Research Paper

Effect of Iodine 131 and Levothyroxine Sodium Tablet on the Removal Rate of Residual Thyroid Tissue after Thyroid Papillary Carcinoma Surgery

CHEN ZHENG AND N. P. WANG*

Department of Thyroid Surgery, Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou 550001, China

The main objective of this study is to analyze the effect of iodine 131 combined with levothyroxine sodium tablet on the postoperative thyroid papillary carcinoma. Clinical data of 113 patients with postoperative thyroid papillary carcinoma who underwent total resection in our hospital from January 2020 to January 2021 were collected. According to the different treatment methods, patients were divided into group A (n=39) treated with levothyroxine sodium tablet, group B (n=38) treated with iodine 131, and group C (n=36) treated with iodine 131 combined with levothyroxine sodium tablet consecutively for 4 w. The levels of thyroid hormones (free triiodothyronine, free thyroxine, thyroid stimulating hormone), thyroid related antibodies (thyroglobulin, anti-thyroglobulin antibody and anti-thyroid peroxidase antibody), removal rate of residual thyroid tissue, adverse reactions and recurrence were compared. The levels of free triiodothyronine and free thyroxine in group C were higher than those in groups A and B after treatment, while those of thyroid stimulating hormone and thyroid related antibodies were lower than those in groups A and B ($p<0.05$). After treatment, there were no differences in the levels of thyroid hormones and thyroid related antibodies in groups A and B ($p>0.05$). The removal rate of residual thyroid tissue in group C was significantly higher than those in groups A and B, and group B was higher than that of group A ($p<0.05$). There was no significant difference in the adverse reaction rates and recurrence rates among the three groups ($p>0.05$). The recurrence rate of patients within 2 y was similar to that of single iodine 131 or levothyroxine sodium tablet treatment. However, the combined treatment strategy was more prominent in improving thyroid hormones and antibody levels, which improved the removal rate of residual thyroid tissue with good safety.

Key words: Papillary thyroid cancer, iodine 131, levothyroxine sodium tablets, residual thyroid tissue

Papillary Thyroid Cancer (PTC) is a common pathological type in thyroid cancers, which accounts for about 87.5 % of all thyroid cancer cases[1]. In clinical practice, PTC is mainly managed with surgical treatment, surgery is an effective means for treating PTC at present, and the patients require hormone or radionuclide therapy after surgery to consolidate the therapeutic effect. Iodine 131 (^{131}I) is a frequently used method to treat thyroid disease, which has a positive effect on reducing postoperative recurrence[2]. But some research suggests that ^{131}I alone can lead to the phenomenon of hypothyroidism. Levothyroxine sodium tablet is a kind of thyroid hormone drug, which mainly functions to suppress the secretion of Thyroid Stimulating Hormone (TSH) and maintain the physiological function of thyroid[3]. At present, research regarding the application effect of ^{131}I and levothyroxine sodium tablet after PTC surgery is lacking. On this basis, this study collected the clinical data from 113 PTC patients admitted and treated in our hospital to analyze the therapeutic effect of ^{131}I combined with levothyroxine sodium tablet on PTC and the removal rate of residual thyroid tissue.

MATERIALS AND METHODS

General information:

Clinical data of 113 PTC patients admitted and treated in The Affiliated Hospital of Guizhou Medical University from January 2020 to January 2021 were collected. This study was approved by the Ethical Committee of Affiliated Hospital

***Address for correspondence**
E-mail: wangnanpeng197301@163.com

of Guizhou Medical University. Patients with complete clinical data; the diagnosis of PTC was made pathologically and confirmed with the PTC diagnostic criteria recommended in "Guidelines for Diagnosis and Treatment of Thyroid Nodules and Differentiated Thyroid Carcinoma"[4]; patients who undergone surgical indication for total resection, and successfully completed surgical treatment, with thyroid tissue residual revealed after examination; patients with one-sided lesion and all the subjects along with their family members were informed and signed the informed consents are included in the study.

Patients with concurrent infectious and immune diseases; patients receiving relevant treatment recently; patients who were allergic to the therapeutics or intolerant to ^{131}I treatment; and patients with co-existing severe heart, liver and kidney diseases are excluded from the study.

