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Original Research

Application of carbon nanoparticles accelerates the rapid recovery of parathyroid function during thyroid carcinoma surgery with central lymph node dissection: A retrospective cohort study

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HIGHLIGHTS

- In this study, carbon nanoparticles was associated with more central lymph nodes dissected and less parathyroid glands removed incidentally.
- The follow-up outcomes showed that Carbon nanoparticles had played a key role in promoting rapid recovery of parathyroid function during thyroid carcinoma surgery with central lymph node dissection.
- It was suggested to routinely use carbon nanoparticles during thyroid carcinoma surgery combined with central lymph node dissection.

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ABSTRACT

Background and Objectives: The aim of this study was to evaluate the efficacy of carbon nanoparticles in identifying lymph nodes and promoting parathyroid gland function recovery after thyroid carcinoma surgery along with central lymph node dissection.
Methods: A total of 231 patients who underwent thyroid carcinoma surgery combined with central lymph node dissection were divided into two groups: the CN group (intraoperative carbon nanoparticles injections) and the control group (no injection). Datas were collected respectively on the pre-operative, 1st, 7th and 30th postoperative days and monthly thereafter. While the pathological results (e.g. amount of incidental removed parathyroid glands and lymph nodes dissected), complications (e.g. rates of vocal cord paralysis, the neuromuscular symptoms, hypocalcemia and hypoparathyroidism), as well as follow-up outcomes of the serum Ca2+ and PTH levels were gathered and measured to be included in.
Results: In regard to the results of the pathological tests, the control group had a relatively higher incidence of incidental parathyroidectomy when compared to the CN group ($P < 0.05$). The mean number of central lymph nodes dissected was rather higher in the CN group than that of the control group ($P < 0.05$).With respect to the follow-up results, the CN group had an earlier and faster recovery of serum PTH levels as compared to the control group ($P < 0.05$). The serum PTH levels of the CN group were apparently higher than that of the control group at the first week and month postoperatively ($P < 0.05$). No significant differences were found in rates of long-term postoperative complications between the two groups ($P > 0.05$).
Conclusion: Carbon nanoparticles play a key role in accurately identifying lymph nodes, reducing mistaken excision of parathyroid glands, accelerating rapid recovery of parathyroid function during thyroid carcinoma surgery with central lymph node dissection, without increasing the probability of postoperative complications.

1. Introduction

It is particularly notorious that central lymph node dissection (CLND) is commonly performed among patients with papillary

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thyroid carcinoma. However, recurrent laryngeal nerve injury and hypoparathyroidism are the two main concerns when it comes to CLND. With the routine exposure of recurrent laryngeal nerve and development of surgical techniques, the incidence of recurrent laryngeal nerve injury is dramatically decreasing. On the contrary, hypoparathyroidism still occurs frequently, because of the expansion of the scope of operation and incidental removal of parathyroid glands (PGs) other than lymph nodes [1]. The transient hypocalcemia incidence rate is 1.6%–50%, and the permanent hypocalcemia incidence rate is 1.5%–4% [2–5]. Therefore, the problem that needs to be solved is how to avoid incidental removal of PGs and devascularization of the PGs.

Long-term follow up data in previous studies demonstrated that autotransplantation cannot recover PG activity to the preoperative levels [6,7]. Careful preservation of PGs in situ especially meticulous capsular dissection without jeopardizing PG blood supply is advocated to accelerate the recovery of PGs function, but usually not technically possible by conventional total thyroidectomy with CLND. Several relevant Chinese studies had confirmed that CNs could help reduce the prevalence of PGs injury after thyroid surgery combined with CLND [8–11]. Nonetheless, these studies mainly put emphasis on short-term follow-up, while the reports concerns long-term outcomes are rather rare [12].

Therefore, the study of this paper turns to focus on the efficacy of CNs in long-term PGs function recovery after thyroid carcinoma surgery combined CLND.

