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The function of carbon nanoparticles to improve lymph node dissection and identification of parathyroid glands during thyroid reoperation for carcinoma

Bin Wang, MD[a,b,c], An-Ping Su, PhD[a], Teng-Fei Xing, MD[a], Han Luo, PhD[a], Wan-Jun Zhao, PhD[a], Jing-Qiang Zhu, MD[a,*]

Abstract

To evaluate the function of carbon nanoparticles during the thyroid reoperation for carcinoma, we conducted this study by retrospectively analyzing the data of patients who underwent at least completion thyroidectomy with bilateral central lymph nodes dissection for thyroid carcinoma from January 2009 to June 2016. The clinicopathologic characteristics and surgical details were compared between the patient who accepted intraoperative carbon nanoparticles injection and those who accepted nothing injection during the surgery. The main monitoring indicators were the number of dissected lymph nodes and metastatic lymph nodes in central zone, the number of identified parathyroid glands and autoplastic parathyroid glands and unintentionally resected parathyroid glands. A total of 69 patients were enrolled into the carbon nanoparticles group and 128 patients were enrolled into the control group.

The average number of lymph nodes harvested in the central zone was higher in the carbon nanoparticles group than that in the control group (11.2±5.7 vs 7.7±4.0, $P<.001$), so was the average number of metastatic lymph nodes (4.5±4.5 vs 2.7±2.9, $P=.004$). The average number of identified parathyroid gland was greater in the carbon nanoparticles group than that in the control group (2.4±1.2 vs 1.6±1.1, $P<.001$). The average number of autoplastic parathyroid gland was comparable between the 2 groups (0.6±0.6 vs 0.4±0.7, $P=.052$). But the average number of unintentionally resected parathyroid gland was less in the carbon nanoparticles group than that in the control group (0.1±0.2 vs 0.2±0.4, $P=.007$). Carbon nanoparticles can improve lymph nodes dissection and identification of parathyroid gland during thyroid reoperation for carcinoma.

Abbreviations: BCND = bilateral central lymph node dissection, BLND = bilateral lymph node dissection, CNs = carbon nanoparticles, CT = completion thyroidectomy, DTC = differentiated thyroid carcinoma, FTA = follicular thyroid adenoma, LT = lobe thyroidectomy, MTC = medullary thyroid carcinoma, NG = nodular goiter, PG = parathyroid gland, PTH = parathyroid hormone, RLN = recurrent laryngeal nerve, sTT = subtotal thyroidectomy, UCND = unilateral central lymph node dissection, ULND = unilateral lymph node dissection.

Keywords: carbon nanoparticles, lymph nodes, parathyroid gland, reoperation, thyroid carcinoma

1. Introduction

Thyroid carcinoma is the most common endocrine tumor, and its incidence has been globally raising in recent decades.[1–5] Surgery is the primary therapy method for thyroid cancer.[6,7] However, standard thyroid surgery methods were not performed in the county and town hospital of China due to the lack of professional surgeon. As a result, reoperation for thyroid cancer was also more and more performed.[8] Because of the destroyed anatomical structure and a large amount of fibrous and scar tissues in the surgical field for the previous surgery, reoperation was very difficult and the incidence of some complications, such as parathyroid gland (PG) damage and recurrent laryngeal nerve (RLN) injury, was increasing.[9–11] Therefore, some methods to identify the anatomical layers and structure were necessary to avoid more injury.

Carbon nanoparticles (CNs) has been widely used to assist to clean the lymph nodes by dyeing them during breast or gastric carcinoma surgery.[12–14] Also it has been used to protect the function of PG and trace the lymph nodes in the initial surgery for thyroid cancer in recent years.[15–18] The average diameter of CNs is 150 nm, which makes it directly enter the lymphatic capillaries (the gap between lymphatic capillary cells is 120–500 nm), not the blood capillaries (the gap between blood capillary cells is 20–50 nm).[19] Moreover, CNs was safety and nontoxic to date.[20–22] Therefore, we conducted the retrospective study to evaluate the function of CNs as lymph nodes tracer during thyroid reoperation.

