Outcomes of radioactive iodine therapy with fixed-activity regimen in pediatric Graves' disease

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Abstract

Objective: To evaluate the success rates of radioactive iodine therapy (RAIT) with fixed activity of 10mCi and 15mCi in pediatric patients with Graves' disease (GD). **Subjects and Methods:** This retrospective study included patients aged ≤18 years diagnosed with GD who received 1st dose of RAIT by fixed activity regimen, either 10mCi or 15mCi. The rates of successful therapy, defined as the induction of hypothyroidism within six months after RAIT, were compared between the two RAIT dosage groups. We also evaluated factors associated with the successful RAIT and median duration for achieving hypothyroidism between the two groups. **Results:** Eighty-seven patients (86.2% females, mean (±standard deviation [SD]) age 14.7±2.5 years, 44.8% received 10mCi radioiodine) were included in the analysis. Patients who received 10mCi radioiodine exhibited a younger age at the GD diagnosis (P=0.038), younger age at the RAIT (P<0.001), and smaller thyroid size (P<0.001). The success rates of 10- vs 15mCi radioiodine were not significantly different (76.9% vs 64.6%, P=0.211). There was also no significant difference in the median duration to achieve hypothyroidism in 10- vs 15mCi groups (4.6 vs 5.1 months, P=0.306). Discontinuation of antithyroid drug (ATD) for more than three days prior to RAIT was the only independent factor for successful RAIT (adjusted odds ratio [OR] 3.67, P=0.015). **Conclusions:** Radioactive iodine therapy with fixed-activity regimen showed high success rates in pediatric patients with GD. Antithyroid drug withdrawal for more than three days prior to RAIT was recommended for the optimal therapeutic outcomes.

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Introduction

Graves' disease (GD) is a common autoimmune disorder in childhood with prevalence ranging from 1-14 cases per 100,000. The incidence of pediatric GD is around 3-4 cases per 100,000 and tends to be rising [1-3]. Pediatric GD has the peak incidence at 10-15 years of age and is more common in girls than boys [3]. Generally, antithyroid medication is the preferred first-line therapy in children. However, only 20%-30% of patients have long-term remission after two years of medical treatment [4, 5]. Furthermore, younger children have poorer remission rate with a higher risk of adverse drug events [6]. Thus, definitive therapy including radioactive iodine therapy or thyroidectomy is considered if there is persistent or relapsed thyrotoxicosis after 1-2 years of antithyroid medical therapy [1, 7].

Radioactive iodine therapy (RAIT) is an effective treatment for pediatric GD. The aim of the treatment is to render patient's hypothyroidism with a single dose of iodine-131 (^{131}I) administration. This strategy could prevent recurrent thyrotoxicosis and decrease future risk of thyroid cancer [1, 2, 7]. The optimal ^{131}I activity is one of the most important factors for complete thyroid ablation. There are two main regimens to determine ^{131}I activity, estimation (fixed activity) and calculation [6, 8]. According to the available evidence, no regimen shows superior efficacy to others [2, 7]. However, the fixed-activity regimen is simpler and more cost-effective [9]. To date, there is no optimal fixed ^{131}I activity recommended for treatment of pediatric GD. Based on the previous literature, the fixed ^{131}I activity prescribed usually ranges from 5-15mCi (185-555MBq) giving the successful ablative rate between 45%-97%. Patients who received higher ^{131}I activity tend to have a higher rate of hypothyroidism [10-12]. However, this group of patients was also exposed to more radiation dose. Thus, the primary aim of this study is to evaluate the outcomes of ^{131}I therapy

with fixed-activity regimen in patients with pediatric GD. Additionally, we also evaluate factors associated with successful RAIT in this group of patients.

Subjects and Methods

This retrospective chart review study was approved by our institutional ethics committee for human research, reference number: HE661233, on April 27, 2023 and in accordance with the 1964 Helsinki Declaration. From September 2016 to April 2023, patients aged ≤18 years who were diagnosed with GD and received the first dose of either 10mCi or 15mCi of radioactive iodine were consecutively enrolled. The diagnostic criteria for GD were based on clinical findings such as thyrotoxicosis, diffuse thyroid gland enlargement, or Graves ophthalmopathy and laboratory evidence of hyperthyroidism including elevated serum free thyroxine (FT4) and/or free triiodothyronine (FT3) with suppressed serum thyroid-stimulating hormone (TSH). Anti-TSH receptor antibodies were measured in some patients to confirm the diagnosis and to help predict treatment outcomes. Those with a history of thyroidectomy or no sufficient data to determine the treatment outcome were excluded.

