Effects of recombinant human thyroid stimulating hormone on ^{131}I therapy for the treatment of differentiated thyroid cancer

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Abstract. The aim of the present study was to compare the advantages and disadvantages of the combined application of recombinant human thyroid stimulating hormone (rhTSH) with thyroid hormone withdrawal (THW) and THW alone prior to ^{131}I therapy for the treatment of differentiated thyroid cancer. Four indicators were compared between the experimental group, who received a combined therapeutic method of rhTSH with THW, and the control group, who received THW therapy alone. With the exception of the elimination half-time of ^{131}I in the blood in the experimental group, which was significantly shorter compared with that in the control group, the other three indicators, including the urinary iodine concentration, the relative ^{131}I uptake ratio of the neck lesions and the one-time cure rate, were not significantly different between the two groups. In addition, the treatment efficacy of ^{131}I therapy exhibited no statistically significant difference between the experimental and control groups. However, in the experimental group, the residence time of ^{131}I in the blood was significantly shorter compared with that in the control group, indicating that the irradiation damage of radioactive iodine exposure to the non-target tissues was lower in the experimental group when compared with the control group. In addition, no evident hypothyroidism was observed in the patients. Thus, the combined application of rhTSH with THW prior to ^{131}I therapy was demonstrated to be superior to the THW therapy alone.

Introduction

Currently, radioiodine therapy is considered to be an effective but low-risk treatment method for cases of advanced differentiated thyroid cancer (DTC) (1-3). The treatment effect of ^{131}I depends on the ^{131}I uptake ability of the lesions, which has two prerequisites. Firstly, the administration of an iodine diet is used to maintain the body in a low iodine environment, in order to avoid the dilution of non-radioactive iodine to radioactive iodine. Secondly, an improvement in the blood thyroid stimulating hormone (TSH) levels can be used to stimulate the ^{131}I uptake ability of the lesions. The TSH level can be elevated via two methods. One method is thyroid hormone withdrawal (THW) for approximately four weeks, which causes the patient to enter a hypothyroidism state, stimulating the production of endogenous TSH from the pituitary gland. An additional method is injections of recombinant human TSH (rhTSH), which improves the exogenous TSH level in the body (3). However, with regard to the injections of rhTSH, continual administration of thyroid hormone has been reported to dilute the concentration of radioactive iodine, thereby influencing the ability of the body to absorb the radioactive iodine (3). Thus, in the present study, a combined pretreatment program was designed, in which the withdrawal of thyroxine administration is conducted temporarily, but without causing overt hypothyroidism in the patients. This avoids the dilution effect of thyroxine on the radioactive iodine and maintains the patient's body in a relatively low iodine state. Subsequently, injections of rhTSH are administered, which is followed by ^{131}I therapy. The aim of the present study was to compare the advantages and disadvantages of the novel pretreatment program with THW therapy alone prior to ^{131}I therapy for the treatment of patients with DTC.

Materials and methods

Clinical data. In total, 15 patients who had been diagnosed with DTC in the Department of Thyroid and Breast Surgery at the People's Hospital of Shenzhen (Shenzhen, China) were enrolled in the study. All patients had undergone a near total resection of the thyroid and intended to undergo ^{131}I therapy in the People's Hospital of Shenzhen. ^{131}I was provided by Guangdong Xi'ai Nucleus Pharmaceutical Center (Guangzhou, China). The patients were divided into two groups. The experimental group (n=6) comprised three males and three females, with an age range of 48-72 years (mean age, 58.33±9.69 years). The control group (n=9) comprised five males and four females, with ages ranging between 24 and 60 years (mean age, 41.22±11.02 years). The study was conducted in accordance with the Declaration of Helsinki, and with approval from the Ethics Committee of the People's

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Table I. Comparison of the urinary iodine concentration prior to and following THW therapy in the two groups (μg/l).

Groups	Urinary iodine concentration prior to THW	Urinary iodine concentration following THW
Experimental	301.67±66.29	119.67±25.50[a]
Control	299.78±63.55	107.33±18.49[b]

Data are expressed as the mean ± standard deviation. [a]P<0.01, vs. concentration prior to THW; [b]P>0.05, vs. experimental group following THW. THW, thyroid hormone withdrawal.

