A NEW SIMPLE, PERSONALIZED, AND QUANTITATIVE EMPIRICAL METHOD FOR DETERMINING ^{131}I ACTIVITY IN TREATING GRAVES' DISEASE

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Abstract

Context. The ^{131}I activity for treating Graves' disease (GD) is usually determined based on physician's experience.

Objective. This study aimed to design an empirical method that was not only personalized and quantitative, but also simple, convenient, and easy to grasp.

Subjects and Methods. The study population comprised patients with GD, selected between May 2013 and May 2016, who received ^{131}I therapy in the Outpatient Department of Shanghai Ninth People's Hospital. The first-visit patients of physician 1 were placed in the traditional group: the activity of ^{131}I (mCi) was calculated using the routine formula: [empirical activity (0.07–0.12 mCi/g) $\times$ thyroid mass]/[24-h thyroid ^{131}I uptake]. The first-visit patients of physician 2 were placed in the personalized group. The activity of ^{131}I (mCi) was calculated in two steps. First, the initial activity was calculated: 0.1 mCi/g $\times$ thyroid mass (g), and then a personalized and quantitative calibration table of ^{131}I activity was used to obtain a final ^{131}I activity. The cure rate with a single activity of ^{131}I was recorded 1 year later.

Results. The traditional and personalized groups included 241 and 282 patients, respectively. Interestingly, the personalized group achieved a higher cure rate [86.5% (244/282) *versus* 73.4% (177/241), $P = 0.000$] with a relatively higher ^{131}I activity for the first treatment [8.7 (7, 3.5–30) mCi *versus* 6.7 (6, 2.5–30) mCi, $P = 0.000$] compared with the traditional group, while the incidence rate of permanent hypothyroidism was not significantly different between the two groups ($P = 0.175$).

Conclusion. The empirical method designed in this study was reliable.

Keywords: Graves' disease, hyperthyroidism, nuclear medicine.

INTRODUCTION

Graves' disease (GD) is the most common type of hyperthyroidism. It can account for up to 90% of cases in iodine-rich areas (1). At present, GD can be

treated with antithyroid drugs (ATD), surgical treatment, and ^{131}I therapy (2). Because ^{131}I is an easy treatment for hyperthyroidism, relatively cheap, reliable, and with good outcomes(3-5), it is increasingly favored by patients with hyperthyroidism(6). However, in clinical practice, how to calculate the acceptable ^{131}I activity is still controversial (7). For example, the conventional empirical formula to calculate the activity of ^{131}I results in a range for the activity per gram of thyroid (mCi/g), which is too broad (8). It takes two working days to measure 24-h thyroid ^{131}I uptake, and hence is not popular with patients. Moreover, the application of mathematical models for calculating activity is too complex and may not produce ideal effects. The fixed-dose method (commonly in the range of 5–15 mCi or 185-555 MBq) was introduced in the 1980s (9). It was simple and less dependent on physician's experience; also, it did not require the measurement of 24-h thyroid ^{131}I uptake. People believed that a higher fixed dose of ^{131}I might achieve a higher cure rate for the first treatment. However, the results varied in the literature. Watson *et al.* reported a success rate of 72.4% with 5 mCi(185MBq) (9), whereas Zantut-Wittmann *et al.* obtained a cure rate of 62% with a fixed dose of 10 mCi(370MBq) (10). The main reason was that the thyroid volume and other personal factors were not considered in the fixed-dose rule. Also, it might result in some patients with GD receiving a too much or too little dose. The first choice for the fixed dose (5, 8, 10, or 15 mCi;370, 296, 370, or 555 MBq) is still an issue confronting the nuclear medicine physicians worldwide. Hyer SL *et al.* reported a personalized dosimetry approach with a planned thyroid absorbed dose of 60 Gy. However, the thyroid uptake should be measured three times in 6 days before treatment(11). In clinical practice, most patients with GD prefer a simple, cost-effective, and time-saving ^{131}I treatment. Therefore, a new simple, personalized, and quantitative empirical method was

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designed to calculate the ^{131}I activity in this study under the premise of not increasing the expenditure and time of patients with GD (patients only needed to measure thyroid hormone levels and have thyroid B-ultrasound before treatment). The new method might make the ^{131}I treatment of GD more simple and convenient for physicians and more acceptable by patients with GD, yielding good outcomes. An observational study of GD treatment was conducted, and the results were compared with those of the traditional empirical formula to verify the efficacy of the new method; the follow-up period was 19 months (range: 12–104 months).