Prior to RAIT, the patients were advised to discontinue antithyroid medication for three to seven days and take a low-iodine diet for seven days. A pregnancy test was done on the day of the treatment in all potentially pregnant patients. Patients received a fixed activity of ^{131}I (10 or 15mCi) selected by experienced attending nuclear medicine physicians, primarily based on thyroid gland size assessed by palpation. Patients with a thyroid gland size larger than 50 grams tended to receive the higher ^{131}I activity, namely 15mCi. Then, patients' clinical symptoms and serum thyroid function tests including FT4 or FT3 and TSH were evaluated approximately at 2nd, 4th, and 6th month after the treatment. A good therapeutic response was defined as a development of hypothyroidism including elevated serum TSH and/or low serum FT3 or FT4 or the need for thyroid hormone replacement within six months after the first RAIT.

Categorical data were presented as number and percentage. Continuous data were presented as mean±standard deviation (SD). Chi-square test was used to compare the success rate of RAIT between patients who received 10- and 15 mCi of ^{131}I. Kaplan-Meier estimate was used to evaluate median duration of successful therapy. A log-rank test was used to compare the difference between median duration of successful therapy in two groups of ^{131}I activity. Univariable analysis was used to test the association between covariates and successful therapy. Variables were included to calculate adjusted odds ratio (OR) by multiple logistic regression if their bivariate logistic regression P-values were <0.25 or if previous literatures had suggested that the variables might be of prognostic significance. All statistics were two-sided and P-values less than 0.05 were considered statistically significant. The 95% confidence interval (95% CI) was calculated where appropriate. Statistical analysis was carried out by STATA 14.0 (StataCorp LP, College Station, TX, USA).

Results

A total of 87 patients with pediatric GD who received RAIT from September 2016 to April 2023 were enrolled. The mean age of the patients at the RAIT was 14.7±2.5 years with most of the females (86.2%). Thirty-nine patients (44.8%) were treated with 10mCi, while 48 patients (55.2%) received 15 mCi of ^{131}I. Patients who received 10mCi radioiodine had significant younger age at the GD diagnosis (P=0.038), younger age at the RAIT (P<0.001), and smaller thyroid size (P< 0.001). There were totally 23 patients (26.4%) receiving the repeated dose of RAIT. Among these, eight and fifteen patients belonged to the 10- and 15mCi groups, respectively. The patient's characteristics are shown in Table 1.

Hypothyroidism was achieved in 61 patients (70.1%) by six months after the RAIT. Based on the radioiodine activity, hypothyroidism was found in 30 patients (76.9%) in the 10 mCi group and 31 patients (64.6%) in the 15mCi group. There was no statistically significant difference between the rates of hypothyroidism among these two groups of patients [proportion difference 12.3% (95% CI: -6.6 to 31.3), P=0.211]. Euthyroidism was found in two patients, each from 10- and 15mCi groups. However, 2 of 61 patients (3.3%) who became hypothyroid within the six months after treatment required an additional RAIT to achieve permanent hypothyroidism; both had initially received 15mCi of ^{131}I. Details of the treatment outcomes are shown in Figure 1.

The median duration for becoming hypothyroid in this study cohort was 5.0 months (95% CI: 4.3 to 5.5 months). There was no statistically significant difference between the median duration to achieve hypothyroid in 10- and 15mCi groups (4.6 vs 5.1 months, P=0.306).

Multiple logistic regression revealed that discontinuation of antithyroid medication more than 3 days prior to RAIT was the only independent predictive factor for successful RAIT (adjusted OR 3.67; 95% CI: 1.29 to 10.46, P=0.015). Other factors including age at diagnosis of GD, interval of GD diagnosis and RAIT, thyroid gland size, and ^{131}I activity showed no significant association with becoming hypothyroid after the RAIT as shown in Table 2.

Serum anti-TSH receptor antibodies, another potential predictor of RAIT success, were tested in ten patients. All had elevated levels ranging from 2.85-40.00IU/L (normal range: 0-1.74IU/L). Six of the ten developed overt hypothyroidism after the first RAIT, while the remaining four had persistent hyperthyroidism.

