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Risk factors of hypoparathyroidism following total thyroidectomy with central lymph node dissection

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Abstract

The risk factors of hypoparathyroidism after total thyroidectomy (TT) with central lymph node dissection (CND) have not been completely defined. The aim of the study was to evaluate the risk factors of hypoparathyroidism after the surgery.

We retrospectively reviewed our patients who underwent TT and CND (including lateral lymph node dissection) for thyroid carcinoma between January 2013 and June 2016. According to the postoperative serum levels of parathyroid hormone within 6 months, the patients were divided into normal, transient hypoparathyroidism, and permanent hypoparathyroidism groups. The clinicopathologic characteristics and surgical details were compared among the 3 groups. The risk factors of hypoparathyroidism were investigated by univariate and multivariate analyses.

Of the 903 patients, 399 (44.2%) were found to have transient hypoparathyroidism and 10 (1.1%) had permanent hypoparathyroidism. On multivariate analysis, female gender ($P < .001$), nonuse of carbon nanoparticles ($P = .038$), parathyroid autotransplantation ($P < .001$), accidental parathyroid resection ($P = .004$), and bilateral CND (BCND, $P = .003$) were the independent risk factors of transient hypoparathyroidism; nonuse of carbon nanoparticles ($P = .041$) and a tumor in the upper pole of thyroid gland ($P = .031$) were the independent risk factors of permanent hypoparathyroidism. Patients with transient hypoparathyroidism were more likely to develop permanent hypoparathyroidism when they had hypertension ($P = .026$) and a tumor in the upper pole of thyroid gland ($P = .010$).

Precise surgical techniques and carbon nanoparticles suspension should be applied for in situ preservation of parathyroid glands (PGs) in thyroid carcinoma patients, especially in females with hypertension and a tumor in the upper pole of thyroid gland. Autotransplantation is only performed when a PG is resected inadvertently or devascularized. TT with BCND should be better performed by an experienced surgeon to reduce the incidence of hypoparathyroidism.

Abbreviations: BCND = bilateral central lymph node dissection, CI = confidence interval, CND = central lymph node dissection, DTC = differentiated thyroid carcinoma, LND = lateral lymph node dissection, MTC = medullary thyroid carcinoma, PG = parathyroid gland, PTC = papillary thyroid cancer, PTH = parathyroid hormone, TT = total thyroidectomy, UCND = unilateral central lymph node dissection.

Keywords: central lymph node dissection, hypoparathyroidism, risk factor, total thyroidectomy

1. Introduction

Total thyroidectomy (TT) with central lymph node dissection (CND) can decrease locoregional recurrence in patients with thyroid carcinoma.[1,2] Central lymph node metastasis has important prognostic values for accurate clinical staging and postoperative treatment.[3,4] Therefore, TT with CND is widely accepted for the treatment of thyroid carcinoma.[5] However, TT with CND, especially with bilateral CND (BCND), is associated with high incidence of transient or permanent hypoparathyroidism.[6] The primary causes of postoperative hypoparathyroidism are direct injury, devascularization, venous engorgement, or inadvertent excision of the parathyroid gland (PG).[7,8] Hypoparathyroidism is a major cause of prolonged outpatient follow-up and hospital care cost.[9] In addition, the quality of life in patients with permanent hypoparathyroidism who require long-term calcium and vitamin D supplementation is seriously affected. Therefore, many surgeons are interested in finding risk factors to predict postoperative hypoparathyroidism and beginning treatment early to prevent serious complications.

Although numerous studies have looked for risk factors of hypoparathyroidism after thyroidectomy, the causative factors of the complication have not been completely defined. Paek et al[10] reported that PG autotransplantation, BCND, gross extrathyroidal extension, and accidental PG resection were associated with postoperative hypoparathyroidism, whereas Cho et al[11] found that female gender, extent of CND, and inadvertent parathyroidectomy were significant risk factors of transient hypoparathyroidism, and no factors correlated significantly with permanent hypoparathyroidism. In addition, the risk factors of hypoparathyroidism after TT with CND are still unknown. Therefore, the aim of the present study was to analyze the risk factors of hypoparathyroidism following TT with CND.

