SPANDIDOS PUBLICATIONS

EXPERIMENTAL AND THERAPEUTIC MEDICINE 10: 2079-2082, 2015

Effect of ^{131}I 'clear residual thyroid tissue' after surgery on the function of parathyroid gland in differentiated thyroid cancer

ZHI-HUA ZHAO[1,2], FENG-QI LI[2], JIAN-KUI HAN[1] and XIAN-JUN LI[2]

[1]Department of Nuclear Medicine, Qilu Hospital, Shangdong University, Jinan, Shangdong 250012;
[2]Department of Nuclear Medicine, Weifang People's Hospital, Weifang, Shandong 261041, P.R. China

Received September 14, 2015; Accepted October 19, 2015

DOI: 10.3892/etm.2015.2812

Abstract. Thyroid cancer is a common malignant tumor of the endocrine glands. Although surgery is the optimal treatment utilized, the disease is characterized by recurrence and metastasis. The aim of the present study was to determine the effect of iodine-131 (^{131}I) 'clear residual thyroid tissue' following surgery on the treatment of differentiated thyroid cancer (DTC) and its effect on the function of the parathyroid gland. A total of 160 patients diagnosed with DTC, who were consecutively admitted to our Hospital between June 2012 and June 2014 and underwent total thyroidectomy or subtotal resection, were included in the present study. After three months, the patients were administered ^{131}I 'clear residual thyroid tissue' treatment and underwent a whole body scan after 1 week to determine whether 'clear residual thyroid tissue' treatment was successful or not. The treatment was repeated within 3 months if not successful. Of the 160 patients, 24 patients had cancer metastasis (15.0%). The average dose of ^{131}I used for the first time was 6.4+1.2 GBq and the treatment was successful in 66 cases (41.3%). The average treatment time was 2.8±0.6 therapy sessions. The results showed that, prior to and following the first treatment and at the end of the follow up, levels of the parathyroid hormone, serum calcium and phosphorus were compared, and no statistically significant difference ($P>0.05$) was observed. There were 5 patients with persistent hypothyroidism and 8 patients with transient hypothyroidism. The levels of thyroglobulin were significantly decreased, and the difference was statistically significant ($P<0.05$). A total of 48 patients (30%) with hypothyroidism were identified. In conclusion, the results have shown that DTC resection and ^{131}I 'clear residual thyroid tissue' treatment did not significantly impair the parathyroid function, thereby improving the treatment effect.

Correspondence to: Dr Jian-Kui Han, Department of Nuclear Medicine, Qilu Hospital, Shandong University, 107 Wenhua Xi Road, Jinan, Shandong 250012, P.R. China
E-mail: hzdp2878@163.com

Key words: differentiated thyroid cancer, iodine-131 'clear residual thyroid tissue' treatment, parathyroid function, thyroid globulin

Introduction

Thyroid cancer is a common malignant tumor of the endocrine glands. Previous findings have shown that the detection rate of thyroid cancer is on the increase, particularly among radiologists, where the rate of thyroid cancer has undergone an increase of approximately 0.9-1.5%. This increase may be the result of diet, work stress, and exposure to radiation (1). Differentiated thyroid cancer (DTC) accounts for approximately 85% of thyroid cancers and early surgical resection is the first choice of treatment. Although the prognosis of DTC is good, recurrence or metastasis in DTC remains at 10-30% (2). The recurrence of the disease is commonly identified in the thyroid bed and local lymph nodes. Metastasis is not common in DTC; however, when lung or bone metastasis occurs, the prognosis is poor.

Radioactive iodine-131 (^{131}I) cleared postoperative residual thyroid tissue (referred to as 'clear residual thyroid tissue' treatment) or treatment of recurrence and metastasis (known as 'clearing kitchen'), simultaneously combined with the L-T4 inhibitor constitute the principal treatment (3). The importantce of 'clear residual thyroid tissue' treatment for patients with DTC lies in the fact that it can destroy microscopic lesions that cannot be idenfitied using visual observance and reduce the local recurrence rate, while simultaneously removing residual thyroid tissue. For patients with DTC metastasis, treatment with ^{131}I is imperative. The first key step in the treatment of local or distant metastasis of DTC is 'clear residual thyroid tissue' treatment. ^{131}I is considered an effective, safe, and simple treatment for patients with DTC, and is capable of improving the survival rate of patients. However, it has been previously reported that due to the anatomical location of tumor, the parathyroid may also suffer from radiation damage, causing hypoparathyroidism and disorders of related electrolytes (such as blood calcium and phosphorus) (4). Additionally, the success rate and curative effect of 'clear residual thyroid tissue' treatment is influenced by a number of factors, such as cancer classification, staging, and diameter (5). Thus, investigations to identify appropriate treatment is of clinical significance.

The aim of the study was to determine the effect of the ^{131}I 'clear residual thyroid tissue' treatment following DTC resection on the parathyroid function. The results suggested that this type of treatment did not significantly impair parathyroid function, thereby improving the treatment effect.

