Efficacy of a fixed low dose of radioactive iodine in the treatment of Graves' disease in Sub-Saharan Africa

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Abstract

Objective: Graves' disease represents 60%-90% of all causes of thyrotoxicosis in different regions of the world. Thyrotoxicosis contributes approximately 66% to thyroid disorders in South Africa and of those Graves' disease contributes about 34%. In most Sub-Saharan African countries, Graves' disease is managed mainly with medical treatment, due to a lack of or poor access to other means of treatment. Despite the primary use of anti-thyroid drugs (ATD) in the management of Graves' disease, the use of radioactive iodine (RAI) is required in many patients, especially in cases where ATD are contraindicated, or in patients who have failed ATD treatment and are poor surgical candidates. There is no consensus on the best method for deciding on how much activity of radioiodine to administer to patients with Graves' disease, that is, whether to use a calculated dose, or an empirical or fixed dose for RAI. The standardized fixed dose is particularly helpful in under-resourced areas or centres with few nuclear physicians and high patient loads. However, little is known about the efficacy of the fixed dose compared to the calculated or empirical dose methods. The purpose of this retrospective observational study was to assess the efficacy of a fixed low dose of radioiodine-131 (^{131}I) in the treatment of Graves' disease. **Subjects and Methods:** Patients treated with a fixed dose of 10mCi between the periods of 2014 to 2017 were evaluated for treatment response after each dose of RAI. Outcome of therapy was evaluated at 3 monthly follow-up using biochemical markers: thyroid stimulating hormone (TSH), total free thyroxine (fT4), and or triiodothyronine (T3), and the presence or absence of clinical symptoms of thyrotoxicosis. According to their response to RAI therapy, patients were classified as responders (if they became euthyroid or hypothyroid), non-responders (if they failed to achieve euthyroidism or hypothyroidism at 6 months) and complete treatment failure (if no response was present within 18 months after two or three fixed low doses of RAI). Percentage uptake, baseline fT4 and patient age were compared according to treatment response. **Results:** Our cohort included 111 patients, 95 (86%) females and 16 (14%) males, with a mean age of 41.9 years. Treatment was successful after the first dose in 89.2% of cases (27.0% euthyroid; 62.2% hypothyroid), with 10.8% requiring a second dose, and only a single patient who remained hyperthyroid after that second empiric dose. Statistical analysis demonstrated that a high percentage thyroid uptake was associated with treatment failure, whereas a low percent thyroid uptake was associated with a good treatment response (P=0.0048). We found no significant difference in FT4 levels or age, between hyperthyroid and non-hyperthyroid (euthyroid or hypothyroid) groups post initial RAI therapy (P=0.5 and P=0.96, respectively). **Conclusion:** The use of a low fixed/empiric radioiodine activity for hyperthyroidism due to Graves' disease performed well in our setting with a nearly 90% response rate achieved after a single dose of 10mCi. Justification for higher activity should be specified, and this method of determining the optimal dose of RAI therapy may be beneficial in resource constrained settings with high patient volumes.

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Introduction

Graves' disease (GD) is an autoimmune disorder caused by the presence of systemic thyroid stimulating autoantibodies directed against the thyrotropin receptor on thyroid follicular cells. Graves' disease represents 60%-90% of all causes of thyrotoxicosis in different regions of the world. Thyrotoxicosis contributes approximately 66% of thyroid disorders in South Africa, and of those Graves' disease contributes about 34% [1]. The reported prevalence of auto-immune thyroid disorders in Africa is 1.2%-9.9%, because of under-diagnosis and under-reporting of these disorders [1, 2].

In most Sub-Saharan African countries, Graves' disease is managed mainly with medical treatment, due to a lack of, or poor access to, other means of treatment. Unless a major contra- indication to medical treatment exists, all Graves' disease patients are given at least 18 months of treatment with anti-thyroid drugs [1-3]. The most commonly used anti-thyroid drugs (ATD) are thionamides, which include methimazole (MMI), carbimazole (BDZ) and propylthiouracil (PTU) [4].

It has been noted that the use of ATD in patients with smaller goitres and lower anti-TSH receptor antibody titres produces a remission rate of 20%-50% after 11-18 months of treatment, without developing hypothyroidism or any of the complications associated with radio-active iodine therapy (RAI) or surgery [5, 6]. The main downsides of ATD are the lower remission rate especially in larger goitres and the high recurrence rate [6].

