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Carbon nanoparticles facilitate lymph nodes dissection and parathyroid glands identification in reoperation of papillary thyroid cancer

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Abstract

The aim of the study was to investigate whether carbon nanoparticles (CNs) can improve the dissection of lymph nodes and protect parathyroid glands (PGs) during reoperation for patients with papillary thyroid carcinoma (PTC).

PTC patients who previously underwent thyroidectomy and later received reoperation between January 2009 and January 2016 were retrospectively recruited. We compared the patients who had CN suspension injected into the residual thyroid gland with a control group of patients who did not have the injection. The primary endpoints were the number of lymph nodes dissected, the number of PGs identified and reimplanted, and the rate of postoperative hypoparathyroidism.

CN suspension injection was conducted in 55 of 174 patients. The total number of lymph nodes and metastatic lymph nodes dissected between the 2 groups were not different (22.8 ± 13.7 vs 21.0 ± 13.3, $P = .481$ and 5.5 ± 3.8 vs 4.8 ± 4.0, $P = .695$). The number of central lymph nodes and metastatic central lymph nodes in the CN group was significantly higher than those dissected in the control group (8.7 ± 6.9 vs 6.2 ± 5.2, $P = .037$ and 2.7 ± 1.9 vs 2.1 ± 1.6, $P = .012$). More PGs were identified (2.42 ± 1.15 vs 1.58 ± 1.12, $P = .001$) and fewer were reimplanted (48 vs 90, $P = .040$) in the CN group. Patients who had CN suspension injection had a lower rate of transient hypoparathyroidism (14/55 vs 50/119, $P = .043$) but no significant difference in the rate of permanent hypoparathyroidism (1/55 vs 9/119, $P = .173$).

CN suspension injection improves dissection of central lymph nodes and identification of PG in PTC patients undergoing reoperation and lowers the rate of postoperative transient hypoparathyroidism.

Abbreviations: CN = carbon nanoparticles, PG = parathyroid gland, PTC = papillary thyroid cancer, LT = thyroid lobectomy, NTT = near-total thyroidectomy, TT = total thyroidectomy, CLND = central lymph nodes dissection, PTH = parathyroid hormone.

Keywords: carbon nanoparticles, central lymph node, papillary thyroid carcinoma, parathyroid gland, reoperation

1. Introduction

Papillary thyroid cancer (PTC) is one of the fastest growing group of cancers in recent years.[1–3] Although the majority of PTC patients have an excellent prognosis,[4] it unfortunately involves cervical lymph nodes in 20% to 90% of the patients. Regional lymph nodes metastases may be present even when the primary tumor is small and intrathyroidal.[1,5–8] The standard surgeries for PTC advocated by American Thyroid Association include thyroid lobectomy (LT), near-total thyroidectomy (NTT), and total thyroidectomy (TT). Until now, it is still controversial about prophylactic central lymph nodes dissection (CLND). Recent studies have found that TT in conjunction with prophylactic CLND could decrease locoregional recurrence in PTC patients.[9,10] Therefore, nonstandard surgeries and without prophylactic CLND often lead to gradually increasing recurrence and reoperation rates of PTC.[11]

Reoperation for PTC is usually difficult because of the destruction of normal anatomical structures, adhesion of surrounding tissues, and formation of cicatrization. Hypoparathyroidism, which may seriously affect the postoperative quality of life, is one of the most common and serious complications in PTC reoperation because of accidental parathyroid gland (PG) resection or damage of glandular blood supply. Previous studies have revealed that the incidence of hypoparathyroidism in reoperation was 3 to 5 times higher than in the primary surgery.[12–15] Therefore, a clear identification of PGs and accurate dissection of lymph nodes are essential for reducing hypoparathyroidism and locoregional recurrence during reoperation for PTC patients.