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2. Patients and methods

2.1. Patients

All the patients with thyroid carcinoma who underwent at least TT with unilateral CND (UCND) in the Department of Thyroid Surgery, West China Hospital of Sichuan University between January 2013 and June 2016 were included retrospectively. All surgeries were performed by an experienced surgeon. Exclusion criteria included previous thyroid or parathyroid surgery, preoperative PGs dysfunction, multiple endocrine neoplasia 2A, lobectomy, TT, near-TT, and incomplete data. According to the postoperative serum levels of parathyroid hormone (PTH) within 6 months, the patients were divided into normal, transient hypoparathyroidism, and permanent hypoparathyroidism groups. All patients in our department were informed and agreed to follow-up meetings at least 6 months after surgery. The study was approved by the medical ethics committee of West China Hospital, Sichuan University.

2.2. Indications of TT with lymph node dissection

In our department, the indications for TT are as followed: high risk; bilateral or multifocal differentiated thyroid carcinomas (DTC); unilateral DTC with contralateral nodule(s); isthmus DTC; DTC > 4 cm (stage T3); DTC with extrathyroidal invasion (stages T3 and T4); pathologic variables including tall cell variant, diffuse sclerosis variant, solid variant, and follicular variant; DTC with bilateral central lymph node or lateral lymph node metastases; DTC with distant metastases; medullary thyroid carcinoma (MTC); and TERT promoter mutation. UCND is performed routinely in patients with papillary thyroid carcinoma (PTC). The indications for BCND include: bilateral PTC; isthmus PTC; PTC with stage T3 and T4; prelaryngeal and pretracheal lymph node metastases; bilateral central lymph node or lateral lymph node metastases; MTC; and TERT promoter mutation. UCND or BCND is performed in patients with follicular thyroid carcinoma if there are ipsilateral or bilateral central lymph node metastases. Lateral lymph node dissection (LND) is performed on patients with lateral lymph node metastases or MTC.

2.3. Surgical procedures

Surgical procedures of TT with lymph node dissection were described as previous.[12] The use of carbon nanoparticles suspension (Lai Mei Pharmaceutical Co, Chongqing, China) was determined by the surgeon. Autotransplantation was performed when a PG was resected inadvertently or devascularized. If a PG could not be retained in situ, a small part was sent to intraoperative frozen biopsy and the remaining was wrapped in gauze which was soaked with normal saline solution. When the PG was ascertained, it was immediately chopped into 1 mm^3 fragments and buried into several pockets in the sternocleidomastoid muscle. Intraoperative neuromonitoring (Medtronic NIM-Response 2.0) was applied to identify and protect recurrent laryngeal nerve.

2.4. Perioperative management

Perioperative management of all patients was standardized. Preoperative examinations included serum calcium, PTH, thyroid function, neck ultrasound, and laryngoscopy. Serum calcium and PTH were routinely tested 1 day, 30 days, and 6 months after surgery. Patients with symptomatic hypocalcemia were treated with oral or intravenous calcium supplementation. Postoperative hypoparathyroidism was defined as any drop in serum PTH below the normal limit (normal range, 1.6–6.9 pmol/L). Permanent hypoparathyroidism was defined as lack of recovery of serum PTH to the normal range within 6 months. If serum PTH returned to normal within 6 months, it was classified as transient hypoparathyroidism.[13]

2.5. Data collection

All the data were collected retrospectively, including patient demographics, preoperative examination, pathological characteristics of the thyroid carcinoma, surgical details, PG autotransplantation, accidental PG resection (found in the surgical specimens by pathologists), postoperative examination, and complications.