2. Materials and methods

2.1. Patients and perioperative management

This study was approved by the Clinical Ethics Committee of Changzheng Hospital. From January 2013 to January 2014, 285 patients who preoperatively diagnosed as micropapillary carcinoma based on ultrasound-guided fine needle aspiration cytology had undergone thyroid carcinoma surgery with CLND. Among them, those patients were excluded when they met one or more of the following terms: (1) a history of neck surgery or radiotherapy; (2) concomitant Grave's disease, (3) preoperative hypoparathyroidism or hypocalcemia; and (4) the inability to comply with the follow-up protocol. Overall, 231 patients were included in this study. According to the surgical protocol, the patients were divided into the CN group (intraoperative CN injections) and the control group (no injection). Their age ranges from 19 to 71 years old (median, 44 years). All patients were evaluated preoperatively with the adoption of ultra-sonography and fine-needle aspiration cytology. All patients took preoperative direct laryngoscopy for the sake of assessing vocal cord motility. The advantages and disadvantages of CNs were fully informed before surgery; it was up to the patients' free will when it comes to choosing or forsaking CNs.

2.2. Outcome measures

The primary outcome measures were pathological results (e.g. amount of incidental removed PGs, central and lateral lymph nodes dissected) follow-up results (e.g. recovery of serum calcium [Ca^{2+}] and parathyroid hormone [PTH] levels). The secondary end-points were the rates of complications (e.g. rate of vocal cord paralysis, the neuromuscular symptoms, hypocalcemia and hypoparathyroidism), in-hospital postoperative hormonal assay, and lymph node metastases.

2.3. Definition

"Hypoparathyroidism" was defined as a condition in which calcium or vitamin D supplementation was required to maintain normocalcemia and the serum intact PTH concentration was less than 15 pg/mL (normal values, 15–65 pg/mL). Hypocalcemia happens when serum Ca^{2+} concentration was less than 1.9 mmol/L. If clinical symptomatic hypocalcemia returned to normal levels within 6 months, hypoparathyroidism would be defined as "transient"; it was otherwise labeled as "permanent".

2.4. Surgical procedures

After dissecting the strap muscles in the midline, the anterior capsule of thyroid would be carefully dissociated and the abnormal lobe would come to light. To reduce the risk of destroying the surrounding thyroid lymphatic network, the dorsal tissue of thyroid was left temporarily unseparated. Then, CN injection to the thyroid lobe should be carried out. At the meantime, a 5 ml syringe was required. The CN puncture site was located in the middle of anterior capsule of thyroid lobe. (Fig. 1). CNs suspension was injected into the thyroid gland thereafter with 0.1–0.2 mL administered per lobe. After injection, the needle puncture site would be pressed with gauze for 2–3 min. As a result, the thyroid, surrounding lymph tissue and level VI of lymph nodes were stained black. PGs were then visibly different from the thyroid gland and lymph nodes in the central compartment (Fig. 2).

All patients had completed abnormal thyroid lobes and isthmus resection. After intraoperative frozen sections confirmed the diagnosis of papillary thyroid carcinoma, lymph node clearance would be carried out in the central zone or lateral zone. Central lymph nodes dissected included the prelaryngeal, pretracheal, and paratracheal lymph nodes. Ipsilateral lymph nodes dissection or bilateral lymph nodes dissection was determined by the size and location of tumor. If patients need to receive radioactive iodine treatment, total thyroidectomy should be performed. The posterior branch of superior thyroid artery and a branch of inferior thyroid artery should be preserved to avoid damages toward the blood supply of the PGs.

2.5. Postoperative follow-ups

Postoperative evaluation of all patients included assessments of serum Ca2+ and PTH levels, and pathological characteristics (e.g. number of removed PGs and lymph nodes). Ca2+ and PTH levels were tested preoperatively as well as on the 1st and 7th days respectively after operation. All patients underwent a complete

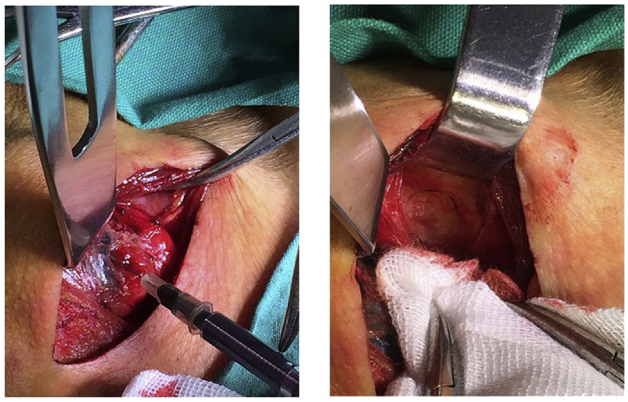

Fig. 1. Carbon nanoparticles were injected into thyroid gland.