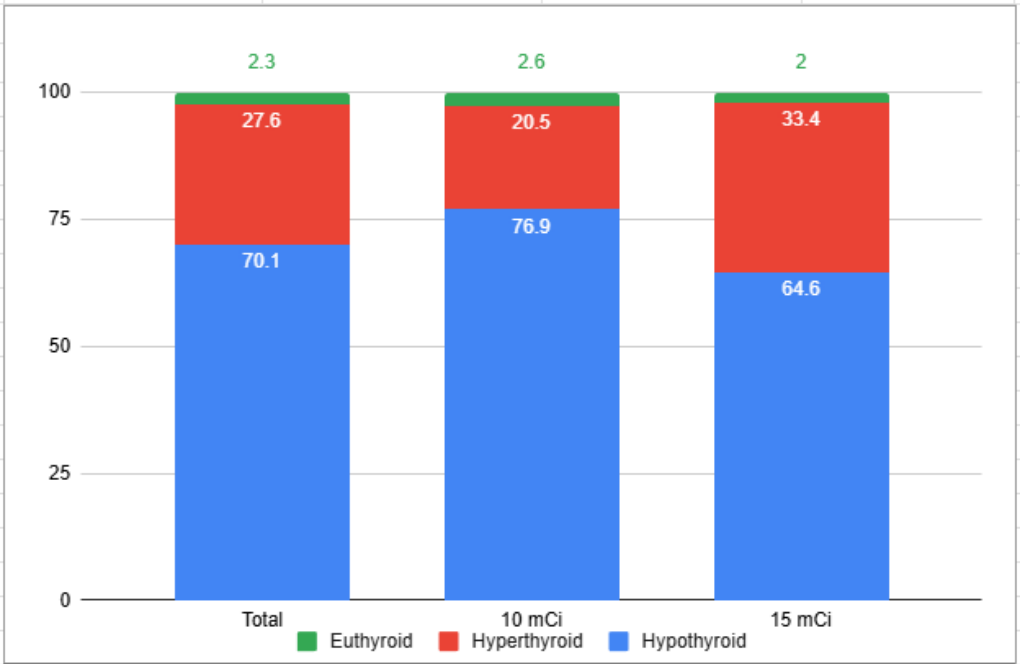
Discussion

Radioactive iodine therapy is a definitive treatment for pati-

Table 1. *Characteristics of the study cohort.*

Characteristics	Total n=87	^{131}I 10mCi n=39 (44.8%)	^{131}I 15mCi n=48 (55.2%)	P
Age at RAIT (year), mean±SD	14.7±2.5	13.7±2.5	15.6±2.0	<0.001
Sex				0.311
Male	12 (13.8%)	7 (18.0%)	5 (10%)	
Female	75 (86.2%)	32 (82.0%)	43 (90.0%)	
Age at diagnosis of GD (year), mean±SD	12.0±3.5	11.1±3.4	12.7±3.4	0.038
Thyroid gland size (gram), mean±SD	61.9±25.5	42.4±12.2	77.7±22.4	<0.001
Duration of ATD withdrawal (day)				0.871
≤3	26 (30.0%)	12 (30.8%)	14 (29.2%)	
>3	61 (70.0%)	27 (69.2%)	34 (70.8%)	
Received repeated dose of RAIT	23 (26.4%)	8 (20.5%)	15 (31.3%)	0.259

RAIT, radioactive iodine therapy; GD, Graves' disease; ATD, antithyroid drug; SD, standard deviation.



I-131 activity	Hypothyroid	Hyperthyroid	Euthyroid
10 mCi	30	8	1
15 mCi	31	16	1
Total	61	24	2

Figure 1. Outcome after radioactive iodine therapy.

Table 2. *Association between variables and successful treatment.*

Variable	Univariable analysis	P-value	Multivariable analysis	P-value
	Crude OR (95% CI)		Adjusted OR (95% CI)	
Age at diagnosis of GD				
<15 years	1	0.757	1	0.417
≥15 years	1.19 (0.40-3.48)		1.69 (0.48-6.01)	
Interval of GD diagnosis and RAIT				
≥2 years	1	0.741	1	0.493
<2 years	1.18 (0.44-3.17)		0.66 (0.20-2.16)	
Thyroid gland size				
>50 grams	1	0.617	1	0.124
≤50 grams	1.27 (0.50-3.25)		0.14 (0.01-1.71)	
Discontinuation of ATD				
≤3 days	1	0.034	1	0.015
>3 days	2.88 (1.09-7.63)		3.67 (1.29-10.46)	
^{131}I activity				
10 mCi	1	0.214	1	0.055
15 mCi	0.55 (0.21-1.42)		0.08 (0.01-1.06)	

GD, Graves' disease; RAIT, radioactive iodine therapy; ATD, antithyroid drug; OR, odds ratio; CI, confidence interval.