According to the different treatments, patients were divided into group A (n=39), group B (n=38) and group C (n=36). Patients in group A received levothyroxine sodium tablet treatment, including 15 males and 24 females, with the age ranging from 38 y-68 y (average, 49.69±3.71) y. With regard to Tumor, Node and Metastasis (TNM) stage, there were 11 patients with stage II, 22 with stage III and 6 with stage IV. Patients in group B received ^{131}I treatment, including 12 males and 26 females, with the age of 36 y-70 y (average, 48.33±3.15) y. Meanwhile, there were 11 patients with stage II, 18 with stage III and 9 with stage IV. Patients in group C received ^{131}I combined with levothyroxine sodium tablet treatment, including 11 males and 25 females, with the age ranging from 37 y-71 y (average, 50.15±3.44) y. As for TNM stage, 8 patients with stage II, 20 with stage III and 8 with stage IV. There was no significant difference in the general data among the three groups ($p>0.05$).

Research method:

Iodine containing foods and drugs were forbidden at 3 w-4 w before surgery, and the basic examinations were completed at 3 w-4 w after surgery, including thyroid function, liver and kidney function, neck color Doppler ultrasound and Computed Tomography (CT), so as to evaluate the thyroid tissue residual and exclude the contraindications of ^{131}I treatment.

Group A patients were given oral administration of levothyroxine sodium tablet (Sichuan Hairong Pharmaceutical Co., Ltd of Yangtze River Pharmacy Group; SFDA approval number: H20041605 with specification: 50 μg) at a dose of 25-50 μg each time, with the maximum daily dose of <100 μg/d. The dose gradually increased thereafter, with an increment of 25-50 μg at the intervals of 2 w, and the maintenance dose was 50-200 μg to maintain basic metabolism. Group B patients were treated with 5.5-7.4 GBq of ^{131}I at 4 w after surgery at a dose of 150-200 mgI adjusted according to the basic patient conditions. ^{131}I whole-body imaging examination was carried out at 5 d- 7 d after surgery to determine the postoperative thyroid tissue residue. Group C patients were treated with levothyroxine sodium tablets in an identical method to that of group A, ^{131}I treatment was administered by the same method as group B, and all the three groups were treated for 4 w consecutively.

Observational indices:

Thyroid hormone levels were compared by extracting 8-10 ml of fasting venous blood from each patient before and after treatment, and centrifuged to collect serum. Thereafter, the levels of Free Triiodothyronine (FT3), Free Thyroxine (FT4) and TSH in serum were measured by laboratory personnel in our hospital using the Mindray BS-380 fully automatic biochemical analyzer (Nanjingdeng Medicine Co., Ltd) equipped with relevant reagents, in strict line with specific instructions.

Before and after treatment, the levels of Thyroglobulin (Tg), anti-Thyroglobulin Antibody (TGAb) and anti-Thyroid Peroxidase Antibody (TPOAb) in patients were detected with the electrochemiluminescence method. The reagents used were provided by Shanghai Kemei Boyang Diagnostics Technology Co., Ltd.

The removal rate of residual thyroid tissue was evaluated and compared[5]. Patients who had normal serum Tg level and whose ^{131}I whole body imaging examination revealed complete disappearance of residual thyroid tissue were classified as complete removal. Patients with stable basic conditions, reduced Tg level and markedly shrunk thyroid tissue revealed by ^{131}I whole body imaging examination were classified as partial removal. Patients with unimproved condition, unchanged Tg levels after treatment and unchanged residual

thyroid tissue revealed by ^{131}I whole body imaging examination were classified as non-removal.

Removal rate=(Complete removal+partial removal)/total cases×100 %

The incidence rates of adverse reactions like chest distress, insomnia, parotid pain and rash and recurrence rate were calculated. The patients were followed up for 2 y after treatment by means of reexamination in the hospital using WeChat and telephone.

Statistical analysis:

The Statistical Package for Social Sciences (SPSS) version 20.0 software was adopted for statistical analysis. Measurement data were described as mean±standard deviation ($\bar{x}\pm s$) and analyzed by t-test. Variance test was applied in multi-group comparisons, and Student-Newman-Keuls (SNK-q) test was utilized in further pairwise comparisons. Enumeration data were expressed as rate or constituent ratio and analyzed by Chi-square (χ^2) test. The $p<0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Before treatment, the differences in thyroid hormone levels among three groups were not statistically significant. After treatment, FT3 and FT4 levels elevated in all the three groups, while TSH level decreased ($p<0.05$). The FT3 and FT4 levels in group C were higher than those in groups A and B, while the TSH level was lower than those in groups A and B ($p<0.05$). There were no significant differences in FT3, FT4 and TSH levels between groups A and B ($p>0.05$) (Table 1).

