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Original article

Adjuvant effect of hydrochlorothiazide on radioiodine treatment in low-iodine uptake Graves' disease patients

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Background: The outcome of radioiodine (RAI) treatment in Graves' disease patients depends mostly on the percentage of RAI uptake in the thyroid gland. Most Graves' disease patients have a high percentage of RAI uptake while some have low uptake even after continuation of a low-iodine diet before RAI treatment. Hydrochlorothiazide has been proven to increase the percentage of uptake in low-iodine diet low-uptake Graves' disease patients. However, the effect on the patient's outcome has never been demonstrated.
Objective: The aim of this study was to investigate the outcome of RAI treatment in low-iodine uptake Graves' disease patients who were pre-treated with hydrochlorothiazide (HCTZ). The results were then compared with those who continued the low-iodine diet alone.
Methods: All patients had Graves' disease and had low iodine uptake at baseline (1st RAI uptake). This retrospective study aimed to compare the treatment outcomes between two groups. The control group consisted of patients who discontinued an iodine-containing diet for 2 weeks before the 2nd RAI uptake. The HCTZ group consisted of patients who discontinued an iodine-containing diet for 2 weeks together with 50 mg of HCTZ in two divided doses for 5 days before the 2nd RAI uptake. ^{131}I treatment doses were calculated based on the size of the thyroid gland, and the second 24-hr RAI uptake. The outcomes of treatment were then compared between the two groups at 3, 6, 9 and 12 months after treatment.
Results: There were 13 subjects in each group. At baseline, there was significantly higher 24-hr RAI uptake in the control group than the HCTZ group. However, in the second RAI uptake, the HCTZ group had significantly higher 3-hr and 24-hr uptake than the control group. Regarding the thyroid size, the HCTZ group had a larger mean of thyroid size than the control group. There was no significant difference in the percentage of remission at each time point between the two groups. However, after adjustment of the thyroid size and baseline 24-hr uptake, patients in the HCTZ group were 3.06 (adjusted OR = 3.06, 95%CI: 0.45, 20.68) times more likely to have disease remission than those in the control group, but this was not statistically significant.
Conclusions: Pre-treatment with HCTZ together with a low-iodine diet in low-uptake Graves' disease patients are more likely to have a higher remission rate than using a low-iodine diet alone.

Keywords: Hyperthyroidism, diuretics, radioiodine treatment, remission, Iodine radioisotopes.

The use of radioiodine (RAI) treatment in patients with hyperthyroidism has been a part of clinical practice for over 50 years. Hyperthyroidism is most commonly caused by Graves' disease worldwide. [1] Often treated by RAI therapy, one critical factor for successful treatment is the efficacy of ^{131}I uptake by the thyroid. Many common methods including a low iodine diet, avoidance of iodine-containing drugs and iodinated contrast media have been used to increase RAI uptake by the thyroid. To enhance the retention of ^{131}I in thyroid, lithium carbonate has been used. Lithium carbonate had been proved to improve the efficacy of RAI treatment in Graves' disease patients.[2] Some studies showed that diuretic drugs increase the 24-hour RAI uptake in euthyroid [3] and high-iodide pool, low-uptake hyperthyroid patients.[4]

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It is still questionable whether or not an increase in 24-hour RAI thyroidal uptake leads to a better therapeutic outcome. [5] There has been no published study about the outcomes after RAI treatment in low-iodine uptake Graves' disease patients who were pre-treated with hydrochlorothiazide (HCTZ).

The aims of the study were to investigate the outcomes of RAI treatment in low-uptake Graves' disease patients pre-treated with HCTZ, and to compare the outcomes in these patients with the outcomes in low-uptake Graves' disease patients who were on a low-iodine diet alone.