2. Patients and methods

2.1. Patients

All patients who underwent at least completion thyroidectomy (CT), which is defined as the reoperation procedures of removing

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[a] Thyroid and Parathyroid Surgery Center, West China Hospital, Sichuan University, [b] Department of Thyroid and Breast Surgery, The Third People's Hospital of Chengdu, Chengdu, [c] Department of Thyroid and Breast Surgery, Dazhou Central Hospital, Dazhou, Sichuan Province, China.

[*] Correspondence: Jing-Qiang Zhu, Thyroid and Parathyroid Surgery Center, West China Hospital, Sichuan University, No. 37, Guoxuexiang, Chengdu 610041, Sichuan Province, China (e-mail: zjq_wkys@126.com).

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residual thyroid tissues, with bilateral central lymph nodes dissection (BCND) for thyroid carcinoma in the Thyroid and Parathyroid Surgery Center of West China Hospital of Sichuan University from January 2009 to June 2016 were included retrospectively. All the surgeries were performed by a professional thyroid surgeon (Zhu J). We excluded these patients whose PGs were dysfunction before this surgery; whose preoperative total serum calcium were not normal; whose vocal cords were paralysis; who had follow-up less 6 months; who could be collected incomplete data. The patients who were injected with CNs into the residual thyroid were assigned to the CNs group, while the other patients were assigned to the control group. We had gotten the informed consents from these patients.

2.2. Surgical procedures

The surgical methods were selected according to the indications described by Su et al,[23] and the operation was performed according to the procedure described by Su et al.[18] The injected volume of CNs (Lai Mei Pharmaceutical Co, Chongqing, China) depended on the volume of residual thyroid. Meticulous capsular dissection was used to protect PG and RLN. During surgery, all the specimens, including thyroid and central tissue, were dissected to avoid to miss PG to the final pathological specimens.[24] When the PG could not be preserved in site on account of being devascularized or found in the intraoperative specimen examination, autotransplantation was performed. All the surgical specimens were routinely examined by pathologists after surgery. Unintentionally resected PG was defined as that PG was presence in the postoperative pathological specimens. Intraoperative neuromonitoring (Medtronic NIM-Response 2.0) was applied to identify and protect RLN.

2.3. Perioperative management

All the patients underwent the standard preoperative examinations, including serum calcium, parathyroid hormone (PTH), thyroid function, neck ultrasound, and laryngoscopy. Serum calcium and PTH were routinely tested at 1 day, 30 days, and 6 months after surgery. Also patients with symptomatic hypocalcemia were prescribed with oral or intravenous calcium supplementation. Laryngoscopy examination was performed to evaluate the function of RLN when the patients felt voice hoarse. Postoperative hypoparathyroidism and hypocalcemia were defined as that the level of them were below the normal limit (range: PTH, 1.6–6.9 pmol/L; calcium, 2.1–2.7 mmol/L). If the serum PTH and calcium recovered to the normal range in 6 months after the surgery, it was classified as transient hypoparathyroidism and hypocalcemia; if not, it was classified as permanent hypoparathyroidism and hypocalcemia.

2.4. Data collection

All the data, such as patient demographics, the information of previous surgeries and the details of this surgery, were collected retrospectively. The primary monitoring indicators were the number of lymph nodes harvested in central zone, the number of metastatic lymph nodes, the number of identified PG, the number of autoplastic PG, the number of unintentionally resected PG, the rate of postoperative hypoparathyroidism and the rate of postoperative hypocalcemia. The secondary monitoring indicators were the postoperative level of serum PTH and calcium and other complications.

2.5. Statistical analysis

The statistical analyses were performed with SPSS computer software (version 23.0). Continuous variables with values were expressed as mean ± standard deviation. Chi-square test (or Fisher exact test if necessary) and Student-*t* test were applied to analyze variables. Statistical significance was set at $P < .05$.

3. Results

A total of 197 patients met the study criteria and were included in the retrospective cohort study. Of them 69 patients accepted intraoperative CNs injection and were allocated to the CNs group, and the other 128 patients with nothing injected during the surgery were allocated to the control group. The demographic and clinical data of the 2 groups were shown in Table 1. There was no significant difference between the 2 groups in gender, age, primary tumor size, multifocality, bilaterality, methods of previous surgery, the previous pathological diagnosis, interval before reoperation, methods of reoperation, preoperative serum PTH, and calcium ($P > .05$).