Recently, a lymphatic tracer—carbon nanoparticle (CN)—has been applied in reoperation for PTC. It was reported that CN could effectively guide cervical node dissection and protect PG.[16,17] However, part of thyroid lymphatic network might be damaged in the initial surgery, leading to some lymph nodes

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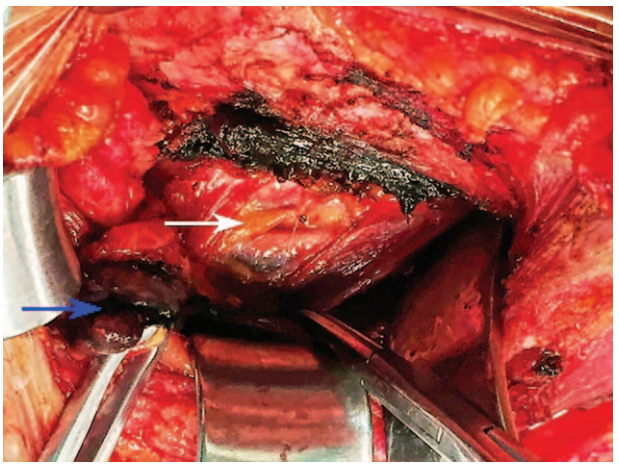

Figure 1. Left inferior parathyroid gland (white arrow) and adjacent black-stained lymph nodes (blue arrow).

unstained black. Therefore, the effect of CN on lymph node dissection and PG protection is still controversial. The aim of the study was to further investigate whether CN could improve lymph nodes dissection and aid to identify and protect PGs during reoperation for PTC patients.

2. Materials and methods

2.1. Patients

PTC patients who previously underwent thyroidectomy and later received reoperation at the Department of Thyroid Surgery of West China Hospital between January 2009 and January 2016 were retrospectively recruited. They were diagnosed as PTC by histopathological examination. According to the application of CN suspension in the reoperation or not, they were divided into 2 groups: the CN group and control group. In the CN group, CN (Lai Mei Pharmaceutical Co, Chongqing, China) suspension (1 mL: 50 mg) was injected into the residual thyroid gland, while it was not used in the control group. All the patients were informed and agreed to follow-up at least 6 months after reoperation. The research was approved by the medical ethics committee of West China Hospital.

2.2. Surgical procedures

The surgical procedures were performed as follows: after anesthesia intubation, the patients were placed supinely with cervical hyperextension. The original anterior cervical curve incision was selected and extended appropriately in most patients. The front part of residual thyroid gland was exposed after entering along with the outside of the linea alba cervicalis or strap muscles. The lateral and posterior parts of residual thyroid gland were not separated to reduce damage to the thyroid capsule and surrounding thyroid lymphatic network, which could prevent the possibility that the extravasation of the CN suspension affected the surgical field. In the CN group, after the front part of residual thyroid gland was exposed, CN suspension was slowly injected into the gland using a skin test needle at 1 or 2 selected points in the residual thyroid (0.1 mL each point). Injection into lesions or blood vessels was avoided. After the injection at each point, the site was gently pressed for 1 minute with sterile gauze to prevent solution leakage. Then, the surgical resection could be started 10 minutes later. The residual thyroid gland and surrounding lymph nodes were stained black, whereas the PGs were not (Figs. 1 and 2). Suspicious PG was partly sent for intraoperative frozen biopsy in both groups. PG was wrapped in gauze soaked with normal saline solution for later autotransplantation. Intraoperative neuromonitoring (Medtronic NIM-Response 2.0, Medtronic Xomed, Inc.) was used to identify recurrent laryngeal nerve. The indication for reoperation of PTC patients was recurrence in residual thyroid gland and/or lymph nodes.

2.3. Perioperative management

Parathyroid hormone (PTH), serum calcium, and thyroid function were routinely measured before reoperation. Thyroid ultrasound and laryngoscope were also carried out in each patient. PTH was routinely measured 1 day, 3 days, 30 days, and 3 months after reoperation. When a PTH measurement was below 1.6 pmol/L (normal range, 1.6–6.9 pmol/L), it was defined as postoperative hypoparathyroidism. Oral calcium supplement or intravenous substitution of calcium therapy was conducted to the patients with symptomatic hypocalcemia. A final PTH measurement was done to these patients 6 months after reoperation. If PTH did not recover to normal, hypoparathyroidism was defined as permanent, otherwise it was defined as transient.