Table II. Comparisons of the indicators between the two groups following ^{131}I therapy.

Groups	Elimination half-time of ^{131}I in the blood (h)	Ratio of the average pixel count of the ROI to the whole body	One-time cure rate (%)
Experimental	7.82±1.43	48.12±5.87	66.7
Control	9.76±1.74	46.96±10.11	55.6
Statistics	t=2.255, P=0.042	t=0.251, P=0.806	χ^2=0.185, P=0.667

Data are expressed as the mean ± standard deviation. ROI, region of interest.

Hospital of Shenzhen. Written informed consent was obtained from all the participants.

Treatment. Patients in the control group received an iodine diet, but withdrew from the administration of thyroxine for four weeks. The urinary iodine concentration was determined prior to ^{131}I therapy. Patients in the experimental group received the same pretreatment, and the urinary iodine determination was performed in the same manner as for those in the control group. However, these patients also received an injection of 0.9 mg rhTSH (Thyrogen; Genzyme Corporation, Cambridge, MA, USA) at one and two days prior to the ^{131}I therapy. The ^{131}I dosage for clearing the residual thyroid was 2,590 MBq (70 mCi) for the two groups.

Calculation of the elimination half-time of ^{131}I. At 2, 6, 9, 24 and 36 h after the patients were treated with ^{131}I, a 0.5-ml blood sample was collected from each patient and placed in a FT603 well-type lead chamber (Beijing Nuclear Instrument Factory, Beijing, China) for radiocounting. The results were analyzed using SPSS 13.0 statistical software (SPSS, Inc., Chicago, IL, USA) to calculate the elimination half-time of ^{131}I in the blood.

Uptake ratio of ^{131}I by the lesions. Patients in the two groups received a total body ^{131}I scan using a single photon emission computed tomography system (Discovery VH; GE Healthcare, Milwaukee, WI, USA), on day seven following ^{131}I therapy. On the scanogram, the neck lesion (region of interest, ROI) was sketched out and the ratio of the average pixel count in the ROI to the whole body was calculated.

Therapeutic effect. At the six-month follow-up examination, patients in the two groups underwent a neck ultrasound and serum thryoglobulin (Tg) analysis. For the patients with cervical lymph node enlargement and elevated serum Tg, a total body ^{131}I scan was performed. The clinical criteria indicating a recovery comprised a neck ultrasound examination revealing no thyroid or swelling lymph nodes, serum Tg concentrations of ≤2 ng/ml and a ^{131}I scan showing no iodophilic hot lesions. In cases where these conditions were not achieved, the patients required additional ^{131}I therapy. The one-time cure rate of the two groups was compared using the χ^2 test.

Statistical analysis. Measurement data are expressed as the mean ± standard deviation, and SPSS 12.0 software was used for statistical analysis. Mean values of the urinary iodine concentration, the elimination half-time of ^{131}I in the blood and the relative uptake ratio of the lesions in the two groups prior to and following THW were compared using the t-test. The one-time cure rate of the two groups was compared using the χ^2 test. P<0.05 was considered to indicate a statistically significant difference.

Results

Urinary iodine concentration. Prior to and at one week following THW therapy, the mean urinary iodine concentrations in the experimental group were 301.67±66.291 and 119.67±25.50 μg/l, respectively, which exhibited a statistically significant difference (t=10.25, P=0.008). However, the mean urinary iodine concentration in the experimental group at one week after THW (119.67±25.50 μg/l) exhibited no statistically significant difference when compared with the concentration in the control group at four weeks after THW therapy (107.33±18.49 μg/l; t=1.05, P=0.331; Table I).

Elimination half-time and uptake ratio of ^{131}I. In the experimental group, the elimination half-time of ^{131}I in the blood was 7.82±1.43 h, which was notably shorter when compared with the control group (9.76±1.74 h; t=2.255, P=0.042). The

ratio of the average pixel count of the ROI to the whole body was 48.12±5.87 in the experimental group, showing no statistically significant difference with that in the control group (46.96±10.11; t=0.251, P=0.806).