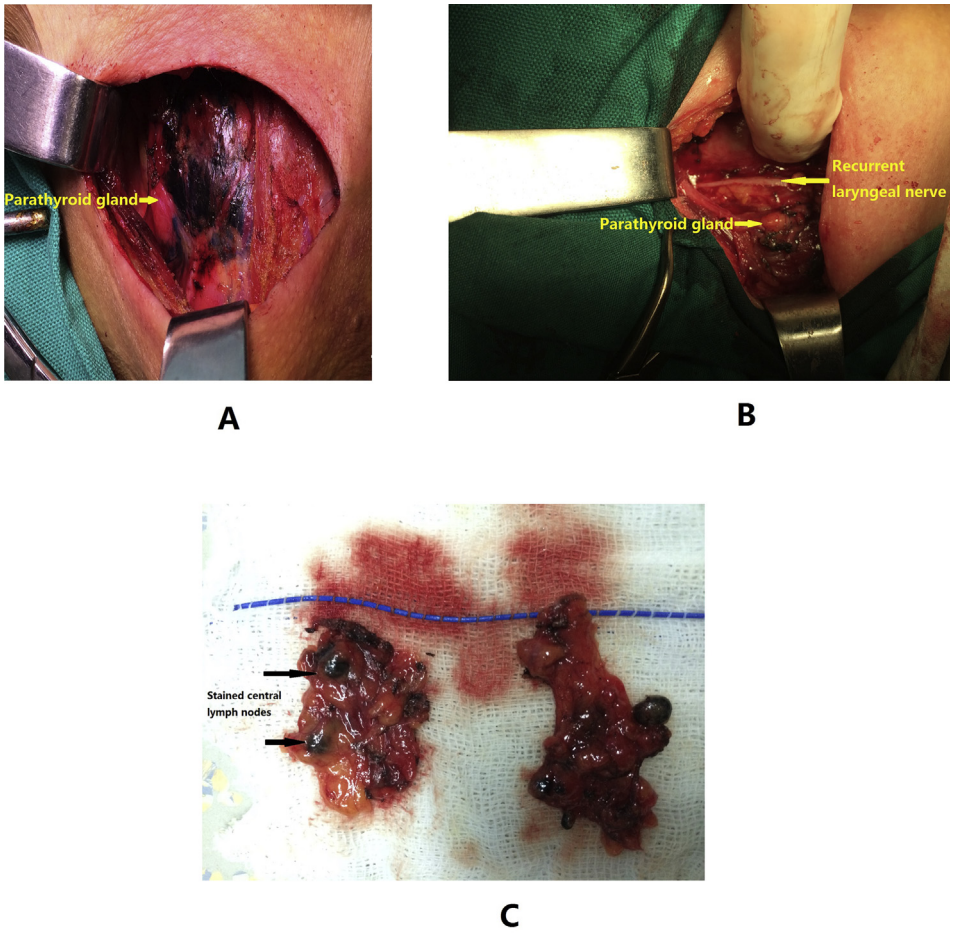

Fig. 2. Thyroid and lymph nodes were stained black and parathyroid gland was identified.

hormonal assay during the follow-up survey. The normal ranges of serum Ca2+ and PTH levels were 2.25–2.75 mmol/L and 15–65 pg/mL. All patients who suffered the decline of serum Ca2+ to less than 1.90 mmol/L, and presented signs of hypocalcemia, (e.g. paraesthesia, tetany) should be received oral calcium carbonate, vitamin D3 chewable tablets (1.2–2.4 g/day) and calcium gluconate (3.6 g/day).Postoperative follow-up was achieved by outpatient visits, telephone records and written correspondences. Data gathered included neuromuscular symptoms, and serum Ca2+ and PTH levels, which were measured respectively on the 7th and 30th postoperative days and monthly thereafter.

2.6. Statistical analysis

A *t*-test was used to compare the mean values between the CN and the control groups. Categorical variables were compared between both groups in virtue of Peason Chi-square or Fisher's exact test. A value of $P < 0.05$ was considered significant. All datas were processed by SPSS 19.0 software.