2.6. Statistical analysis

The statistical analyses were conducted with SPSS computer software (version 21.0). Parametric continuous variables with values expressed as mean ± standard deviation. Statistical comparison between groups was calculated using the χ^2 test or Student *t* test. A multivariate analysis was performed by using logistic regression to identify the perioperative factors, which were considered to influence on postoperative hypoparathyroidism. The results of the multivariate analysis were expressed as odds ratio, 95% confidence interval, and *P* value. Statistical significance was set at $P < .05$.

3. Results

Of the 1492 patients whose medical records were reviewed, 903 met the study criteria and were included in the present analysis (Fig. 1). Of the 903 patients, 649 were female and 254 were male. The mean age was 43.2 ± 13.9 years. Four patients were diagnosed as follicular thyroid carcinoma and 15 were diagnosed as MTC. The remaining patients were diagnosed as PTC. TT with UCND and TT with BCND were performed on 288 and 465 patients, respectively. A total of 121 patients underwent TT with BCND and unilateral LND, and 29 accepted TT with BCND and bilateral LND. Among the 903 patients, postoperative hypoparathyroidism occurred in 409 patients (45.3%), transient hypoparathyroidism in 399 patients (44.2%), and permanent hypoparathyroidism in 10 patients (1.1%).

In comparing patients with transient hypoparathyroidism and without hypoparathyroidism, univariate analysis revealed that transient hypoparathyroidism was more common in patients with female gender ($P = .001$), nonuse of carbon nanoparticles ($P = .021$), bilateral carcinoma ($P = .013$), cN1 stage ($P = .007$), accidental PG resection ($P = .004$), PG autotransplantation ($P < .001$), and BCND ($P < .001$) (Table 1). No statistically significant association was found for age, body mass index, comorbidity, preoperative serum levels of PTH and calcium, tumor location, largest tumor size, largest size of lymph nodes, multifocality, gross extrathyroidal extension, numbers of harvested and metastatic lymph nodes, and pN stage (all $P > .05$). Multivariate analysis demonstrated that female gender ($P < .001$), nonuse of carbon nanoparticles ($P = .038$), PG autotransplantation ($P < .001$), accidental PG resection ($P = .004$), and BCND ($P = .003$) were the independent risk factors of transient hypoparathyroidism (Table 2).