One-time cure rate. The one-time cure rate was 66.7% (4/6) in the experimental group and 55.6% (5/9) in the control group. As compared using the χ^2 test, no statistically significant difference was identified between the two groups (χ^2=0.185, P=0.667; Table II).

Discussion

THW has traditionally been used to increase the serum TSH concentration, which can improve the sensitivity of DTC diagnosis, as well as optimize the capture and retention of radioactive iodine in the treatment of patients with DTC. However, THW can cause clinical hypothyroidism, resulting in the appearance of complications, such as cognitive impairment, mood disorders and other physical discomfort or health hazards, which consequently damage the patient's quality of life and ability to work (4-6). Since rhTSH was first approved by the Food and Drug Association as a diagnostic aid for DTC in December 1997, the hormone has been progressively and widely used in a number of European and American countries for the diagnosis, follow-up and treatment of DTC, with good results obtained (7-10).

The conventional method for elevating the TSH level is to stop the administration of levothyroxine (LT4) for approximately four weeks, in order to induce thyroid dysfunction. However, this method has a number of disadvantages. Firstly, patients have to endure the distress of hypothyroidism, which seriously affects their quality of life. Secondly, as a result of hypothyroidism, fluid retention and poor kidney function, the retention time of ^{131}I in the normal tissues is too long, which may substantially increase the radiative damage to the bone marrow, blood and other vital organs. Thirdly, for certain patients, THW is unable to effectively stimulate the pituitary gland to secrete TSH, thereby affecting the uptake of ^{131}I and the subsequent therapeutic effect. Finally, THW applied for a longer time period and continued TSH stimulation may have a risk of deteriorating the condition of the DTC. However, since rhTSH is yet to be introduced comprehensively in China, THW remains the primary method for DTC treatment in China.

Application of rhTSH may overcome the deficiencies of the THW method. However, if patients continue to receive thyroxine, the ability of the lesions to uptake ^{131}I may reduce due to the dilution of the non-radioactive iodine (7,11-13). In one LT4 molecule, the iodine atomic weight accounts for two-thirds of the entire LT4 molecular weight. Thus, it can be calculated that in the LT4 replacement therapy, a daily dose of 100-150 μg LT4 represents a daily supplement of 70-100 μg iodine. In this regard, oral administration of triiodothyronine and then an injection of rhTSH was proposed for patients prior to ^{131}I treatment, as this may reduce the dilution of non-radioactive iodine (7,12-15). In the present study, THW was applied for a short time, which was followed by the injection of rhTSH prior to ^{131}I therapy. The results revealed that the urinary iodine levels were similar between the experimental and control groups after THW, and the patients in the experimental group did not appear to exhibit evident hypothyroidism. Furthermore, the results indicated that there was no statistically significant difference between the experimental and control groups with regard to the treatment effect of ^{131}I, which was consistent with a number of previous studies that reported no significant difference in the treatment effect of ^{131}I therapy between patients pretreated with rhTSH and THW (16-18).

In addition, the present study demonstrated that the retention time of ^{131}I in the blood in the experimental group was significantly shorter compared with that in the control group, indicating that the injection of rhTSH may reduce the irradiation damage of ^{131}I to the non-target tissues. Adjuvant treatment of rhTSH has been reported to be preferred for patients with a high risk of complications with regard to thyroid dysfunction or in those who are unable to produce a sufficient amount of endogenous TSH (19-23). However, whether this treatment method can be applied in the early stages of DTC in younger patients requires further study. The results of the current study also demonstrated that prior to treatment with ^{131}I, pretreatment with rhTSH combined with THW may cause less radioactive damage to the non-target organs of the patients with DTC compared with THW application alone. The combined treatment also avoided the occurrence of clinically significant hypothyroidism. However, due to the small number of patients included, the present study can only be used as a preliminary study investigating the role of rhTSH as an adjuvant treatment for patients with DTC. Therefore, the efficacy of the novel pretreatment method, using rhTSH combined with THW, in clinical practice should be further studied in the future.

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