Materials and methods

This study has been approved by the institutional review board (IRB), the Faculty of Medicine, Chulalongkorn University. Some patients in this study were subjects in our previous study. [4] After that publication, our institution used HCTZ for enhancement of ^{131}I uptake in patients with low uptake in selected cases. In this study, we further recruited hyperthyroid patients who were referred to the Nuclear Medicine Division for ^{131}I treatment using the same inclusion criteria as the previous study [4] and were retrospectively reviewed, regarding their clinical and laboratory data during follow-up visits. Graves' disease patients were diagnosed by physical examination, laboratory investigation and thyroid scans in selected cases. According to our institution's protocol, patients were instructed to discontinue anti-thyroid drugs for at least 5 - 7 days and to have a low-iodine diet for 2 weeks, not to take any iodine-containing drugs or multivitamins within 14 days, and to avoid iodinated contrast media within a 1-month period before undergoing RAI uptake. RAI uptake was measured at 3 hours and 24 hours after a tracer dose of ^{131}I were administered. The average 24-hour RAI uptake in the normal Thai population is 39.5 ± 8.6% (range between 19 - 58%). [6] Graves' disease patients usually have a higher RAI uptake than the normal population. In this study, low RAI uptake in Graves' disease patients was defined when the 24-hr RAI uptake is less than 50% at baseline. Low-uptake Graves' disease patients were divided into two groups. The control group consisted of patients who were instructed to receive a low-iodine diet for 2 weeks before the second RAI uptake. The HCTZ group was made up of patients on a low-iodine diet for 2 weeks and received 50 mg of HCTZ in two divided doses for 5 days before the second RAI uptake. Patients were excluded if they violated the protocol or had other identifiable causes of low RAI uptake. ^{131}I treatment was calculated based on thyroid size and 24-hour uptake with an assigned dose of 100 microCi/gram of the thyroid. The size of the thyroid gland was determined by palpation by the same experienced nuclear medicine physician. Uptake was measured using an ADAC machine model Atom 940. The total duration of count collection was 1 minute.

The researchers reviewed data from patient's medical records and by phone interviews in a few cases. We evaluated the outcome in each patient as remission or non-remission at 3, 6, 9 and 12 months after ^{131}I treatment. Remission was defined when the patient was in an euthyroid or hypothyroid state assessed by clinical and laboratory investigations (free thyroxine and thyrotropin levels) at each time interval. Other conditions were defined as non-remission. The outcomes of the two groups were then compared using Chi-square tests (SPSS version 20). Statistical significance was defined at $P < 0.05$. A generalized estimating equation for adjusted patients' baseline characteristics was done (R Version: R - 3.3.2).

Results

There were 13 subjects in each group. Table 1 shows the patients' baseline data in each group. At baseline, there was significantly higher 24-hr RAI uptake in the control group than the HCTZ group ($P = 0.041$). However, in the second RAI uptake, the HCTZ group had significantly higher both 3-hr and 24-hr uptakes than the control ($P = 0.046$ and 0.028, respectively).

With respect to the thyroid size, the HCTZ group had a larger mean thyroid size than the control group ($P = 0.015$); 46% of the patients from the HCTZ group had remission by 3 months and the rate of remission increased to 77%, 85% and 85% at 6, 9 and 12 months, respectively. The corresponding percentages in the control group were 69%, 77%, 85% and 92% (Table 2). There was no significant difference of the percentages of patient remission between the two groups.

After having adjusted for thyroid size and first 24-hr uptake, patients in the HCTZ group were 3.06 (adjusted OR = 3.06, 95%CI: 0.45, 20.68) times more likely to have remission than those in the control, but this was not statistically significant.

Table 1. Baseline data of patients in HCTZ and control groups.

Data	HCTZ group	Control group	*P* - value*
Sex (number of patients; F:M)	10:3	10:3	1.000
Age (years)	37.5 ± 9.9	43.8 ± 14.4	0.213
Duration of hyperthyroidism (months)	59.2 ± 84.8	56.5 ± 44.6	0.920
Thyroid gland size (g)	53.8 ± 25.3	33.5 ± 8.3	0.015*
1st ^{131}I uptake at 3 h (%)	19.2 ± 9.9	16.8 ± 5.5	0.783
1st ^{131}I uptake at 24 h (%)	30.5 ± 12.2	39.8 ± 9.8	0.041*
2nd ^{131}I uptake at 3 h (%)	40.2 ± 26.4	23.1 ± 10.9	0.046*
2nd ^{131}I uptake at 24 h (%)	64.3 ± 18.9	49.2 ± 13.3	0.028*
Duration between 1st and 2nd uptake (days)	15.3 ± 4.5	12.7 ± 7.0	0.271
Dose of ^{131}I treatment (mCi)	9.8 ± 5.4	7.5 ± 2.3	0.184

*$P < 0.05$ means significant difference. Data are expressed as mean ± SD. F: Female; M: Male.

Table 2. Number and percentage of patients with remission in each group at each time interval.

Time after treatment (months)	Number of patient with remission in HCTZ group (percentage)	Number of patient with remission in control group (percentage)	*P* - value*
3	6 (46.2%)	9 (69.2%)	0.234
6	10 (76.9%)	10 (76.9%)	1.000
9	11 (84.6%)	11 (84.6%)	1.000
12	11 (84.6%)	12 (92.3%)	0.539

*$P < 0.05$ means significant difference.

Discussion

The results showed that HCTZ could significantly increase both 3-hr and 24-hr thyroid uptake, even if the mean baseline 24-hr uptake was lower. The second 24-hr uptake was higher because of the HCTZ's boosting effect. This corresponded with data from our previous study. [4] Another difference in patients' baseline characteristics was the thyroid size, in which the HCTZ group had a larger mean of thyroid size than the control group. This factor might have influenced the outcome of treatment because a larger size is prone to be underestimated in clinical practice. We calculated the ^{131}I treatment dose upon both thyroid size and RAI uptake percentage; thus, underestimation of the thyroid size was attributed to a lower ^{131}I treatment dose and resulted in non-remission. This was one of our limitations due to the nature of a retrospective study.

In general, the remission may occur from 4 weeks onwards, but more often it occurs between 2 to 6 months. [7] From our findings, there was no significant difference in the percentage of patient remission between the two groups at 3, 6, 9 or 12-month intervals, although the HCTZ group showed a lower remission rate at 3 months. However, after adjustment of thyroid size and first 24-hr uptake, patients in the HCTZ group were 3.06 (adjusted OR = 3.06, 95%CI: 0.45, 20.68) times more likely to have remission than those in the control group, but this was not statistically significant.

The mechanism of HCTZ to increase RAI thyroid uptake has been postulated, however. It was previously proposed to be related to the reduction of the circulating stable iodide pool and intracellular iodine by increasing urinary iodine excretion.[3, 8]

Urinary excretion of inorganic iodide occurs through a combination of glomerular filtration and partial tubular re-absorption, as well as secretion of plasma iodide.[8] Because hydrochlorothiazide inhibits reabsorption of sodium (Na^+) and chloride (Cl^-) in the distal convoluted tubule and loop of Henle, the result is increased excretion of Na^+, Cl^-, and iodide (I^-) as negative anions. Patients who received HCTZ have shown to have increased urinary iodide excretion, and a reduced iodide blood pool.[9]

The ideal concepts in ^{131}I treatment are to increase RAI retention in the thyroid gland and accelerate elimination of unbound RAI to reduce its adverse effects.

There are many studies about using diuretics as an adjuvant therapy in RAI treatment for differentiated thyroid cancer (DTC) patients, and some in non-toxic goiter patients. There is, however, no prior study demonstrating the effects of HCTZ on ^{131}I treatment outcomes in hyperthyroid patients.

Matovic MD, *et al.* [10] demonstrated that mice receiving furosemide after ^{131}I administration had a lower percentage of RAI thyroid retention than those not receiving furosemide. Decreased retention of ^{131}I in the thyroid gland in mice receiving furosemide was explained by a well-known increase of renal iodide excretion and thus a decrease of the iodide blood pool. In our study, the patients were designed to receive HCTZ before ^{131}I treatment aimed to decrease the iodide blood pool, and enhance RAI retention in thyroid gland. With regards to reducing the adverse effects of radiodione, there are many studies using diuretic drugs aiming to decrease the whole body radiation burden in DTC patients receiving ^{131}I ablation/ treatment. However, the results therein have been contradictory. Seabold JE, *et al*. [11] showed that administration of furosemide after ^{131}I treatment enhanced ^{131}I clearance in DTC patients and shortened the hospital stay, while Matovic MD, *et al*. [12], and Ignjatovic [13] demonstrated that diuretics slowed down the elimination of ^{131}I in DTC patients treated with this radionuclide. Barbaro D, *et al*. [14] proved that diuretic drugs can improve ablation outcomes in rhTSH-stimulated low-risk DTC patients. However, those patients were in a hypothyroid/ or euthyroid state in which the iodide turnover rate or percentage of RAI uptake may differ from the hyperthyroid condition as in our study.

Kapucu LO, *et al.* [15], studied the effects of a diuretic on iodine uptake in non-toxic goiter patients. Their study revealed that treatment with furosemide prior to administration of RAI increases the RAI thyroid uptake, without a significant difference in urinary iodine clearance as compare with patients who were on a low-iodine diet alone.

Our study is the first study to show that the application of HCTZ before ^{131}I treatment in low-uptake Graves' disease patients tended to enhance RAI efficacy and had better outcome than those having a low-iodine diet alone, even without statistical significance. Due to the limited sample size in our study, an additional large prospective study is warranted.

Conclusions

Pre-treatment with HCTZ in low-uptake Graves' disease patients tends to enhance disease remission more than those who were on a low-iodine diet alone. Additional prospective trials with larger sample sizes may be needed to confirm this evidence.

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Conflict of interest

None of the authors has any potential conflict of interest to disclose.

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