As shown in Table 2, a total of 770 central lymph nodes were dissected in CNs group, with an average of 11.2 ± 5.7 per patient. Among these, 308 (40.0%) lymph nodes were confirmed to be cancer metastasis. In control group, 982 lymph nodes were harvested in the central zone, with an average of 7.7 ± 4.0 per patient, of them 342 (34.8%) lymph nodes were confirmed to be cancer metastasis. The difference in the average number of lymph nodes harvested was statistically significant ($P < .001$), so was in the average number of metastatic lymph nodes (4.5 ± 4.5 vs 2.7 ± 2.9, $P = .004$). In comparison of the number of the dissected and metastatic lymph nodes in 2 categories between the 2 group, the differences were also significant ($P = .001$, $P = .034$).

In the CNs group and control group, 168 and 207 PGs were identified during surgery, respectively. The average number of identified PG and the identification rate of more than 2 PGs were both greater in the CNs group than that in the control group (Table 3). The average number of autoplastic PG was comparable between the 2 group, but a significant difference of the rate of PG autotransplantation was observed between the CNs group and the control group (43.5% vs 28.9%, $P = .039$). Postoperative pathological examinations confirmed that PG was unintentionally resected in 4 (5.8%) patients in the CNs group and in 22 (17.1%, $P = .024$) patients in the control group. The average number of unintentionally resected PG was also less in the CNs group than that in the control group (0.1 ± 0.2 vs 0.2 ± 0.4, $P = .007$). The difference in the average number of total PGs (identified PGs plus unintentionally resected PGs) was significant between the 2 groups (2.5 ± 1.1 vs 1.8 ± 1.1, $P < .001$), but the average number of PGs not preserved in site (autoplastic PGs plus unintentionally resected PGs) was similar (0.6 ± 0.6 vs 0.6 ± 0.8, $P = .912$).

Table 4 summarized the postoperative complication in the 2 groups. The incidence of transient hypoparathyroidism was higher in the CNs group than that in the control group (47.8% vs 32.8%, $P = .038$). The average value of serum calcium was greater in the CNs group than that in the control group at 30 days and 6 months after this surgery. No significant difference was found between the 2 groups in terms of the incidence of permanent hypoparathyroidism, transient and permanent hoarseness, chylous fistula, and wound infection.

Table 1

Clinical characteristics of the patients in the 2 groups.

	CNs group (n=69)	Control group (n=128)	*P* value
Gender (M: F)	13:56	15:113	.172
Age, years	40.9±14	40.3±14.9	.763
≤45	44	86	.629
>45	25	42	
Hypertension	2	10	.221
Diabetes	2	2	.527
Hashimoto's thyroiditis	7	9	.445
The methods of previous surgery			
LT	37	63	.278
LT+UCND	8	8	
sTT	18	39	
sTT+UCND	5	12	
sTT+BCND	1	6	
The postoperative pathological diagnosis of previous surgery			
NG/FTA	13	19	.39
DTC	48	108	
MTC	8	11	
Interval between previous and this surgery (mean±standard, months)	51.1±93.9	59.1±67.6	.579
Tumor size, mm	17.6±14.4	15.2±19.5	.447
Multiplicity of carcinoma	13	15	.172
Bilaterality of carcinoma	9	10	.235
The methods of this surgery			
CT+BCND	27	43	.121
CT+BCND+ULND	35	57	
CT+BCND+BLND	7	28	
Gross extrathyroidal extension	13	13	.086
Preoperative PTH, pmol/L	4.75±1.12	4.54±1.16	.216
Preoperative serum calcium, mmol/L	2.32±0.11	2.31±0.11	.838

BCND=bilateral central lymph node dissection, BLND=bilateral lymph node dissection, CNs=carbon nanoparticles, CT=completion thyroidectomy, DTC=differentiated thyroid carcinoma, FTA=follicular thyroid adenoma, LT=lobe thyroidectomy, MTC=medullary thyroid carcinoma, NG=nodular goiter, PTH=parathyroid hormone, sTT=subtotal thyroidectomy, UCND=unilateral central lymph node dissection, ULND=unilateral lymph node dissection.