Despite the use of ATD in the management of Graves' disease, RAI is still required in many patients, including those with severe symptoms of Graves' disease, those with ATD side effects or contraindications, and those who have failed ATD treatment, in particular when they are poor surgical candidates [6, 7].

A systematic review by Sundaresh et al. (2013) looked at the comparative effectiveness of Graves' disease therapies, between ATD, RAI mean dose 8.5mCi (range, 6.8 to 12.6), and surgery. Their results showed a high failure rate and relapse with ATD, with no statistical difference in relapse between RAI and surgery [8].

There is no consensus on whether to use a calculated dose or fixed dose for RAI [9]. Depending on the algorithm used, calculating a dose may be complex and time consuming and may result in delays and increased costs [5, 9]. Dose calculation may require a 24hr ^{131}I or ^{123}I uptake scan, and measurement of thyroid size by ultrasonography to calculate an absorbed dose of 50-100 gray to the thyroid and those may not be available at some centres.

The empirical dose strategy for Graves' disease only requires confirmation of the diagnosis of Graves' diseases, prior to administration of a fixed dose of 10mCi given to all eligible patients [10]. The standardized fixed dose is particularly helpful in under-resourced areas or centres with few nuclear physicians and high patients loads. However, little is known about the efficacy of the standardized dose, as compared to calculated dose methods.

In this retrospective study we assessed the efficacy of a fixed low dose of ^{131}I (10mCi), in patients treated for Graves' disease at Inkosi Albert Luthuli Central Hospital (IALCH) between 2014 and 2017.

Subjects and Methods

Study population

All patients with Graves' disease treated at our institution with a fixed dose of radioactive iodine of 10mCi between the periods of 2014 to 2017 were included in the study. Data was collected retrospectively from the Inkosi Albert Luthuli Central Hospital IALCH registry.

Inclusion criteria were patients with Graves' disease confirmed on technetium-99m-pertechnetate ($^{99m}TcO_4$) scan who underwent RAI therapy.

Exclusion criteria were patients who had RAI for other causes of thyrotoxicosis such as multinodular goitre (MNG) or solitary nodule, or Graves' disease treated with doses other than 10mCi, unavailability of follow-up thyroid function results on the NHLS, and pregnancy in- between the RAI doses. Between 2014 -2015 only about 19 patients were treated with dose 8-8.5mCi for Graves' disease and they were excluded from the study.

The study was approved by the Human Research Ethics Committee of the University of KwaZulu Natal (protocol reference number: BREC /00004382/2022), who waived the need for individual informed consent. All procedures were performed in accordance with the ethical standards of the institutional research committee in alignment with the 1964 Helsinki declaration and its later amendments.

Imaging

Quantitative evaluation of thyroid uptake was based on pre- and post-therapy thyroid uptake scans using $^{99m}TcO_4$ for all cases. The reference range was 0.5%-4%.

Treatment outcome

Response to RAI therapy was assessed clinically and biochemically 6 month after each RAI therapy dose. Clinical assessment was based on the disappearance of the hyperthyroid symptoms or development of hypothyroid symptoms, all together with the biochemical results; at no time the two did not correlate. For patients who were referred to their base hospital for follow-up after RAI therapy, response evaluation was only based on their latest thyroid function test results accessed electronically from the National Laboratory Services (NHLS). Assessment of biochemical response was based on measurements of thyroid stimulating hormone (TSH), total free thyroxine (fT4) and or triiodothyronine (T3) with the following references, TSH: 0.5-4.5ulU/mL, T3: 2.3-4.2pg/mL, fT4: 0.89-1.76ng/dL, at baseline and within 6 months after RAI. The clinical response was based on the improvement of thyrotoxic symptoms.

Response to RAI therapy was classified into three categories: responders, non-responders and/or complete treatment failure. Responders included both euthyroid and hypothyroid patients. Euthyroid patients were defined as those with normal TSH levels together with normal fT4/T3, whereas those with high TSH levels together with low fT4/T3 were classified as hypothyroid. Patients who failed to achieve euthyroidism or hypothyroidism at 6 months post re-treatment with RAI, were classified as non-responders. Treatment failure was defined as no response after two or three fixed low doses of RAI received with intervals of at least 6 months. These patients did not achieve hypothyroidism or euthyroidism within 18 months after the second or third dose of RAI.