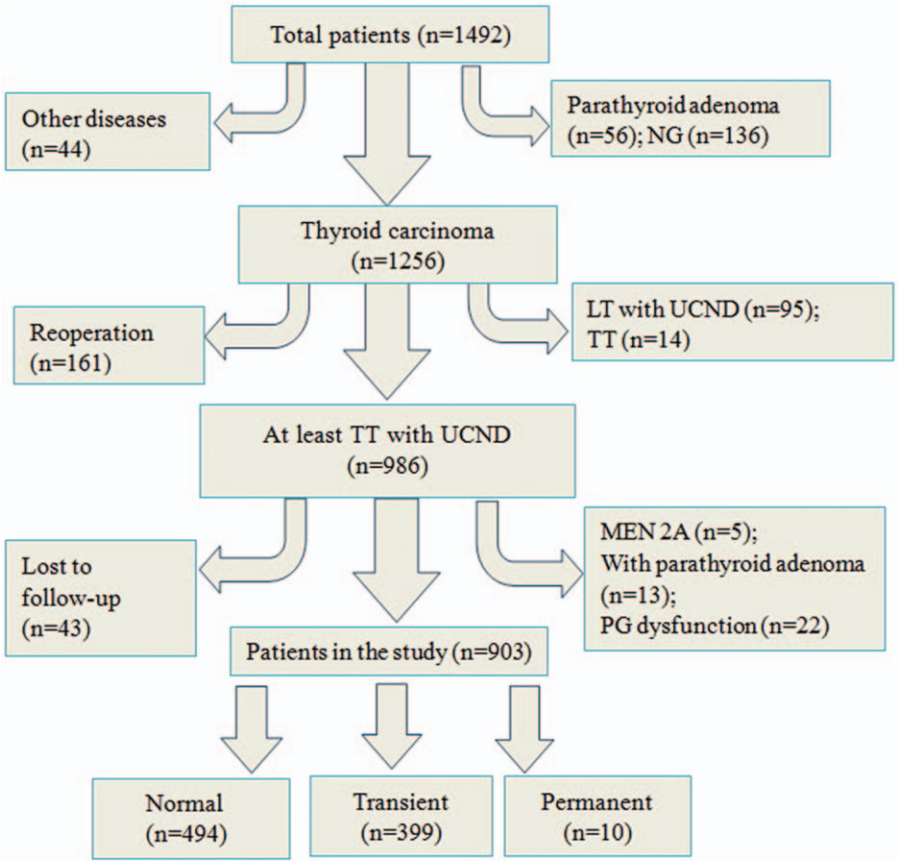

Figure 1. Flow chart of the patients investigated. LT = lobectomy, MEN = multiple endocrine neoplasia, NG = nodular goiter, PG = parathyroid gland, TT = total thyroidectomy, UCND = unilateral central lymph node dissection.

Table 1

Variables of patients affecting the development of hypoparathyroidism at univariate analysis.

Variables	Normal (n = 494)	Transient (n = 399)	Permanent (n = 10)	*P*1	*P*2
Gender (female/male)	333/161	308/91	8/2	.001	.512
Age (<45/≥45), y	262/232	236/163	4/6	.068	.528
BMI, kg/m^2	23.5 ± 3.4	23.2 ± 3.4	23.4 ± 4.1	.247	.933
Hypertension	66	37	3	.057	.145
Diabetes	12	13	0	.455	–
Hypothyroidism	6	7	0	.503	–
Graves' disease	16	9	0	.576	–
Thyroiditis	141	120	3	.617	>.99
Nodular goiter	288	232	5	.963	.749
Preoperative PTH, pmol/L	4.93 ± 1.09	4.71 ± 1.18	4.37 ± 1.69	.100	.326
Preoperative calcium, mmol/L	2.30 ± 0.12	2.32 ± 0.10	2.28 ± 0.16	.524	.390
Carbon nanoparticles	449	343	7	.021	.026
PG autotransplantation	277	297	5	<.001	.755
Accidental PG resection	17	31	2	.004	.006
Tumor location (upper/middle/lower/isthmus)	141/197/120/36	93/173/103/30	6/3/1/0	.366	.030
Largest tumor size, mm	13.9 ± 9.2	14.9 ± 10.5	15.7 ± 12.8	.131	.242
cN stage (cN0/cN1)	386/108	280/119	6/4	.007	.240
Largest size of lymph nodes, mm	12.3 ± 5.0	12.5 ± 5.3	16.0 ± 6.2	.974	.197
Surgery (UCND/≥BCND)	188/306	97/302	3/7	<.001	.749
Multifocality	110	111	2	.056	>.99
Bilateral carcinoma	89	99	2	.013	>.99
Gross extrathyroidal extension	179	148	6	.791	.182
Number of harvested lymph nodes*	11.6 ± 6.4	12.5 ± 6.5	12.9 ± 9.6	.065	.537
Number of metastatic lymph nodes*	2.8 ± 3.8	3.0 ± 4.3	3.0 ± 3.4	.811	.840
pN stage (pN0/pN1)	181/313	125/274	3/7	.096	.753

BCND = bilateral central lymph node dissection, BMI = body mass index, *P*1 = normal versus transient, *P*2 = normal versus permanent, PG = parathyroid gland, PTH = parathyroid hormone, UCND = unilateral central lymph node dissection.

* Number of lymph nodes in the central compartment.

Table 2

Variables of patients affecting the development of hypoparathyroidism at multivariate analysis.