4. Discussion

The diagnosis of thyroid cancer was increasing due to the growing incidence of thyroid cancer and the more and more widespread use of high-frequency ultrasound and other imaging modalities and fine-needle aspiration biopsies.[4,25–27] The number of patients who needed reoperation was also rising for lack of professional thyroid surgeon. Because of the anatomic damage and the fibrosis tissue formation, reoperation was a technical challenge. Some literatures had indicated CNs was useful for lymph nodes dissection and protection of PG through dyeing thyroid and the lymph system in the initial thyroid surgery.[28–30] However, the lymphatic system was damaged in the surgical field of reoperation for the previous surgery. The function of CNs as lymph nodes tracer during thyroid reoperation was evaluated in the present study.

In the current study, a significantly higher average number of central lymph nodes dissected were confirmed in the CNs group than that in the control group. The rate of patients who were dissected ten or more lymph nodes was also higher in the CNs group than that in the control group, which was consistent with the previous study.[8] The follow reasons may be responsible for the result. First, some tiny lymph nodes were identified and dissected during the surgery in the CNs group. Second, some tissue which might be preserved to avoid to injury RLN or/and PG and the blood vessel which supplied them in the control group was resected in the CNs group. Third, it was easier for pathologists to identify the black-stained lymph nodes, especially the tiny lymph nodes. The average number of metastatic lymph nodes was significantly higher in the CNs group than that in the control group, so was the rate of patients who were dissected 5 or more metastatic lymph nodes. The discovery indicated CNs

Table 2

Lymph nodes dissection in the 2 groups.

	CNs group (n=69)	Control group (n=128)	*P* value
Number of lymph nodes in the central zone (mean±standard)	11.2±5.7	7.7±4.0	<.000
≥10	39	42	.001
<10	30	86	
Number of metastatic lymph nodes in the central zone (mean±standard)	4.5±4.5	2.7±2.9	.004
≥5	26	30	.034
<5	43	98	

CNs=carbon nanoparticles.

Table 3

The details of PG protection in the 2 groups.

	CNs group (n=69)	Control group (n=128)	*P* value
Number of identified PG (mean±standard)	2.4±1.2	1.6±1.1	.000
≤2	41	109	<.001
>2	28	19	
Number of autoplastic PG (mean±standard)	0.6±0.6	0.4±0.7	.052
0	39	91	.039
1	26	27	
2	4	9	
3	0	1	
Number of unintentionally resected PG (mean±standard)	0.1±0.2	0.2±0.4	.007
0	65	106	.024
1	4	20	
2	0	2	
Number of total PG (mean±standard)	2.5±1.1	1.8±1.1	<.001
Number of PG not preserved in site (mean±standard)	0.6±0.6	0.6±0.8	.912

CNs=carbon nanoparticles, PG=parathyroid gland.

Table 4

The postoperative complications in the 2 groups.

	CNs group (n=69)	Control group (n=128)	*P* value
1 day after surgery			
Serum PTH	1.99±1.04	2.21±1.25	.218
Serum calcium	2.10±0.15	2.07±0.18	.338
Hypoparathyroidism	33	42	.038
Hypocalcemia	37	66	.782
30 days after surgery			
Serum PTH	3.78±1.46	3.60±1.89	.558
Serum calcium	2.28±0.15	2.18±0.19	.002
Hypoparathyroidism	3	9	.547
Hypocalcemia	7	16	.623
6 months after surgery			
Serum PTH	3.87±1.28	3.69±1.57	.475
Serum calcium	2.28±0.15	2.17±0.17	<.001
Hypoparathyroidism	0	5	NK
Hypocalcemia	4	12	.38
Transient hoarseness	2	7	.499
Permanent hoarseness	1	4	.477
Chylous fistula	4	9	.974
Wound infection	2	5	.716

CNs=carbon nanoparticles, PTH=parathyroid hormone.

facilitated lymph nodes dissection, which even may change the subsequent scheme of therapy and follow-up according to Haugen et al.[7]

