Purbhoo
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	22/06/2016

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 Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised 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 to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in May and will therefore be due in the month of May each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES