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Radio-iodine Ablation for the Treatment of Thyrotoxicosis: Outcomes and Patient Perceptions from Multiple Specialised Centres in Colombo, Sri Lanka

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Abstract

Background:
Radioactive iodine therapy (RI) is widely practised worldwide to treat thyrotoxicosis.

Aims:
To determine the clinical outcomes and the perception of patients on RI for thyrotoxicosis.

Methods:
We conducted a retrospective study on patients who underwent RI and were followed up at selected endocrine clinics in Colombo, Sri Lanka. Data on outcomes (treatment failure - persistent hyperthyroidism at 12 months after RI and/ or need for repeat RI/ anti-thyroid / surgery; remission – euthyroidism or hypothyroidism without anti-thyroid medication; relapse-thyrotoxicosis after at least one euthyroid or hypothyroid test result, in the absence of thyroxine treatment) and patient perceptions were obtained via a structured interviewer-administered questionnaire and reviewing medical records.

Results:
Among 100 patients (mean age 49.3 [SD 14.8] years, females 83%) with thyrotoxicosis (Graves' disease 61%, toxic adenoma 10%, toxic multinodular goitre 13%, uncertain aetiology 16%), who had received RI (10 mCi in 28.7%, 15mCi in 21.8%, 20 mCi in 49.4%) and had a median follow up of 18 months, outcome data were available in 93. Among them, 67 subjects (72%) achieved remission. Patients' age, sex, aetiology of thyrotoxicosis, duration of pre-RI medical therapy or RI dose did not predict the treatment failure. Abnormal thyroid functions were common in the first year after RI (affecting 38.1%, 24.2%, 33.3% and 43.2% at 1, 3, 6 and 12 months respectively). New onset and relapsing thyroid eye disease developed in 5/87 (5.8%) and 2/13 (15.5%) respectively. Majority of the subjects admitted fear of developing alopecia, malignancies as misconceptions when evaluated post RI. None of the patients reported malignancies during follow-up. 98% patients were satisfied with the overall treatment response.

Conclusion:
RI remains very effective in treatment of thyrotoxicosis with high patient satisfaction. It was well tolerated with adverse effects being mild and transient. Abnormal thyroid functions are common after RI and regular monitoring is needed.

Keywords: Radioiodine therapy, Hyperthyroidism, Graves' disease, toxic multinodular goitre, solitary toxic adenoma, Graves's orbitopathy, patient-reported outcomes

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Introduction

Thyrotoxicosis is the presence of excess thyroxine level in the body culminating in a hypermetabolic state. RI using I^{131} had been a well-recognised treatment modality of thyrotoxicosis since 1941 when it was introduced first in United States of America [1]. It is widely practised in Sri Lanka now to manage all three main aetiologies of thyrotoxicosis: Graves' disease, toxic multinodular goitre and solitary toxic nodule.

I^{131}, a beta emitting radionuclide, is used to destroy the hyperfunctioning thyroid cells. The dose of I^{131} varies from centre to centre. It could be determined using dosimetry considering the size of the gland, half-life of I^{131}, distribution of the isotope inside the gland and the amount of absorbed dose[2]. The American Thyroid Association guideline recommends 10-15 mCi (370-555 MBq) for Graves' disease. Fernando et al concluded that a dose of 6 mCi is adequate for both Graves' and toxic multinodular goitre in Sri Lankans[3].

RI is carried out as an oncology supervised service in the state sector of Sri Lanka. Significant proportion of patients have many fearful thoughts and anxiety about RI. These per se lead to delay in commencing the treatment and treatment fall out. There had been few studies done in the UK to assess patient satisfaction on RI service [4]. However there had not been any studies exploring patient perspectives in similar socioeconomic and cultural setting.

There is scarcity of data on treatment outcome and acceptance of RI therapy for thyrotoxicosis among patients in South Asia. Therefore, we aimed to determine the efficacy, safety, and patients' perceptions on RI therapy for treatment of thyrotoxicosis.

Methods

A retrospective observational study was conducted in the Endocrine clinic of University Medical Unit, Endocrine clinic of National Hospital of Sri Lanka, Center for Diabetes Endocrinology and Cardio-Metabolism and at selected private sector endocrine clinics in Sri Lanka. A combined sample of patients who had undergone RI for thyrotoxicosis and followed up at these clinics were recruited over a period of twelve months from 01.01.2022 up to 31.12.2022 in a consecutive manner.