Before treatment, the differences in thyroid related antibody levels of the three groups were not statistically significant ($p>0.05$). After treatment, the levels of Tg, TGAb and TPOAb of the three groups decreased ($p<0.05$). Meanwhile, the levels of Tg, TGAb and TPOAb in group C apparently decreased compared to groups A and B ($p<0.05$), and there was no significant difference in Tg, TGAb or TPOAb levels between groups A and B ($p>0.05$) (Table 2).

The removal rate of residual thyroid tissue in group C was 97.22 %, while that in group A was 51.28 % and group B was 81.57 %. The removal rate of residual thyroid tissue in group C was apparently higher than those in groups A and B, while that in group B was higher than group A ($p<0.05$) (Table 3).

The adverse reaction rate in group A was 5.12 %, and those in groups B and C were 7.89 % and 13.89 %, respectively. There was no significant difference in adverse reaction rate among the three groups ($p>0.05$). After symptomatic treatment, the adverse reactions in patients gradually improved. No recurrence was reported in patients of group C, while the recurrence rates in groups A and B were 7.69 % and 5.26 % respectively, and the difference in recurrence rate among the three groups was not significant ($p>0.05$) (Table 4).

At present, PTC is mainly treated with surgery, and most patients can obtain satisfactory clinical effects after treatment. But some scholars discover through follow-up research that, recurrence and hypothyroidism can also be reported after surgery[6]. Therefore, the treatment methods to reduce the recurrence rate and improve the therapeutic effect are the urgent problems to be solved in clinical practice at present.

TABLE 1: COMPARISON OF THYROID HORMONE LEVELS AMONG THREE GROUPS OF PATIENTS ($\bar{x}\pm s$)

Group	n	FT3 (pmol/l)		FT4 (pmol/l)		TSH (mU/l)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
A	39	2.12±0.33	5.96±0.59[a]	11.54±1.55	17.26±2.11[a]	4.36±0.77	2.11±0.33[a]
B	38	2.09±0.27	5.87±0.37[a]	12.03±1.50	18.15±2.30[a]	4.22±0.61	2.16±0.15[a]
C	36	2.13±0.36	7.35±0.21[abc]	11.48±1.33	22.33±2.79[abc]	4.30±0.80	0.71±0.10[abc]
F	-	0.16	140.38	1.59	46.71	0.36	515.18
p	-	0.855	<0.001	0.207	<0.001	0.701	<0.001

Note: [a]$p<0.05$, indicates comparison of the same group before and after treatment; [b]$p<0.05$, indicates comparison with group A and [c]$p<0.05$, indicates comparison with group B

TABLE 2: COMPARISON OF THYROID RELATED ANTIBODY LEVELS AMONG THREE GROUPS OF PATIENTS (x̄±s)

Group	n	Tg (ng/ml)		TGAb (U/ml)		TPOAb (U/ml)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
A	39	12.16±1.33	0.91±0.33[a]	168.96±13.58	38.16±5.88[a]	211.60±13.44	34.15±2.69[a]
B	38	11.98±1.71	0.86±0.31[a]	166.85±13.47	37.85±5.70[a]	213.14±13.60	33.20±2.41[a]
C	36	12.20±1.54	0.61±0.10[abc]	1.69.58±13.41	30.20±5.24[abc]	212.46±13.58	28.30±2.34[abc]
F	-	0.22	13.04	0.42	23.68	0.13	58.73
p	-	0.803	<0.001	0.657	<0.001	0.882	<0.001

Note: [a]p<0.05, indicates comparison of the same group before and after treatment; [b]p<0.05, indicates comparison with group A and [c]p<0.05, indicates comparison with group B

TABLE 3: COMPARISON OF REMOVAL RATE OF RESIDUAL THYROID TISSUE AMONG THREE GROUPS OF PATIENTS, n (%)

Group	n	Complete removal	Partial removal	Non-removal	Removal rate
A	39	2 (5.13)	18 (46.15)	19 (48.72)	20 (51.28)
B	38	18 (47.37)	13 (34.21)	7 (18.42)	31 (81.57)[a]
C	36	25 (69.44)	10 (27.78)	1 (2.78)	35 (97.22)[ab]
χ^2	-				22.669
p	-				0

Note: [a]p<0.05, indicates comparison with group A and [b]p<0.05, indicates comparison with group B

TABLE 4: COMPARISON OF ADVERSE REACTIONS AND RECURRENCE RATES AMONG THREE GROUPS OF PATIENTS, n (%)