2.4. Data Collection

General characteristics, preoperative tests, intraoperative factors, pathologic examination, the number of lymph nodes and metastatic lymph nodes retrieved in the resected specimens, and postoperative complications were collected retrospectively. Accidental PG resection was defined as not finding PG during

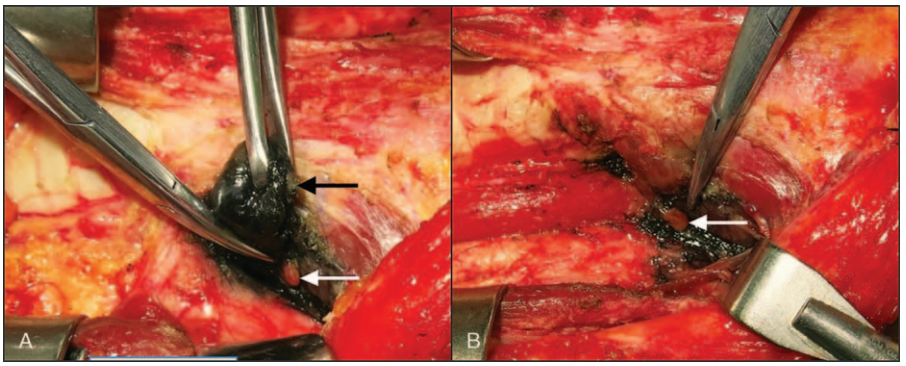

Figure 2. Residual thyroid gland (A, black arrow) and left superior parathyroid gland (A and B, white arrow).

reoperation (including careful inspection of the resected specimens) but finding it in the final pathological examination. The seventh edition of American Joint Committee on Cancer (AJCC) staging was used for all the recruited patients.[18] The primary endpoints were the number of lymph nodes dissected, the number of PGs identified and reimplanted, and the rate of postoperative hypoparathyroidism.

2.5. Statistical analysis

All the continuous variables were presented as mean ± standard deviation. Statistical analyses were performed by using SPSS computer software (version 19.0, SPSS, Inc, Chicago, IL). Statistical comparisons were done between the CN group and control group by using the χ^2 test or the Student t test. $P < .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

Of the 174 patients recruited in the study, 55 received CN suspension injection and 119 were in the control group. As summarized in Table 1, no significant difference was noted for clinical characteristics between the 2 groups. There was also no significant difference between them in terms of PTC pathological stages, the first surgical approach, the interval between the first surgery and reoperation, reason for reoperation, tumor size, and the surgical approach of reoperation. None of them accepted radioactive iodine ablation after the initial surgery because of the residual thyroid gland.

Table 1

Clinical characteristics of the patients in the 2 groups.

	CN group (n = 55)	Control group (n = 119)	P
Age, y	42.2 ± 13.9	40.3 ± 15.1	.427
Sex (male/female)	7/48	13/106	.799
Thyroiditis	6	8	.376
Calcium, mmol/L	2.28 ± 0.13	2.27 ± 0.33	.166
PTH, pmol/L	5.11 ± 2.31	4.97 ± 1.81	.674
Laryngoscope (abnormal)	10	31	.337
AJCC stage			
I–II	28	76	.134
III–IV	27	43	
First surgical approach			
Partial hemithyroidectomy/ hemithyroidectomy	40	73	.173
Hemithyroidectomy plus contralateral partial hemithyroidectomy	8	19	
Partial hemithyroidectomy and CLND	7	27	
Interval			
<3 mo	5	17	.463
≥3 mo	50	102	
Reason for reoperation			
Recurrence of residual thyroid	19	36	.601
Recurrence of lymph node	15	38	
Recurrence of residual thyroid and lymph node	21	45	
Tumor size, mm			
Residual thyroid	13.71 ± 12.30	16.35 ± 20.20	.671
Lymph node	17.26 ± 9.32	18.59 ± 13.68	.826
Surgical approach of reoperation			
rTT+UCLND	9	15	.489
rTT+BCLND	18	37	
rTT+BCLND+ULND	21	50	
rTT+BCLND+BLND	7	17	

BCLND = bilateral central lymph nodes dissection, BLND = bilateral lateral lymph nodes dissection, CLND = central lymph node dissection, CN = carbon nanoparticles, PTH = parathyroid hormone, rTT = residual total thyroidectomy, UCLND = unilateral central lymph nodes dissection, ULND = unilateral lateral lymph nodes dissection.

Table 2

Lymph nodes dissection per patient in the 2 groups.