Data collection was done by the principal investigator and a trained medical graduate using a structured interviewer-administered questionnaire and by reviewing medical records.

We collected clinic-demographic details (age at the time of RI, sex, aetiology of thyrotoxicosis, treatment prior to RI), data on RI therapy (dose, number of doses), thyroid functions after RI, patient-reported outcomes (subjective improvement in the compressive symptoms, perceived reduction in goitre size), adverse effects (immediate post-RI, effect on thyroid eye disease, pregnancy and malignancies), patient perceptions before and after RI (awareness, concerns, fears and expectations, problems regarding contraception, social problems including isolation in the immediate post therapy period, stigma and fears associated with seeking RI at the National Cancer Institute and anticipated, feared side effects such as alopecia, risk of malignancy) and overall patient-satisfaction (rated as happy/ indifferent/ unhappy) on receiving RI therapy.

Remission of thyrotoxicosis was defined as achieving biochemical euthyroidism or hypothyroidism (ie, normal or increased TSH and normal or low free T4) without any medical therapy / further RI or thyroid surgery. Treatment failure was defined as persistence of thyrotoxicosis at 12 months after RI, in keeping with previous studies [5,6].

We used a questionnaire to assess the commonly encountered patient concerns and fears both pre-RI and post RI. Most recognised side effects were gathered from patient information platforms of public domains such as Cambridge University, Mayo clinic, Cleveland clinic etc.

Data was analyzed using SPSS version 17.0. The differences in efficacy outcomes were compared according to the aetiology of thyrotoxicosis. A p value of less than 0.05 was considered significant in comparisons. The study was reviewed by the ethical committee of National Hospital of Sri Lanka.

Results

Population characteristics

A total of 100 patients were recruited in sequential manner from multiple endocrine clinics as mentioned above. Their characteristics are summarised in Table 1.

Efficacy outcomes

Data on treatment outcome was obtained in 93 subjects as 7 had lost to follow up. Sixty-seven of them (72%) achieved remission. Median time to remission was 6 months (3-24). Among them, seven (11.5%) developed relapse at a median time of 12 months (3-24) from RI. Those who relapsed were treated with surgery (n=1), repeat radio-iodine therapy (n=1) or long-term medical management (n=5). Among those who did not respond to RI, thyroidectomy, repeat RI therapy or medical therapy were offered to 14, 2 and 12 patients respectively.

Treatment failure was not statistically significantly associated with age at RI (median age at RI 50.0 [37.5-63.0] among patients who achieved remission vs 48.0 [37.0-57.0] among those who did not, $p = 0.895$), sex (men 7.1%, women 29.1%, Chi^2 2.99, $p = 0.073$), aetiology of thyrotoxicosis (Graves' disease 26.3%, toxic adenoma 22.2%, toxic MNG 30.8%, Chi^2 0.375, $p = 0.945$) dose of RI (10 mCi – 21.7%, 15 mCi – 15.8%, 20 mCi 32.5%,

Chi_2 2.139, p = 0.343), median duration of medical therapy prior to RI (12.5 [8-36] months among those who achieved remission vs 12.0 [2.5-27.0] among those who did not, p = 0.405). None of these parameters predicted RI outcome in a logistic regression model.

Adverse events

The commonest immediate side effects reported were dysgeusia (50%), dry mouth (48%), local tenderness (44%) and nausea (39%). These side effects resolved within days to few weeks in all patients. These were not associated with the dose of RI (Table 2).

Deranged thyroid functions were common in the months following RI therapy. Figure 1 shows changes in TSH over time. Proportion with euthyroid thyroid functions (with or without treatment) at 1, 3, 6 and 12 months were 38.1%, 24.2%, 33.3% and 43.2% respectively. Only two patients had normal TSH values at all these time points.

Thirteen study subjects had thyroid eye disease pre-RI. At the time of RI, all of them had mild and inactive disease. Five out of the 87 patients who did not have TED developed new onset TED after RI while two of the thirteen with previous TED developed relapse after RI.

Patient perceptions

Common fears and concerns before RI reported by participants are hair loss (77%), long-term cancer risk (77%), stigma associated with receiving radiation therapy (16%), difficulties in avoiding close contact with others after RI (15%), unplanned conceptions after RI (12%), difficulties in using public transport (5%) and sexual dysfunction (2%).

Among those who had fears of risks of long-term cancer, 81.8% considered that it was a misconception after RI. Similarly, 77.6% of those who were concerned about alopecia, felt it was a misconception. There was a single unplanned conception within a year post RI which was

Table 1: Baseline characteristics and RI doses of the study population

Parameter	Value
Number of participants	100
Females	83 (83%)
Mean age, years	49.3 (SD 14.8)
Mean body weight, kg	62.5 (SD 17.9)
Aetiology of thyrotoxicosis	
Graves' disease	61 (61%)
Toxic multinodular goitre	13 (13%)
Toxic adenoma |	10 (10%)
Unknown	16 (16%)
RI dose* (number and % of patients)	
370 MBq (10 mCi)	10 (28.7%)
555 MBq (15 mCi)	19 (21.8%)
740 MBq (20 mCi)	43 (49.4%)
Duration of follow up after RI, median (IQR) in months	18 (3-24)

*RI dose data were available in 87 patients

Table 2: Incidence of adverse events after radio-iodine therapy

Adverse event	Radio-iodine dose (MBq)[1]				Total sample (n=100)
	370	555	740	P	
Altered taste	48.0	36.8	60.5	0.21	51.7
Dry mouth	40.0	36.8	62.8	0.08	50.6
Thyroid pain / tenderness	32.0	57.9	53.5	0.15	48.3
Nausea	36.0	31.6	48.8	0.36	41.4
Salivary gland swelling	16.0	26.3	37.2	0.16	28.7
New onset TED[2]	4.3	7.1	8.1	0.84	6.8
Relapse of pre-existing TED[3]	7.7	7.7	0	-	15.4

[1] among 87 patients in whom RI dose data were available.
[2] among 87 patients who did not have TED before RI
[3] among 13 patients who had TED before RI
RI: radio-iodine treatment, TED: thyroid eye disease

uncomplicated. The post RI analysis revealed that none of those 16 patients who had fears of being social stigmatisation were stigmatised post therapy. One patient who did not anticipate stigmatisation reported being stigmatised post therapy. Isolation was not a challenge in any who anticipated about it prior to RI. One patient had experienced unanticipated problems with isolation facilities.

None of the study subjects developed thyroid malignancies during the follow up period. 97 % of the patients reported that they opted to choose RI as definitive therapy as per doctor's recommendation. Overall, 98% patients were very satisfied with RI therapy.

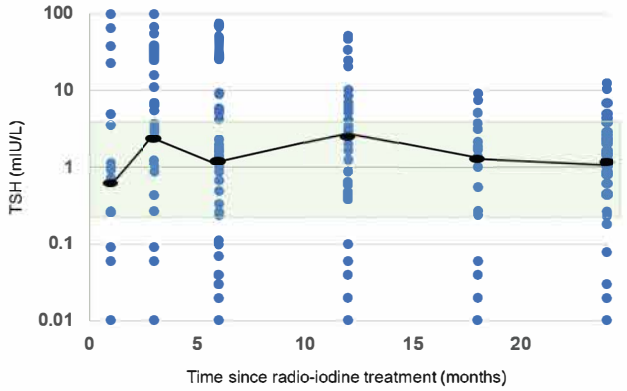

Figure 1. Change in thyroid status (TSH) over time after RI. Y-axis in logarithmic scale. Reference range for TSH highlighted in green. Median TSH value at each time point in black circles.

Discussion

In this retrospective observational study of hundred patients with thyrotoxicosis receiving RI therapy in Colombo district, Sri Lanka, we observed 72% response rate, achieved at a median of 6 months after RI therapy with 98% of patients reporting good satisfaction on the treatment. It was well tolerated with adverse effects being mild and transient. To the best of our knowledge, this is the first study from Sri Lanka to report on efficacy, safety, patient-reported outcomes and patient perceptions.

Remission rate observed in our cohort are comparable with what has been reported in the past [7,8]. Stan et al had concluded that 40% of patients attain hypothyroidism by 8 weeks and 80% by 16 weeks [5].

We did not find any predictors of RI treatment success. The reported predictors of treatment failure are certain ethnicities, younger age, use of propyl thiouracil (rather than methimazole), use of antithyroid drugs (ATD) within 7 days prior to RI, longer duration (>4 months) of ATD before RI, high TSH-receptor antibody titre [9,10,11]. All were treated with carbimazole. 92% received medical therapy for more than four months and treatment was stopped for 5-7 days in almost all prior to RI. The patient cohort was homogeneous in ethnic distribution, all being South Asians. These may explain the lack of association between previously reported factors and treatment failure.