ents with pediatric GD. According to the recent standard clinical practice guidelines, the objective of the treatment is to completely ablate the thyroid with rendering patients' hypothyroid by single ^{131}I therapy for decreasing the chance of recurrent thyrotoxicosis and radiogenic-induced thyroid cancer [2, 7, 13]. Thus, the successful therapy in our study was defined as patients becoming hypothyroid within six months after the first dose of RAIT. The overall success rate of RAIT in our study was 70.1% which is aligned with the previous studies with the fixed-activity regimen that showed the rate of hypothyroidism between 55%-98% after the first course of RAIT [10, 14, 15]. However, 3.3% of patients who initially responded well later had persistent hyperthyroidism and required an additional RAIT dose. This may reflect transient post-RAIT hypothyroidism, which can occur within six months of therapy. These findings underscore the importance of long-term follow-up after RAIT in pediatric patients to ensure sustained remission and to promptly identify those who may require retreatment.

Regarding the treatment regimens, a prior systematic review found that both fixed activity and calculation-based dosing provided good therapeutic outcomes and a safe profile [4]. However, a fixed-dose method is simpler and faster, does not require a radioiodine uptake study or neck ultrasound for thyroid sizing and is therefore more cost-effective with fewer logistical demands and less treatment delay compared with calculated dosing. Accordingly, we mainly select a fixed-activity RAIT approach in children with GD.

Our study showed no statistically significant difference between the rate of hypothyroidism in patients who received 10- and 15mCi of ^{131}I (76.9% vs 64.6%, P=0.211). Thus, patients who had a small thyroid gland size, especially those less than 50 grams, should receive 10mCi of ^{131}I to avoid overtreatment. However, patients in the 15mCi group tended to have a lower success rate even treated with a higher activity of ^{131}I. There is a major reason which could explain this finding. Patients who received 15mCi of ^{131}I had significantly larger thyroid gland size than those who received 10mCi (77.7 grams vs 42.4 grams, P<0.001). The thyroid gland size is one of the important predictive factors for successful treatment. Patients with a large thyroid gland size or high thyroid volume tend to have a lower rate of hypothyroidism after RAIT [9, 16]. Regarding the dose-response relationship, the previous studies found that the efficacy of treatment tended to increase with higher RAI activity. One study used a fixed RAI activity of 15mCi and achieved a high hypothyroidism rate in 39 of 40 patients (97.5%). For calculated regimen, fewer than 50% of patients developed hypothyroidism after receiving

120μCi of ^{131}I per gram of thyroid tissue, whereas up to 85% did so after receiving 300μCi per gram [4, 10].

Regarding the median time to achieve hypothyroidism after RAIT, there was no different interval between the 10- and 15mCi groups (4.6 months vs 5.1 months). However, these figures were longer than the previous studies that showed the average time to hypothyroidism was approximately 2-3 months after receiving the average 15mCi dose of ^{131}I [10, 17]. This discrepancy may be explained by differences in the timing of outcome assessment. In our study, thyroid function tests were performed at approximately 2, 4, and 6 months after therapy, whereas prior studies often included earlier assessments (e.g., at 1 and 3 months). As a result, cases of early-onset hypothyroidism may not have been captured at the exact time of occurrence in our cohort and were instead identified at subsequent follow-up visits. Consequently, the recorded time to hypothyroidism may appear prolonged, reflecting the assessment schedule rather than a true delay in biological response.

Interestingly, we found that discontinuation of an ATD more than three days prior to RAIT was the only variable that was associated with successful RAIT. This finding could be explained by the radioprotective effect of the antithyroid agent which possibly decreases the therapeutic action of ^{131}I [16]. Thus, if there are no concerning symptoms of thyrotoxicosis, it is advisable to withdraw the methimazole and propylthiouracil for more than three days before ^{131}I therapy in patients with pediatric GD for the optimal treatment outcome. With regard to multivariable analysis, potential multicollinearity should be considered. In particular, thyroid gland size and administered ^{131}I activity are likely to be correlated, as patients with larger thyroid glands were more frequently treated with higher fixed activity. Such collinearity may inflate standard errors and obscure the independent effects of these variables.

There were some limitations to our study. First, due to its retrospective design, selection bias, particularly for prescribed ^{131}I activity, is unavoidable. In addition, potential predictor for the treatment outcome such as serum anti-TSH receptor antibodies was not tested in most of the cases. Second, the estimation of thyroid gland size may be subjective among the attending physicians which led to the variation of determining ^{131}I activity. Lastly, the long-term treatment response and side effects of RAIT were not available to be reported in our study.

In conclusion, our study demonstrated that fixed-activity RAIT regimen effectively induced hypothyroidism in pediatric patients with GD. Moreover, withholding ATD for more than three days before RAIT was advised for the optimal treatment effect.

The authors declare that they have no conflicts of interest.

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