Materials and methods

Subjects. A total of 160 patients who were consecutively admitted in our Hospital and diagnosed with DTC underwent total thyroidectomy or subtotal resection between June 2012 and June 2014. The patients were diagnosed as DTC by color doppler ultrasound, fine needle aspiration and postoperative pathology.

The inclusion criteria for the study were: i) The patient age was ≥18 and <75 years; ii) patients were confirmed to suffer DTC and underwent complete thyroidectomy or subtotal thyroidectomy; iii) were previously treated in our Hospital.

Exclusion criteria of the study were: i) Thyroid secondary tumor, combined with malignant tumor in other organs; ii) pregnancy, infection, autoimmune diseases, and severe heart, liver, kidney and other organ dysfunction; iii) parathyroid gland injury or parathyroid transplantation owing to surgical resection; iv) patient already undergoing ^{131}I 'clear residual thyroid tissue' treatment, and assessment of parathyroid hormone (PTH), serum calcium and phosphorus levels; v) recently ingested calcium or vitamin D; vi) patients with poor compliance and intolerance to ^{131}I treatment, and rejection of the study.

The subjects included 91 females and 69 males, aged 29-73 years, with an average age of 48.2±9.6 years. Of the 160 cases included in the study, 74 cases were thyroid papillary carcinoma, 60 cases were follicular carcinoma and 26 cases were mixed type.

Methods. The therapeutic equipment for ^{131}I 'clear residual thyroid tissue' treatment used was: Hamamatsu BHP6602 miniature gamma camera (General Electric Co., Fairfield, CT, USA), and SN-697 fully automatic, reflex and immune R counter with dual probes (Shanghai Nuclear FI Power Equipment Co., Ltd., Shanghai, China). The treatment was administered according to the guidelines of American College of Nuclear Medicine, which recommends that when tumor-node-metastasis is above T2, patients with N1 or M1 should be treated with ^{131}I 'clear residual thyroid tissue'. When the wound is completely healed, thyroid preparation is terminated for 2-4 weeks and an iodine diet is rigorously avoided for 4 weeks. The drugs were administered via the ^{131}I automatic filling instruments of HTA Co., Ltd. (Beijing, China). Generally the dose administered was 2.96-5.55 GBq depending on whether metastatic lesions were present *in vivo* and the postoperative residual thyroid tissue was adjusted for the initial ^{131}I dose, which was ingested, without prior food consumption, orally once. Following drug administration, the patients immediately remained in the auxiliary hospital ward, and consumed a light diet on the specific day. Thyroid hormone suppression therapy was initiated 3 days later. Within one week, patients underwent a whole body scan (WBS). If WBS showed no abnormal radionuclide concentration in the whole body and the thyroglobulin (TG) of patients continued to be <1 ng/ml, 'clear residual thyroid tissue' treatment was considered successful, otherwise ^{131}I treatment was repeated again within 3 months.

Observation index. Prior to and following the initial treatment, and the end of the follow up, the changes in PTH, serum calcium and phosphorus levels were analyzed. PTH levels of <5 ng/dl were regarded as hypoparathyroidism, while PTH levels of <5 ng/dl lasting 6 months, were regarded as persistent hypoparathyroidism. PTH levels that returned to a normal state within 6 months, were regarded as transient hypoparathyroidism. Of these, the normal reference range of FT3 was from 3.67 to 10.43 pmol/l, of FT4 was from 11.2 to 20.1 pmol/l, and of thyroid-stimulating hormone (TSH) was from 0.34 to 5.06 IU/ml. The normal reference range of TG was from 5 to 40 ng/ml, of PTH was from 5 to 20 ng/dl, of serum calcium was 2.25-2.75 mmol/l and of serum phosphorus was from 0.97 to 1.61 mmol/l.

TSH luminescent reagents. FT3 and FT4 reagents were provided by Siemens AG, Munich, Germany. TSH was assessed by the ADVIA Centaur automatic chemiluminescence analyzer. TSH utilizes the immunoradiometric assay method of the direct chemiluminescence technique, and FT4 and FT3 were estimated using the competitive ELISA method of direct chemiluminescence technique. HG detection reagents for the radioimmunoassay method were provided by Beijing Northern Institute of Biological and Technology (Beijing, China).

Statistical analysis. The data were processed using SPSS 19.0 statistical software package (SPSS, Inc., Chicago, IL, USA). The measurement data were presented as mean ± standard deviation (SD). The comparisons between groups were analyzed by means of variance analysis, and the count data were expressed as a percentage. The χ^2 test was used for the comparison between groups. P<0.05 was considered to indicate a statistically significant difference.

Results

General state of patients. Of a total of 160 patients, 24 patients (15%) had cancer metastasis with 11 cases of cervical lymph node metastasis, 7 cases of mediastinal lymph node metastasis, 4 cases of pulmonary metastasis, and 2 cases of bone metastasis. There were 114 cases of total thyroidectomy and 46 cases of subtotal resection. The first ^{131}I dose administered was 2.6-8.2 GBq and the average dose was 6.4+1.2 GBq. The treatment of 'clear residual thyroid tissue' was successful in 66 cases (41.3%). The average treatment time of ^{131}I was 2.8±0.6 therapy sessions. Until the termination of the follow-up period in June 2015, a total of 142 successful cases were identified.