Statistical analysis

Statistical analysis was performed using Python (version 3.9.12). Age, fT4, TSH and percent uptake were compared between outcome groups using t-tests.

Results

Our data was collected from 2014 to 2017. Hundred fourteen patients were enrolled. Three patients were excluded due to loss of follow up. Ninety six (86.5%) were female and 16 (14.4%) male. Prior to therapy our patients had a mean age 41.9

years, with mean fT4 29.70, TSH 0.01, and 16.5% uptake (Table 1).

Of the 111 patients with follow-up data, treatment was successful in 89.2% (99/111 patients) after the first dose (27.0%, 30/111 euthyroid; 62.2%, 69/111 hypothyroid). Just over 10% (10.8%, 12/111) required a second dose, and only a single patient remained hyperthyroid despite a second empirical dose (Figure 1).

High thyroid uptake was associated with failed first dose therapy (P=0.005). The median baseline thyroid uptake was 16.5% in the total population. For the non-responders it was 25.2%±3% compared to 15%±2% for those who responded (Figure 2). No significant difference in fT4 levels (P=0.5) or age (P=0.96) were found between hyperthyroid and non-hyperthyroid groups.

Discussion

Although ^{131}I has shown good results in the treatment of Graves' thyrotoxicosis, there is no consensus on the dosis regimen. The regimes involved are fixed low/high dose, as opposed to dosimetric calculations based on thyroid gland size and results of isotope uptake or turnover [5, 10]. Conflicting results have been reported as to which regimen is superior in terms of cure rate and/or development of hypothyroidism or side effects.

A number of studies found no superiority of dosimetry over empirical in this respect [11]. However, a prospective study by Schiavo et al. (2011) demonstrated that dosimetry dosing is superior to a fixed dose especially when individualised ^{131}I effective half-life is considered. These authors further noted that actual administered activity when using dosimetry dose are lower than fixed dose [12].

On the other hand, a randomised trial by Peters et al. (1995) looked at success/cure rate between calculated doses based on thyroid size and 24 RAIU percent, against a fixed dose of

Table 1. *Patient characteristics and pre-radioiodine therapy results.*

Variable	Median	Range
Age	43.00	10 - 71
fT4	29.70	2.6 - 149.0
TSH	0.01	0.01 – 0,95
Uptake percent	16.50	3.2 - 52.0

Total free thyroxine (fT4) – normal value 0.89- 1.76 ng/dL, Thyroid Stimulating Hormone (TSH), normal value 0.5-4.5 uIU/mL

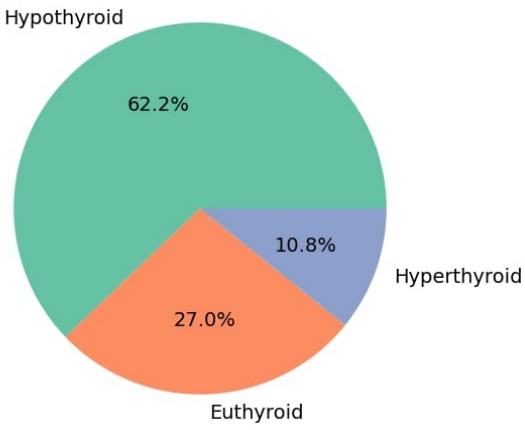

Figure 1. Outcome

Table 2. *Treatment outcome after initial iodine dose of 10mCi.*

Ender	Hyperthyroid	Euthyroid	Hypothyroid	Total
Female	11	28	56	95
Male	1	2	13	16
Total	12	30	69	111

15mCi in patients with Graves' disease. They found the cure rate to be higher (71%) for fixed dose than for calculated dose (58%) when thyroid gland size was below 75g. When thyroid size was above 75g the results were reversed [9]. These results were further echoed by Doi et al. (2001) who used a mathematical model to optimize RAI therapy, demonstrating superiority of a fixed dose to achieve euthyroidism whereas a calculated dose was recommended for ablative therapy as it achieved early hypothyroidism [13].

A single centre retrospective study by Salama et al. (2023) demonstrated a favorable therapeutic outcome in 83% when using a formula that was modified from the De Groot formula [14]:

$$^{131}I\ Dose = \frac{Thyroid\ weight\ (g) \times 5}{Thyroid\ uptake\ percent\ \%}$$

However, as the authors of this study indicate, this results still needs to be verified by multicentre prospective studies [14].