Variables	Odds ratio	95% CI	*P*1	*P*2	*P*3
Gender (female)	1.818	1.327–2.491	<.001		
PG autotransplantation	2.296	1.701–3.100	<.001		
Accidental PG resection	2.538	1.347–4.781	.004		
Surgery (≥BCND)	1.597	0.958–1.892	.003		
Carbon nanoparticles	0.630	0.408–0.974	.038		
	0.255	0.059–0.962		.041	
Tumor location (upper)	4.273	1.145–15.941		.031	
	5.674	1.516–21.233			.010
Hypertension	5.226	1.223–22.337			.026

BCND = bilateral central lymph node dissection, CI = confidence interval, *P*1 = normal versus transient, *P*2 = normal versus permanent, *P*3 = transient versus permanent, PG = parathyroid gland.

In comparing patients with permanent hypoparathyroidism and without hypoparathyroidism, factors found on univariate analysis that significantly increased the risk of permanent hypoparathyroidism were nonuse of carbon nanoparticles ($P=.026$), accidental PG resection ($P=.006$), and a tumor in the upper pole of thyroid gland ($P=.030$) (Table 1). After logistic regression analysis, nonuse of carbon nanoparticles ($P=.041$) and a tumor in the upper pole of thyroid gland ($P=.031$) were the significant factors that affected the development of permanent hypoparathyroidism (Table 2).

In comparing patients with permanent hypoparathyroidism and transient hypoparathyroidism, univariate analysis revealed that permanent hypoparathyroidism was more common than transient hypoparathyroidism for hypertension ($P=.029$), a tumor in the upper pole of thyroid gland ($P=.016$), and cN1 stage ($P=.041$). Multivariate analysis of the 3 factors revealed that patients with transient hypoparathyroidism were more likely to develop permanent hypoparathyroidism when they had hypertension ($P=.026$) and a tumor in the upper pole of thyroid gland ($P=.010$) (Table 2).

4. Discussion

Hypoparathyroidism is the most common significant complication following TT with CND, with the reported incidence varying from 14% to 51.9% in patients with transient hypoparathyroidism and 0% to 16.2% in those with permanent hypoparathyroidism.[2,14,15] In the current study, the incidence of transient and permanent hypoparathyroidism were 44.2% and 1.1%, which is in line with previous studies. Various factors may cause the development of hypoparathyroidism following TT with CND. Numerous studies have investigated the possible risk factors of postoperative hypoparathyroidism,[10,11] some of which have been generally accepted. Nevertheless, establishing these risk factors remains a challenge.

The results of the present study revealed female gender, nonuse of carbon nanoparticles, PG autotransplantation, accidental PG resection, and BCND as significant risk factors for postoperative transient hypoparathyroidism. Nonuse of carbon nanoparticles and a tumor in the upper pole of thyroid gland were identified as significant risk factors for permanent hypoparathyroidism. In addition, patients with transient hypoparathyroidism were more likely to develop permanent hypoparathyroidism when they had hypertension and a primary tumor in the upper pole of thyroid gland.

In this study, females appeared to encounter postoperative transient hypoparathyroidism almost twice as frequently as males. Although female gender was reported as an independent risk factor for postoperative transient hypoparathyroidism,[11,16] the exact mechanisms underlying the gender disparity can only be speculated. Previous studies have reported that differences in gender may exist at a number of physiologic and anatomic levels. First, the gender difference may be related to the effects of sex steroids on PTH secretion.[17] Second, patients of different genders may have various regulators of monoclonal proliferation and mitosis of PG tissue.[18,19] Third, anatomic and morphologic differences of PG may exist between male and female patients.[20,21] Therefore, this implies that females may benefit from earlier and possibly preoperative calcium supplementation to reduce the occurrence of hypocalcemic symptom.