The impact of RI dose is a subject of debate. A similar retrospective multicentre study found that remission rates were not different between individuals who received less than 500 MBq, compared to those received more than 500 MBq [12]. Majority of the patients who received fixed dose of 370 MBq attained remission in several studies [13]. In contrary, a relatively higher remission rates (87.7%) had been reported in patients who received higher RI dose (740–1110 MBq) [14]. It is postulated that a higher dose could be beneficial to younger patients, patients with larger thyroid gland, higher I^{131} uptake, higher TRAb titres and when antithyroid are used pre-RI for longer than four months [15,16]. We did not observe a difference in remission rate across three different doses. This needs to be interpreted with caution due to possible selection bias given the retrospective observational nature of our study. Furthermore, we did not have data on TRAb levels, goitre size or radioiodine uptake of thyroid glands before RI, as these are not routinely assessed in our practice.

Derangement of thyroid functions in the first-year post RI is well recognised [17]. Most patients although had thyroid function test during the first year of follow up, did not have all four quarterly TFTs for 12 months. Thus, analysis on rates of occurrence of transient hypothyroidism was not conclusive in the current study and is an area to improve clinical practice.

Incidence of adverse events in the initial weeks following RI in our cohort are similar to what was reported in previous studies [18].

RI induced thyroid autoimmunity and de novo worsening of preexisting TED is a recognised adverse effect. It has been associated with risk factors such as smoking [19]. Five out of 86 patients (5.8%) reported new onset TED in this study. This is comparable to a figure of 3.3% who reported new TED in a study with a similar size of cohort but is lower than several other studies which reported new-onset and worsening of pre-existing TED to affect 15 to 20% patients [7,20]. Number of smokers was relatively small (9/100 at the time of receiving RI) and may have contributed to the lack of the association.

Another adverse effect of controversial evidence is the occurrence of thyroid and extrathyroid malignancies. Numerous studies had concluded that RI for thyroid cancer increases risk of malignancies [21]. However, the risk of malignancy following RI given at relatively lower dose for thyrotoxicosis is yet to be proven [22]. The overall cancer risk was not

significantly increased among patients exposed to RI in a recent meta-analysis. However, a linear dose response association has been reported with higher dose of RI and breast, solid organ cancers [23]. None of the participants reported developing thyroid or nonthyroidal cancers in the follow up in the current study, but it is not possible to derive conclusions as the duration of follow up is short. More studies with longer duration of follow up remain warranted to assess potential carcinogenic risk of RI.

Only a single patient experienced an unplanned conception post RI. This positively reflects the success of patient education, awareness of potential teratogenic risk of RI and the importance of contraception.

Majority (98%) of our patients reported to be satisfied with RI therapy. This is comparable to the patient satisfaction reported in the survey in the UK in year 2000 [24]. Furthermore, majority reported that their fears (on intolerable adverse events, stigma, difficulties in self-isolation) held before RI proved to be misconceptions after receiving therapy. These findings can be used to support the pre-RI counselling.

Findings of this study should be interpreted with caution due to several limitations. Retrospective design may have introduced recall bias and selection bias. Some clinically useful data were not available for analysis (like TSH receptor antibody titre, thyroid gland volume, thyroid gland uptake of RI, quality of life before and after RI therapy). Short duration of follow up limits the ability to determine long term outcomes like delayed relapse of thyrotoxicosis, thyroid and extra-thyroid malignancies.

Nevertheless, our study findings have several important clinical implications. First, we show that the efficacy of RI in thyrotoxicosis is comparable to studies from other regions. We have also demonstrated that it is safe and adverse events are only transient. We have identified several misconceptions among patients regarding RI, which should be addressed during pre-treatment counselling. High prevalence of deranged thyroid functions following RI is a concern. Inadequate monitoring of thyroid functions in this period may be a contributory factor. Regular and frequent monitoring of thyroid status, implementation of protocols for managing antithyroid medication before and after RI and liaison between endocrinology and oncology colleagues are necessary to minimize the abnormal thyroid functions in these patients.

Conclusion

RI remains an effective definitive treatment modality in all types of thyrotoxicosis. Most common side effects are mild and transient. Abnormal thyroid functions are common after RI therapy. Thyroid functions should be regularly monitored to identify and treat these individuals. Accurate assessment of TED is vital given the increased risk of new development of TED.

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