Hypoparathyroidism was a common complication after thyroidectomy. According to the previous study, the incidence of transient hypoparathyroidism was 17.6% to 55.9%,[31–33] while the permanent hypoparathyroidism was 2.2% to 16.2%.[34–36] In the present study, the transient and permanent hypoparathyroidism was 38.1% and 2.5%, respectively, which was line with the previous study. It was the key to avoid hypoparathyroidism that preserving the PG in situ. Also professional thyroid surgeons and meticulous capsular dissection were considered to the major factors to protect PG.[24,37] But identification of PG was the precondition for protection of PG. Because of previous surgery, the blood vessel which supplied PG and even the PG may be wrapped by the hyperplastic scar and fibrosis tissue, which made it difficult to identify PG.[8,22] In the present study, the average number of identified PG and total PG were both higher in the CNs group than that in the control group, which indicated CNs contributed to the identification of PG (Fig. 1). The average number of unintentionally resected PG was less in the CNs group than that in the control group, but the average number of PGs not preserved in site was similar between the 2 groups, which suggested CNs helped protect PGs from unintentional resection by assisting to identified PGs from the intraoperative specimens. It was interesting that the incidence of transient hypoparathyroidism was higher in the CNs group than that in the control group. This might result from lymph node dissection which was more radical in the CNs group than that in the control group. However, the average value of postoperative serum PTH was similar between the 2 groups, and even the average value of serum calcium at 30 days and 6 months after surgery were both higher in the CNs group than that in the control group, and there was no occurrence of permanent hypoparathyroidism in the CNs group. This phenomenon indicated that CNs could facilitate radical lymph nodes dissection with restorable PG damage.

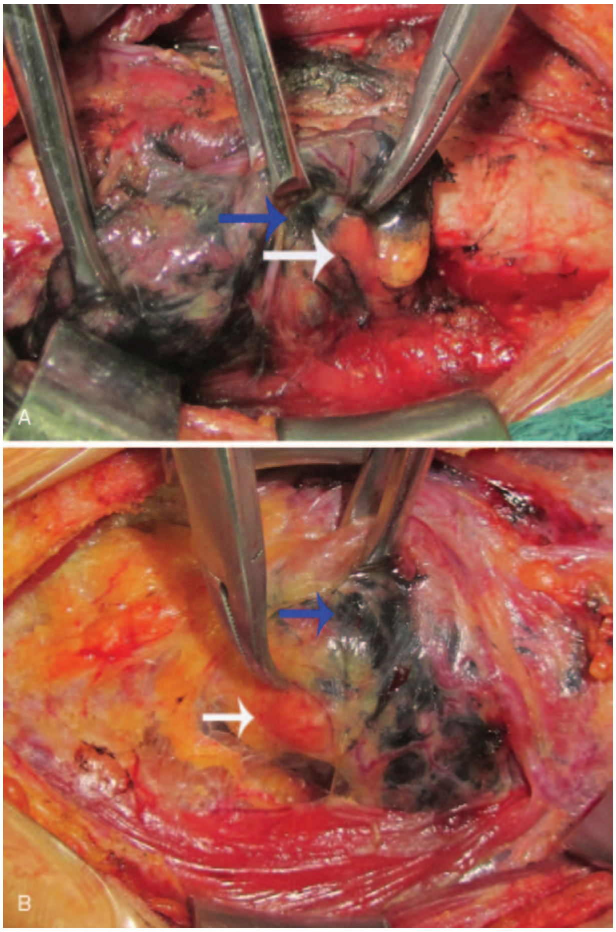

Figure 1. Left inferior parathyroid gland (A, white arrow), right inferior parathyroid gland (B, white arrow), and black-stained lymph nodes (A and B, blue arrow).

5. Conclusions

In conclusion, the study demonstrates that CNs can improve lymph nodes dissection and identification of PG during thyroid reoperation for carcinoma. Therefore, it is worthy of clinical application and promotion for the use of CNs in thyroid reoperation. However, due to the small size in the retrospective study, large sample and prospective study for this should be considered.

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Author contributions

Data curation: Bin Wang, Teng-Fei Xing.
Formal analysis: Bin Wang, An-Ping Su, Wan-Jun Zhao.
Investigation: Bin Wang, Teng-Fei XIng, Han Luo.
Methodology: Bin Wang, An-Ping Su, Wan-Jun Zhao.
Project administration: Jing-Qiang Zhu.
Resources: Teng-Fei Xing, Han Luo, Wan-Jun Zhao, Jing-Qiang Zhu.
Software: Bin Wang, An-Ping Su, Han Luo.
Supervision: Bin Wang, Jing-Qiang Zhu.
Validation: Jing-Qiang Zhu.
Writing – original draft: Bin Wang.
Writing – review & editing: Bin Wang, An-Ping Su.

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