Group	n	Chest distress	Insomnia	Parotid pain	Rash	Overall incidence rate	Recurrence
A	39	0 (0.00)	1 (2.56)	1 (2.56)	0 (0.00)	2 (5.12)	3 (7.69)
B	38	1 (2.63)	1 (2.63)	0 (0.00)	1 (2.63)	3 (7.89)	2 (5.26)
C	36	0 (0.00)	1 (2.78)	2 (5.56)	1 (2.78)	4 (11.11)	0 (0.00)
χ^2	-					0.914	2.714
p	-					0.633	0.257

Thyroid hormones can promote development/metabolism in the body, improve the nervous system excitation, increase the heart rate and respiratory saturation rate[7]. There is TSH receptor on the PTC cell membrane and TSH can affect cancer cell growth in the patients. After the loss of TSH stimulation, tumor growth slows down gradually and may even stops[8]. After PTC surgery, the FT3 and FT4 levels apparently decrease, while TSH level increases, which thus stimulate the development of thyroid cancer, promote its recurrence, and are unfavorable conditions for postoperative recovery[9]. Consequently, positive suppression of TSH is needed after PTC surgery, and in clinical practice, life-long administration of thyroid hormone tablet is recommended for total thyroidectomy or near-total thyroidectomy to suppress TSH[10]. Levothyroxine sodium tablet is a kind of thyroid hormone drug and one of the common drugs used to inhibit TSH secretion. Previous research has indicated that levothyroxine sodium tablet can mitigate thyroid oxidative injury and reduce the TGAb and Tg levels[11].

^{131}I is the radioisotope of iodine element, and its half-life period is 8.03 d. Clinically, ^{131}I can be directly applied in clinical treatment in a form of sodium iodine[12,13]. Previous studies have suggested that, ^{131}I plays a key role in decreasing the tumor metastatic lesions and improve patient prognosis[14]. According to our results, compared with ^{131}I and levothyroxine sodium tablet treatment alone, the combined treatment of the two apparently reduced the TSH, Tg, TGAb and TPOAb levels, and increased the FT3 and FT4

levels, revealing the better therapeutic effect of combined treatment and promotion of thyroid functional recovery. It has also been demonstrated previously that, ^{131}I combined with levothyroxine sodium tablet treatment can better promote thyroid functional recovery in patients[15]. The reason may be that the combined treatment can aggressively suppress the TSH secretion in cells, maintain the thyroid physiological functions and weaken the cancer cell invasion capacity[16,17]. Thyroid surgery can attain favorable therapeutic efficacy, but some patients experience disease metastasis, and surgical treatment alone cannot completely clean the cancerous tissue[18]. According to our research results, the removal rate of residual thyroid tissue in group A was the lowest, followed by group B, while the removal rate in group C was the highest (97.22 %). This indicates that combined treatment can improve the removal rate of residual thyroid tissue, which can provide favorable medical basis of patient prognosis. Based on previous research results, this may be related to the fact that, ^{131}I can actively eliminate the undetected tumor lesion tissues and eliminate the Tg source, while levothyroxine sodium tablet can suppress TSH secretion and block tumor tissue growth[19,20]. As discovered when comparing the adverse reaction and recurrence rates, there was no significant difference in adverse reaction or recurrence rate among the three groups, suggesting the favorable safety of combined treatment. However, some research studies indicate that the recurrence rate in thyroid cancer patients after ^{131}I treatment is lower compared to the levothyroxine sodium tablet treatment[21]. Such result is different from our results, which may be related to the long follow-up period and small sample size in this study.

In summary, when applying ^{131}I combined with levothyroxine sodium tablet in the treatment of PTC after PTC surgery, the 2 y recurrence rate of patients is similar to that of ^{131}I or levothyroxine sodium tablet treatment alone, but the combined treatment can more significantly improve the thyroid hormone and antibody levels, and increase the removal rate of residual thyroid tissue, with favorable safety.

Conflict of interests:

The authors declared no conflict of interests.