MATERIALS AND METHODS

Patients and groups

Inclusion criteria: From May 2013 to May 2016, patients with GD and indication of ^{131}I therapy, who received ^{131}I therapy in the Outpatient Department of Shanghai Ninth People's Hospital, were all from iodine-rich areas of southeastern China. GD is characterized by hyperthyroidism, diffuse goiter, and serum thyroid autoantibodies. Patients with GD were randomly divided into two groups: the first-visit patients of physician 1 were placed in the traditional group, and the first-visit patients of physician 2 were placed in the personalized group. Physicians 1 and 2 were in the south (Huangpu District) and north parts (Baoshan District) of Shanghai Ninth People's Hospital, respectively. The straight distance between the two parts was about 23 km. Patients did not know which physician was the one in charge when he or she was first referred to the outpatient. However, each of them was informed about the way of determining ^{131}I activity before treatment. Patients who disagree with the new method may choose the traditional method and receive treatment in the south part of our hospital. All of the patients who first referred to the northern part of our hospital accept the new method we designed finally. The traditional and personalized groups included 241 and 282 patients with GD, respectively. All patients gave informed consent, and the study was approved by the hospital ethics committee.

Patient preparation

(a) The values of serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone receptor antibody (TRAb) were measured 24 h before ^{131}I therapy. FT3 and FT4 were measured by a chemiluminescence method (Beckman Coulter Access 2; Beckman Company, CA, USA). The normal values of FT3 and FT4 were 1.71–3.71 pg/mL and

0.70–1.48 ng/dL, respectively. TRAb was measured by a radioimmunoassay method (Johnson and Johnson, Clinical Diagnostics Ltd, OH, USA); the normal value was <10 U/L (b). The thyroid mass was calculated from the measurements obtained by B-mode ultrasonography: thyroid volume (cm^3) = (length $\times$ width $\times$ thickness) $\times$ π (pi)/6 (10). (c) Patients were asked to keep calm; not to squeeze their neck; avoid alcohol, fatigue, and mood swings, and prevent infection. (d) Patients with obvious symptoms received symptomatic treatment in advance. Patients with severe symptoms (heart rate >150 bpm) were not observed at this time. (e) The 24-h thyroid ^{131}I uptake of patients in the traditional group was measured within 1 week prior to ^{131}I treatment and determined 24 h after the patients were administered 5 μCi (185KBq) ^{131}I under fasting conditions. Reference values were 15%–35%.

Determination of ^{131}I activity

For the traditional group, the activity of ^{131}I was calculated by physician 1:

$$^{131}\text{I} \text{ activity (mCi)} = \frac{(\text{Empirical activity (0.07-0.12 mCi/g)} \times \text{thyroid mass (g)})}{24\text{hr thyroid } ^{131}\text{I uptake}}$$

Empirical activity was appropriately adjusted based on the physician's experience and patient status.

For the personalized group, the activity of ^{131}I was calculated by physician 2:

$$^{131}\text{I} \text{ activity (mCi)} = [0.1 \text{ mCi/g} \times \text{thyroid mass (g)}] \text{ with calibration}$$

The first step was to calculate the initial activity of ^{131}I (mCi): $0.1 \text{ mCi/g} \times \text{thyroid mass (g)}$. The second step was to correct the initial activity and quantitatively increase or decrease the activity based on an increase or decrease in each of the personal factors by 1 mCi (37MBq). As shown in Table 1, the activity of 84 patients without ATD was corrected by personalized factors 1–8 before ^{131}I therapy, while those with ATD (198 cases) were altered by factors 1–12. All patients were treated with ^{131}I therapy in the outpatient department. If the calculated activity of ^{131}I exceeded 30 mCi (1110MBq), then 30 mCi (1110MBq) was considered to be a therapeutic activity.

Treatment strategy and follow-up

The patients with GD were orally administered ^{131}I (liquid) which was measured by radioactive meter (CRC-25R, CAPINTEC, Ramsey, NJ, USA) under fasting conditions to facilitate ^{131}I absorption and maintained in the fasting state for 2 h. After receiving ^{131}I , ATD adjuvant therapy was no longer used. Three

Table 1. Calibration table of ^{131}I activity

No. Personalized factors	Activity correction		
	-1 mCi (N)	0 (N)	+1 mCi (N)
1 Age	<25(32)	25–40 (102)	>40 (148)
2 Gender	–	Female (208)	Male (74)
3 Course of disease (year)	–	<5 (218)	≥5 (64)
4 Heart rate	–	<120 (245)	≥120 (37)
5 Complication ^a	–	–	Yes (34)
6 Iodine diet or drugs in the month prior to therapy	–	No or unclear (10)	Clear evidence of (272)
7 Thyroid hardness ^b	Soft (111)	Medium (145)	Hardening (26)
8 Postoperative recurrence	–	–	Yes (5)
9 Sensitivity to ATD treatment ^c	Sensitive (18)	Effective (264)	Invalid (0)
10 Number of recurrences after ATD treatment remission	–	≤1 (260)	≥2 (22)
11 Cumulative duration of ATD therapy (year)	–	<3 (233)	≥3 (49)
12 Withdrawal time of ATD prior to therapy (week)			
MMI	–	≥2 (96)	<2 (65)
PTU	–	≥4 (21)	<4 (16)

ATD, Antithyroid drug; MMI, methimazole; PTU, propylthiouracil. 1mCi=37MBq.

“N” in the parentheses indicated the frequency of the factor used in the personalized group. “–” indicates that the factor did not exist or was not set.

a) Graves ophthalmopathy, or atrial fibrillation, or abnormal liver function/blood routine test. b) Evaluated by physician's palpation.

c) Sensitivity indicated that the patient was rapidly relieved of the symptoms, or the level of thyroid hormones decreased to normal, or the patient had drug-induced hypothyroidism within 1 week after taking ATD. Invalid indicated a patient with worsened disease or increased level of thyroid hormones within 1 week after taking ATD. All other instances were indicated by the term effective

Table 2. Patient conditions prior to ^{131}I therapy

Characteristics	Traditional group	Personalized group	P
Age (year)	42.3 ± 13.3	41.8 ± 13.2	0.700
Female (%)	168 (69.7)	205 (71.7)	0.452
Thyroid mass	65 (40–200)	70 (35–250)	0.985
Patients with ATD (%)	182 (75.5)	198 (70.2)	0.175
Course of disease (mo)	22 (1–276)	24 (0.5–300)	0.559
Postoperative (%)	1 (0.4)	5 (1.7)	0.225

ATD, Antithyroid drug.

months later, any patient still having hyperthyroidism was asked to receive further ^{131}I therapy with the same method used in the first treatment until cured (The time interval was three months between the two ^{131}I treatments). The cure rate with a single activity of ^{131}I was recorded at least 1 year after receiving the first ^{131}I treatment. Each patient was advised to seek immediate medical attention in the case of exacerbated thyrotoxicosis symptoms.

Efficacy determination and cure criteria

^{131}I therapy was considered to be successful if euthyroidism or hypothyroidism was achieved with the discontinuation of ATD after 1 year with a single treatment of ^{131}I (13).

Statistical analysis

Data were statistically analyzed using SPSS, version 17.0 (SPSS Inc., IL, USA). The normal distribution data were expressed as the mean ± standard deviation, and the data with non-normal distribution were represented by the median (range). For comparing

the data from the two groups, the χ^2 test or Fisher's exact test was used to determine the qualitative parameters. The normal distribution of data was assessed using the t test, and the non-normal distribution of data was evaluated using the Mann–Whitney U test. A value of P less than 0.05 was considered statistically significant.

RESULTS

All patients were cured with a single treatment or after repeated treatments. No significant difference in age, gender, thyroid mass, rate of patients pretreated with ATD, course of disease, and rate of postoperative patients was found between the two groups prior to ^{131}I therapy (Table 2). The ^{131}I activity for the first treatment in the traditional and personalized groups is shown in Figure 1. The mean activity (median, range) in the traditional group and personalized group was 6.7(6, 2.5–30) and 8.7 (7, 3.5–30)mCi or 247.9(222, 92.5–1110) and 321.9(259, 129.5–1110) MBq, respectively. Most patients (258/282, 91.5%) in the personalized group were administered with a ^{131}I activity of 5–15

mCi(185-555 MBq) for the first treatment finally. The calculated activity exceeded 30 mCi(1110MBq) in four patients, one in the traditional group and three in the personalized group.

Interestingly, the personalized group achieved a higher cure rate [86.5% (244/282) versus 73.4% (177/241), $P = 0.000$] with a relatively higher ^{131}I activity for the first treatment ($P = 0.000$) compared with the traditional group. However, the difference in the incidence rate of permanent hypothyroidism during the follow-up period [19 (range: 12–104) months] between the two groups was not statistically significant [44.7% (126/282) versus 50.6% (122/241), $P = 0.175$].