	CN group (n = 55)	Control group (n = 119)	P
Total number of lymph nodes	22.8 ± 13.7	21.0 ± 13.3	.481
Metastatic lymph nodes	5.5 ± 3.8	4.8 ± 4.0	.695
Number of central lymph nodes	8.7 ± 6.9	6.2 ± 5.2	.037
Metastatic lymph nodes	2.7 ± 1.9	2.1 ± 1.6	.012
Number of lateral lymph nodes	14.1 ± 5.6	14.8 ± 5.2	.809
Metastatic lymph nodes	2.8 ± 2.2	2.7 ± 2.4	.991

CN = carbon nanoparticles.

3.2. Lymph nodes dissection

In the CN group, a total of 479 central lymph nodes and 775 lateral lymph nodes were dissected, with an average of 22.8 ± 13.7 per patient. Among them, 303 lymph nodes (24.2%) were confirmed to be metastatic lymph nodes. The metastatic rates of central lymph nodes and lateral lymph nodes were 31.1% (149/479) and 19.9% (154/775), respectively. In the control group, a total of 2499 lymph nodes were dissected, with an average of 21.0 ± 13.3 per patient. The difference of the total number of lymph nodes and metastatic lymph nodes between the 2 groups was not statistically significant ($P = .481$ and $P = .695$). But the number of central lymph nodes and metastatic central lymph nodes in the CN group was significantly higher than those dissected in the control group ($P = .037$ and $P = .012$) (Table 2).

3.3. PG identification and protection

A total of 133 and 188 PGs were identified, respectively, in the CN group and control group. Forty-eight PGs (36.1%) in the CN group and 90 (47.9%) in the control group were reimplanted ($P = .040$). Final pathological examination revealed 2 cases of accidental PG resection in the CN group, whereas 13 cases of accidental PG removal occurred in the control group. There was statistically significant difference between the 2 groups ($P = .030$) (Table 3).

3.4. Postoperative complications and follow-up

Table 4 summarizes the postoperative complications in the 2 groups. Transient hypoparathyroidism was documented in 14 of the 55 patients (25.5%) in the CN group and in 50 of the 119 patients (42.0%) in the control group ($P = .043$). No significant

Table 3

The details of PG identification and protection in the 2 groups.

	CN group (n = 55)	Control group (n = 119)	P
PG identification per patient	2.42 ± 1.15	1.58 ± 1.12	.001
PG reimplantation	48	90	.040
Accidental resection	2	13	.030

CN = carbon nanoparticles, PG = parathyroid gland.

Table 4

The postoperative complications in the 2 groups.

	CN group (n = 55)	Control group (n = 119)	P
Transient hypoparathyroidism	14 (25.5)	50 (42.0)	.043
Transient hoarseness	5 (9.1)	13 (10.9)	.795
Chylous fistula	2 (3.6)	8 (6.7)	.507
Bleeding	1 (1.8)	1 (0.8)	.534
Pneumonia	1 (1.8)	4 (3.4)	1.000
Permanent hypoparathyroidism	1 (1.8)	9 (7.6)	.173
Permanent hoarseness	2 (3.6)	3 (2.5)	.652

Data are no. (%) of patients.
CN = carbon nanoparticles.

differences were found between the 2 groups in terms of occurrence of transient hoarseness, chylous fistula, bleeding, and pneumonia. All the patients completed a 6-month follow-up. One patient (1.8%) in the CN group and 9 (7.6%) in the control group were diagnosed as permanent hypoparathyroidism ($P = .173$). Permanent hoarseness was found in 2 patients (3.6%) in the CN group and 3 (2.5%) in the control group. There was no statistically significant difference between the 2 groups ($P = .652$).

4. Discussion

In recent years, the increasing incidence of PTC in China is accompanied by the elevated reoperation rate. The primary causes of reoperation are insufficient resection in the initial surgery and postoperative cervical recurrence of residual thyroid or regional lymph node (s). The aforementioned standard surgeries for PTC only include LT, NTT, and TT. However, subtotal or partial hemithyroidectomy, partial thyroidectomy, and tumorectomy are always performed in the initial surgery in China because of the serious medical environment and lack of well-trained thyroid surgeons and intraoperative frozen biopsy. The reported incidence of cervical recurrence was 20% in low-risk PTC patients and 59% in high-risk PTC patients.[19–21] Although there is no direct relationship between reoperation and the development of extracervical metastasis as well as the reduction of survival time, reoperation is independently associated with a high incidence of postoperative complications.[20,22]