Carbon nanoparticles suspension was firstly considered as a protective factor for transient and permanent hypoparathyroidism, which further confirms its effectiveness on PG protection. In recent years, many researches indicated that carbon nanoparticles suspension could significantly reduce the incidence of hypoparathyroidism after TT with CND.[12,22,23] Carbon nanoparticles could only pass through lymphatic capillaries rather than blood capillaries due to the difference in permeability. There are rich lymphatics and lymphatic capillaries in thyroid gland, whereas almost none within the PG.[24] As a result, carbon nanoparticles suspension can make thyroid gland and the surrounding lymph nodes black-stained, but not for PGs, which facilitates lymph node dissection and PG preservation.[25] Hence, we recommend application of carbon nanoparticles suspension during TT with CND, especially with BCND, to lower the incidence of postoperative hypoparathyroidism.

Whether PG autotransplantation can prevent postoperative hypoparathyroidism is still a controversial issue. At present, the general recommendation is firstly to preserve all PGs in situ during the surgical procedure. Autotransplantation is only performed as a remedial measure when a PG is resected inadvertently or devascularized. All authors agree that PG autotransplantation causes higher incidence of transient hypoparathyroidism, but some have proposed that it prevents postoperative permanent hypoparathyroidism in the long-term follow-up.[26,27] Some studies, however, reported that both PG autotransplantation and accidental parathyroidectomy increased the prevalence of transient and permanent hypoparathyroidism.[28,29] In the present study, we found that PG autotransplantation and accidental PG resection were closely correlated with transient hypoparathyroidism, which is in accordance with the previous studies. But the 2 factors were found no significant influence on the occurrence of permanent hypoparathyroidism. This finding can probably be explained by the fact that there is a strong association between permanent hypoparathyroidism and the number of autotransplanted and/or accidentally resected

PGs.[13,30] Most patients in our study had autotransplantation and/or inadvertent resection of no more than 2 PGs. Precise surgical techniques are needed to try to preserve all the PGs in situ. Surgeons should take care not to unintentionally resect any of the PGs during CND. PGs should also be carefully searched in all surgical specimens before sending for pathologic examination.

Most literatures have shown that routine BCND is related to an increased incidence of postoperative transient and permanent hypoparathyroidism.[31,32] A previous study reported that the rates of transient and permanent hypoparathyroidism following TT with BCND were 51.9% and 16.2%, while they were 36.1% and 7% after TT with UCND (all $P < .05$).[15] However, 1 study found no correlation between CND and hypoparathyroidism.[9] In our study, multivariate analysis also revealed that BCND had no statistically significant relation with permanent hypoparathyroidism, which is contrary to the findings of the previous studies. The result may be attributed to the surgeon's experience, which has been regarded as the most important risk factor for postoperative complications after thyroidectomy.[10,33] For this reason, after careful consideration of benefit, TT with BCND should be better performed by an experienced surgeon.

Interestingly, gross extrathyroidal extension and the number of harvested lymph nodes were not associated with either transient or permanent hypoparathyroidism, whereas a tumor in the upper pole of thyroid gland was firstly identified as a risk factor of permanent hypoparathyroidism following TT with CND. This finding may probably be explained by the facts that more difficult to identify superior PGs, more direct invasion to superior PGs, and more difficult to preserve superior PGs in situ are noted when a primary tumor locates in the upper pole than other sites of thyroid gland. It is of interest to discover that transient hypoparathyroidism patients with hypertension tend to develop permanent hypoparathyroidism than nonhypertensive patients. Hypertension can affect angiogenesis and delay the healing process to vascular injury.[34,35] So, these patients may benefit from ameliorating the microcirculation to reduce the occurrence of permanent hypoparathyroidism.

5. Conclusions

In conclusion, this study provides potentially useful information to prevent the occurrence of hypoparathyroidism after TT with CND. We recommend combination precise surgical techniques with application of carbon nanoparticles suspension for in situ preservation of PGs in thyroid carcinoma patients, especially in females with hypertension and a tumor in the upper pole of thyroid gland. Autotransplantation is only performed when a PG is resected inadvertently or devascularized. TT with BCND should be performed by an experienced surgeon after careful consideration of the possible risks and benefits. If these risk factors verified in our study could be properly controlled, the patients would be managed more efficiently to reduce the incidence of hypoparathyroidism following TT with CND.

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