REFERENCES

1. Sun Y, Wu Y. Progress in diagnosis and treatment of isthmic papillary thyroid carcinoma. Chin J Endocr Surg 2020;14(1):77-9.
2. Yang Y, Ding L, Li Y, Xuan C. Hsa_circ_0039411 promotes tumorigenesis and progression of papillary thyroid cancer by miR-1179/ABCA9 and miR-1205/MTA1 signaling pathways. J Cell Physiol 2020;235(2):1321-9.
3. Li M. Effect of levothyroxine sodium tablet in treating senile hypothyroidism. Chongqing Med J 2019;48(2):96-8.
4. Chinese Society of Endocrinology, Endocrinology Group, Surgery Society of Chinese Medical Association, Head and Neck Tumor Committee of Chinese Anti-cancer Association. Guidelines for the diagnosis and treatment of thyroid nodules and differentiated thyroid carcinoma. Chin J Nucl Med Mol Imaging 2013;33(2):149-94.
5. Liu Y, Cheng T, Xu T. Predictive value of lymph node metastasis rate for clinical outcome of patients with papillary thyroid carcinoma after ^{131}I treatment. Chin J Clin Res 2021;34(1):52-5.
6. Dong P. Therapeutic effect and prognosis of patients with differentiated thyroid cancer under different age backgrounds of ^{131}I chemotherapy. Pract J Cancer 2019;34(5):818-20.
7. Xindi L, Qing Z, Yuan Z, Hui Z, Liangsicheng T, Zhiyong L. Relationship between the ratio of pre-ablation stimulated thyroglobulin to corresponding thyroid stimulating hormone and the excellent response in patients with papillary thyroid carcinoma. J Mod Oncol 2020;28(10):1646-51.
8. Zhao W, Zhang Y. Effect of large-dose ^{131}I treatment on the removal of residual thyroid tissue and metastatic lesion after surgery for differentiated thyroid carcinoma and the influencing factors. J Inner Mongolia Med Univ 2019;41(3):253-5.
9. Xie J, Shi X. Effect of total laparoscopic thyroidectomy combined with Yangyin Yishen therapy on differentiated thyroid carcinoma and its effect on quality of life. Mod J Int Trad Chin West Med 2019;28(9):951-4.
10. Crockett DJ, Faucett EA, Gnagi SH. Thyroid nodule/differentiated thyroid carcinoma in the pediatric population. Pediatr Ann 2021;50(7):e282-5.
11. Li H, Dai H, Li H, Li B, Shao Y. Polymorphisms of the highly expressed IL-6 gene in the papillary thyroid cancer susceptibility among Chinese. Curr Mol Med 2019;19(6):443-51.
12. Zhao T, Zhao T, Wei Y. Effect of levothyroxine sodium tablet combined with selenious yeast tablet on the immune function after thyroid cancer. Chin J Clin 2021;49(11):1328-30.
13. Zhang E. Comparisons of the clinical effects and adverse reactions between levothyroxine sodium tablet and ^{131}I radionuclide in the treatment of nodular goiter accompanied by hyperthyroidism. Chin Remedies Clin 2020;20(19):3236-8.
14. Wang Y, Liu Z, Liu Y, Qiu G, Zhou Y, Ren M. Clinical efficacy and influencing factors of ^{131}I in the removal of residual thyroid tissue after differentiated thyroid carcinoma. Pract J Cancer 2020;35(4):578-82.
15. Tuttle RM, Ahuja S, Avram AM, Bernet VJ, Bourguet P, Daniels GH, *et al.* Controversies, consensus, and collaboration in the use of ^{131}I therapy in differentiated thyroid cancer: A joint statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association. Thyroid 2019;29(4):461-70.

16. Wang Y, Cao X, Jiang T. Effect of ^{131}I treatment on the immunoregulation in patients after papillary thyroid cancer surgery. J Harbin Med Univ 2021;55(4):402-6.
17. Nie W. m6A mRNA methylation initiated by METTL3 inhibits KDR translation to increase the efficacy of ^{131}I therapy in papillary thyroid carcinoma. J Radioanal Nucl Chem 2023;332(7):2749-58.
18. Ma P. Clinical effect of levothyroxine sodium tablet combined with thyroid mass resection for the treatment of thyroid nodule. Shanxi Med J 2021;50(1):73-5.
19. Zhao T, Zhao T, Wei Y. Clinical effect of levothyroxine sodium tablet combined with selenious yeast tablet after differentiated thyroid carcinoma and the influences on thyroid hormones and autoantibody levels. Chin J Clin 2022;50(3):301-4.
20. Miccoli P, Materazzi G, Rossi L. Levothyroxine therapy in thyrodectomized patients. Front Endocrinol 2021;11:1-7.
21. Guo L, Yao L, Liu B. Study on the clinical efficacy of iodine ^{131} combined with levothyroxine sodium in the treatment of differentiated thyroid cancer. J Clin Exp Med 2022;21(5):542-5.

This article was originally published in a special issue, "Recent Progression in Pharmacological and Health Sciences" Indian J Pharm Sci 2024:86(2) Spl Issue "14-19"