In one randomised controlled trial, patients were randomized to one of four dose calculation methods: low-fixed 6mCi; high-fixed 10mCi; low-adjusted dose, 80μCi (80 μCi)/g thyroid adjusted for 24-hour radioiodine uptake; and high-adjusted dose, 120μCi (120μCi)/g thyroid for the 24-hour radioiodine uptake. Clinical outcomes in terms of euthyroidism, hypothyroidism, or hyperthyroidism were almost identical in the four treatment arms. No advantage was demonstrated using adjusted dose methods, but lower doses showed a trend towards development of recurrence or persistent hyperthyroidism. It was therefore inferred that for the treatment of hyperthyroid Graves' disease, fixed ^{131}I doses are more effective and more economical to use [15].

It is still unclear what the adequate fixed empirical dose for the treatment of Graves' disease is. A range of doses from 3mCi, over 5mCi, 10mCi, to 15mCi have been assessed for cure rate. These studies indicated that low doses of 3mCi or 5mCi accomplish only very low cure rates and delayed development of hypothyroidism [16]. On the other hand a comparison of RAI doses of 10mCi and 15mCi indicated no statistical difference in cure rate [17, 18]. In a trial by Esfahani et al. patients were randomized to receive RAI 5mCi vs 10mCi and followed up over two years for outcome assessment. The findings demonstrated a high cure rate, favouring 10 mCi with a cure rate of 88.5% over of 5mCi with a cure rate of 48.5% [19]. These findings were confirmed by Malapure et al. (2020) also demonstrating superiority of 10mCi over 5mCi [19].

Our results likewise demonstrate that a fixed 10mCi RAI is able to produce a successful outcome, with a cure rate of 89.2% after a single treatment. Of note, the thyroid size was not measured or determined with ultrasound, and patients were treated solely on the basis of proven diagnosis of Graves' disease.

The use of a single fixed dose of RAI to treat Graves' diseases is supported by the American Thyroid Association (ATA) 2016 guideline, which favours a mean dose of 10-15mCi, and by the European Thyroid Association (ETA) guidelines 2018, which describe the use of the calculated or dosimetry dosing as meticulous [20, 21].

Pre-treatment of selected patients is indicated in older patients, in those with severe hyperthyroidism and cardiovascular complications. In such patients, it is common practice to achieve euthyroid state prior to administration of RAI to reduce the risk of worsening of thyrotoxicosis due to radiation induced leakage of stored thyroid hormone, which can occur soon after RAI therapy [22]. Hence our patients were pre-treated with at least 6 months of ATD prior to RAI therapy whenever no contra-indications existed.

Multiple studies have shown that pre-treatment with ATD is associated with treatment failure especially if patients are treated with PTU. This radio-resistance has been linked to the presence of a sulfhydryl group on PTU [23-25]. However, these effects are avoided if treatment was stopped 3-5 days for BDZ and MMI but for PTU 2 weeks before RAI treatment [26-28]. The only ATD available in our population is BDZ, hence it was only the drug that was used for all patients. Prior to RAI therapy ATD was stopped in all patients for at least 3 days prior to administration of RAI, and dietary iodinated salt content was stopped. This is in keeping with previous results recommending the use of BDZ and its cessation for at least 3-5 days prior to therapy [23-28].

In the present study, we found an association between failure or initial 10mCi RAI treatment and high thyroid uptake before treatment. We could not find association between failure of treatment and fT4 levels, nor with gender or age. A number of studies have indicated that high baseline fT4 and high thyroid uptake are associated with initial treatment failures [29-31]. Conflicting results have been published as to whether male gender and age below 40 years are predictors of treatment failure [25, 29, 32, 33]. Similar to the findings in the present study, studies by Santos et al. (2004), and Al-Qahtani et al. (2023), found that pre-treatment with ATD had no impact on cure rate [25, 34].

In conclusion, this study confirms that a fixed low empiric radioiodine activity of 10mCi cures a large majority of hyperthyroidism due to Graves' This method of therapy may be beneficial where resources are limited and patient numbers are high.

Study limitations

This study is limited by its small sample size, its retrospective nature and the fact that it was performed in a single centre.

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