DISCUSSION

The ^{131}I activity for treating Graves' disease is usually determined using a routine empirical formula, which is aimed at improving the cure rate and reducing the amount of ^{131}I radiation (7). Although the empirical formula involves three indicators accounting for personal factors (the value of mCi/g, thyroid mass, and 24-h thyroid ^{131}I uptake), the value of mCi/g is difficult to determine in clinical practice. Therefore, physicians consider factors including the age of the patient, disease course, ATD therapy, and complications. However, these influencing factors lack quantitative criteria and largely depend on the personal experience of physicians, which is difficult to master and leads to a larger deviation of results (14). Therefore, some scholars suggest the use of fixed-dose methods instead of using the routine formula(10,13,14). The fixed-dose

method was simple and less dependent on physician's experience; also, it did not require the measurement of the 24-h thyroid ^{131}I uptake. However, a higher fixed dose of ^{131}I may not surely achieve a higher cure rate for the first treatment. The main reason is that the thyroid volume and other personal factors were not fully considered in the fixed-dose rule. In addition, it may result in some patients with GD receiving a too much or too little dose. Furthermore, which fixed dose is the first choice is still a tricky issue.

In this study, a new method was designed based on the initial activity and a subsequent personal calibration. As the thyroid mass is decisive in determining the activity of ^{131}I (10,13), the initial activity was based on the weight of the thyroid mass with a fixed activity of 0.1 mCi per gram of thyroid. The new method made the empirical therapy personalized and quantitative. Until recently, the influencing factors lack quantitative criteria and largely depend on the personal experience of physicians. Table 1 includes not only factors that might have led to the failure of ^{131}I treatment reported in the literature (15-18), such as male patient, older age, longer course of disease, iodine-rich diet (drugs), and ATD pretreatment, but also factors found in clinical practice, such as the hardening palpation of the thyroid, swift heart rate, complications, and postoperative recurrence. Hence, a higher ^{131}I activity was necessary. Most patients with GD were administered with ^{131}I in a range of 5–15 mCi (185-555 MBq) for the first treatment, not only in our previous study, but also in the literature (8). Therefore, an increase by 1 mCi (37MBq) was set for each personal factor, which was not only easy for physicians to grasp but also made the final corrected activity in an appropriate range. Three other factors were also introduced, each with a decrease by 1 mCi(37MBq), for hypothyroidism. The initial activity was increased or decreased according to the 12 personal factors. The 24-h uptake was removed because (a) Nordyke *et al.* reported no significant relationship between cure and 24-hr uptake if more than 30% (19) and (b) it takes two working days, which is not preferred by most patients with GD.

The results of this study showed no significant differences between the two groups in terms of age, gender, thyroid mass, rate of patients pretreated with ATD, course of disease, and rate of postoperative patients before ^{131}I therapy. However, after ^{131}I therapy, the cure rate with a single treatment in the personalized group was higher than that in the traditional group. This was because the number of factors that increased in the personalized group was much higher than the number of

Figure 1. The calculated activity exceeded 30 mCi in 4 patients, 1 in the traditional group and 3 in the personalized group. The mean activity (median, range) in the traditional group and personalized group was 6.7 (6, 2.5-30) and 8.7 (7, 3.5-30) mCi respectively.

factors that reduced. Therefore, the activity of ^{131}I for the first treatment in the personalized group was significantly higher than that in the traditional group. Another reason was that the activity of ^{131}I determined by physician 1 was too conservative [mean (median, range): 6.7(6, 2.5-30) mCi]. The advantages of the personalized method in the study were as follows: (a) A relatively low activity [mean (median, range): 8.7(7, 3.5-30) mCi] resulted in a higher cure rate with a single treatment (86.5%) compared with other reports in the literature (10,13). (b) It also quantified the personal factors, improving the ease with which the physicians could determine the personal activity of ^{131}I . As a result, the dependence on the personal experience of the physician was low, the determination of activity by different physicians was standardized, the operability and repeatability were strong, and the curative effect was ensured. (c) The 24-h thyroid ^{131}I uptake measurement was removed as for the fixed-dose method. (d) The personalized method itself was simple, cost-effective, time-saving, and objective. Metso *et al.* reported that the incidence rate of hypothyroidism could be up to 82% after 25 years of ^{131}I therapy for GD (20). However, in the present study, the incidence rate of permanent hypothyroidism during the follow-up period (median: 19 months) in the two groups was at a reasonable level with no significant difference.

In conclusion, the empirical method designed in this study was reliable. Still, the study had some limitations. First, the hardness of thyroid was assessed by the physician's palpation, which was subjective. Second, the patients with GD were confined to the Asian race on the southeast coast of China. Third, under special circumstances, such as for some patients with reduced heart rate and symptoms but a poor curative effect of ^{131}I therapy, it was often necessary to repeat and increase the activity of ^{131}I to cure. Finally, the number of patients was relatively small. Hence, studies with a larger number of patients should be conducted to validate the findings.

Conflict of interest

The authors declare that they have no conflict of interest.

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