Hypoparathyroidism is a common complication after thyroid surgery, especially after reoperation.[23] In literature, the incidence of transient hypoparathyroidism after resurgery is reported to be 0% to 47.3%, while that of permanent hypoparathyroidism is 0% to 7.6%.[24–26] In the present study, the incidences of transient hypoparathyroidism and permanent hypoparathyroidism were 36.8% (64/174) and 5.7% (10/174), respectively, which are consistent with the previous studies. Patients with mild transient hypoparathyroidism often present as hand and foot numbness, while severe cases always have hypocalcemic tetany. These symptoms can return to normal after oral or intravenous administration of calcium. Moreover, transient hypoparathyroidism can rapidly improve during the next 1 to 2 months after reoperation.[26] However, hypocalcemic tetany, depression, confusion of consciousness, and other mental symptoms frequently occur in patients with permanent hypoparathyroidism. Therefore, long-term oral or intravenous supplement of calcium and medical testing are required to keep the level of serum calcium, which would cause a heavy physical, mental, and economic burden to them and also lead to medical disputes.

The main causes of postoperative hypoparathyroidism include accidental PG resection and damage of PG or its blood supply.[27,28] Surgical experience and good familiarity of the normal anatomical variations of the PGs are essential for diminishing the incidence of postoperative hypoparathyroidism. However, as to the PTC reoperation, these factors are necessary but not sufficient because of accidental resection or devascularization of the PGs during the first surgery. In addition, due to the disappearance of the anatomical structures and formation of strong adhesions, it is more difficult to seek and identify the PGs.[14]

Several strategies have been applied to visualize PGs intraoperatively. Use of loupes magnification and microsurgical technique can facilitate PGs identification and avoid their devascularization.[29] Although ^{99m}technetium-sestamibi (^{99m}TC-MIBI) is always used as a radiotracer for intraoperative localization of adenomatous PGs, it can label normal PGs for gamma probe identification.[30,31] Staining agents play an important role in the PGs identification. Methylene blue is the most widely used agent. It can sensitively stain enlarged PGs, such as parathyroidoma. However, it may falsely stain thyroid, lymph nodes, and normal PGs. Toxic metabolic encephalopathy occasionally occurs in patients taking serotonin reuptake inhibitors and serotonergic medication after intravenous application of methylene blue.[32] In recent years, some studies have reported that the application of CN suspension could significantly improve the dissection of lymph nodes and reduce the incidence of postoperative hypoparathyroidism during TT with CLND, regardless of the first surgery or resurgery.[16,17,33–35] The crucial components for CN suspension injection are nanocarbon granules with an average diameter of 150 nm, which could only pass through the lymphatic capillaries rather than the blood capillaries due to the difference in permeability. There are rich lymphatics and lymphatic capillaries in the thyroid, whereas almost none within the PGs. In addition, there are anatomically independent external capsules between them.[36] Therefore, CN can make the thyroid gland and the surrounding lymph nodes black-stained, but not for PGs. After rapidly identifying PGs and distinguishing them from thyroid and surrounding lymph nodes by CN, complete lymph nodes dissection and preservation of PGs become feasible.[37]

However, in the present study, CN could not significantly improve lymph nodes dissection, except for the CLND. The main reasons are as follows: Partial thyroid capsule and surrounding thyroid lymphatic network may be destroyed in the previous surgery, resulting in some lymph nodes maintaining original color. CN may stain the central lymph nodes around the recurrent laryngeal nerve, particularly the smaller ones underneath it, leading to more radical CLND. Black-stained lymph nodes, especially the small ones, are more easily identified by pathologists. Lateral lymph nodes dissection is performed standard in our center. Sample size of the study is limited. In accordance with the previous studies, CN could not only effectively aid in identifying PGs but also significantly reduce the accidental resection and reimplantation rates during PTC reoperation, resulting in the significantly lower incidence of transient hypoparathyroidism (25.5% vs 42.0%). Although the difference was insignificant, the incidence of permanent hypoparathyroidism was lower in the CN group than in the control group (1.8% vs 7.6%). The main causes of the aforementioned results may be the small sample size and experienced surgeons.

Meanwhile, application of CN did not increase the postoperative complications and no adverse side effects were found in the study, which further confirmed the safety.

5. Conclusion

The present study shows that CN suspension injection improves dissection of central lymph nodes and identification of PG in PTC patients undergoing reoperation and lowers the rate of postoperative transient hypoparathyroidism.

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