Comparison of PTH, serum calcium and phosphorus levels. Prior to and following the first treatment, and at the end of the follow up, the PTH, serum calcium and phosphorus levels were compared. The difference was not statistically significant (P>0.05). Five patients were identified with persistent hypoparathyroidism and 8 patients with transient hypoparathyroidism (Table I).

Comparison of thyroid function. The TG and FT3 levels were significantly decreased and the difference was statistically significant (P<0.05). There was no significant difference between FT4 and TSH (P>0.05). There were 48 patients with hypothyroidism (30%) (Table II).

Table I. Comparison of PTH, serum calcium and phosphorus levels.

Group	PTH (ng/dl)	Serum calcium (mmol/l)	Phosphorus (mmol/l)
Prior to the first treatment	15.9±3.4	2.6±0.3	0.8±0.3
Following treatment	13.6±3.5	2.5±0.4	0.7±0.2
Until termination of follow-up	10.2±2.8	2.4±0.2	0.7±0.3
F-value	0.527	0.638	0.129
P-value	0.835	0.415	0.637

PTH, parathyroid hormone.

Table II. Comparison of thyroid function.

Group	TG (ng/ml)	FT3 (pmol/l)	FT4 (pmol/l)	TSH (IU/ml)
Prior to the first treatment	4.2±0.5	8.6±1.1	16.9±3.4	0.4±0.1
Following treatment	2.3±0.3	5.4±0.8	13.5±3.2	0.6±0.2
Until termination of follow-up	0.8±0.2	3.7±0.6	12.4±2.9	0.8±0.4
F-value	5.127	4.518	1.532	1.924
P-value	0.032	0.036	0.629	0.088

TG, thyroglobulin; TSH, thyroid-stimulating hormone.

Discussion

Although the degree of malignany is decreased in cases of DTC, recurrence or distant metastasis occurs in approximately 30% of patients (5). Radioactive ^{131}I 'clear residual thyroid tissue' treatment is usually utilized by β rays in ^{131}I to damage the residual thyroid tissue, achieving the effect of maximum reduction of cancer recurrence (6). The parathyroid gland is located near the thyroid gland. In the course of radiation therapy, the radioactive ^{131}I uptake in the thyroid gland produces β ray of ≤2 mm that is likely to damage the adjacent parathyroid gland. The phenomenon of declined adjacent parathyroid tissue function is considered a bystander effect of radiation therapy (7).

The most common complications of the ^{131}I 'clear residual thyroid tissue' treatment include radioactive thyroiditis, radioactive sialadenitis, nausea and vomiting. However, there controversy regarding whether radiation therapy causes the functional impairment of the parathyroid glands (8). As early as 1987, Glazebrook and other researchers demonstrated that the parathyroid function of patients treated with ^{131}I was decreased mainly after 18 months of treatment (9). In subsequent studies, Guven and others demonstrated that the parathyroid function of the patients treated with ^{131}I was decreased mainly after 6 months of treatment (10). In addition, recent findings demonstrated that the level of PTH in the third month after radiation therapy had an insignifant increase, and required 6 months to return to normal (11). In 2004, Chatterjee reported that there was a persistent decrease in parathyroid function in patients with hyperthyroidism after radioactive ^{131}I treatment (12). However, in previous studies it was reported that the dose of ^{131}I radiation did not affect the parathyroid function (13). Therefore, this study determined whether radioactive ^{131}I 'clear residual thyroid tissue' treatment following the resection of differentiated thyroid carcinoma resulted in the decrease of the parathyroid function and the thyroid treatment effect.

The results of the present study have shown that, the initial average dose of ^{131}I at 6.4+1.2 GBq yielded a success rate of 41.3% for 'clear residual thyroid tissue'. Average ^{131}I treatment times were 2.8+0.6 and until the termination of the follow-up at 1.8±0.5 years, the success rate of the treatment had increased to 88.8%. In related studies (14,15), the first ^{131}I dose was associated with the success rate of 'clear residual thyroid tissue'. The treatment dose and number of times treatment was administered were associated with hypothyroidism and the effect of the parathyroid gland. However, unlike previous studies, the results of the present study show that when the PTH, serum calcium and phosphorus levels prior to the initial treatment, following treatment and termination of the follow-up were compared, the difference was not statistically significant. This finding may be associated with the treatment dose and time of treatment. At the same time, our findings show that the appropriate dose and number of times treatment was administered were safe for the function of the parathyroid. In the present study, 5 patients had persistent parathyroid hypofunction and 8 patients had transient parathyroid hypofunction. The total incidence rate was only 8.1%. At the same time, the level of TG was significantly decreased, and the difference was statistically significant. There were 48 cases (30.0%) with parathyroid hypofunction. No serious complications occurred after supplementation of thyroid tablets (16).

In summary, the results have shown that, DTC resection and ^{131}I 'clear residual thyroid tissue' treatment did not significantly impair the parathyroid function, thereby improving the treatment effect.

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