3. Results

3.1. Patient characteristics

Together, 90 patients were allocated to the CN group and 141 to the control group. Table 1 showed that the distribution of patient characteristics (e.g. age and gender) was similar between the CN group and the control group. The 2 groups were well matched with respect to preoperative laboratory data, tumor anatomic features, and operative details (Table 1).

3.2. Postoperative histopathology

PGs were present in the thyroid or central nodal specimens of 28 Patients', with 5 in the CN group and 23 in the control group. The control group had a relatively higher incidence of incidental parathyroidectomy as compared to the CN group ($P = 0.015$). Among the 28 patients with incidental parathyroidectomy, 21 patients experienced transient hypothyroidism. Two PGs were incidentally removed from 3 patients. Two patients experienced paraesthesia on postoperative day 1 and developed into muscle cramps on postoperative day 2. As to the other 25 patients, only 1 PG was incidentally removed.

CLND was performed in all patients. A total of 640 lymph nodes in the CN group and 769 lymph nodes in the control group were detected. The mean number of detected lymph nodes was significantly higher in the CN group than that of the control group ($P = 0.010$). A total of 567 lymph nodes were stained black with a staining rate of 88.6%. The CN group had 135 metastatic lymph nodes while the control group had 178 metastatic lymph nodes. No significant differences existed between the 2 groups regarding the mean number of metastatic lymph nodes ($P = 0.451$). Lateral lymph node dissection was performed in 8 patients of the CN group and 10 patients of the control group. The total number of detected lymph nodes was 93 in the CN group and 76 in the control group. The mean number of detected lymph node and metastatic lymph node

Table 1
Patient characteristics and baseline data.

	CN group	Control group	P value
Patients number	90	141	
Age (y)	44.36 ± 11.48	44.09 ± 12.41	0.868
Gender(male/female)	27.8% (25/90)	26.2%(37/141)	0.797
Serum calcium (mmol/L)	2.40 ± 0.16	2.41 ± 0.16	0.754
Serum PTH (pg/ml)	48.40 ± 23.30	46.20 ± 18.92	0.432
Tumor size (mm)	11.27 ± 8.33	9.61 ± 6.46	0.092
Tumor distribution			
Left side	26.7%(24/90)	38.3%(54/141)	0.227
Right side	44.4%(40/90)	39.0%(55/141)	
Double side	22.2%(20/90)	18.4%(26/141)	
Isthmus	6.7%(6/90)	4.3%(6/141)	
Tumor position			
Superior pole	20.9%(23/110)	20.4%(34/167)	0.459
Middle pole	56.4%(62/110)	50.3%(84/167)	
Inferior pole	22.7%(25/110)	29.3%(49/167)	
Tumor location			
Dorsal side	23.6%(26/110)	16.2%(27/167)	0.196
Middle side	58.2%(64/110)	68.3%(114/167)	
Anterior side	18.2%(20/110)	15.6%(26/167)	
Type of surgery			
Left thyroidectomy	17.8%(16/90)	27.0%(38/141)	0.270
Right thyroidectomy	35.6%(32/90)	17.7%(125/141)	
Double thyroidectomy	46.7%(42/90)	11.3%(16/141)	

were not significantly different in both groups (see Table 2). In the lateral neck area, only 52 lymph nodes were stained black, with a low staining rate of 30.7%.

3.3. Complications

Vocal cord paralysis occurred in 6 patients (6.7%) of CN group and in 6 patients (4.3%) of control group. The incidence of vocal cord paralysis failed to show significant difference between the 2 groups ($P = 0.545$). There were no cases of permanent recurrent laryngeal nerve injury. Skin black staining of CN occurred in 12 patients of CN group with a rate of 13.3%.

Paraesthesia occurred in 52 patients on postoperative day 1, incorporating 16 patients in the CN group and 36 patients in the control group. The incidence of paraesthesia was higher in the control group compared to the CN group, even if not statistically significant ($P = 0.169$). Among the 52 patients with paraesthesia, tetany occurred in 16 patients (12 patients in the control group and 4 patients in the CN group) while muscle cramps occurred in 6 patients in the control group on postoperative day 1 or 2.

On postoperative day 1, hypocalcemia (<1.90 mmol/L) occurred among 16 patients in the CN group compared with 24 patients in the control group. The incidence of hypocalcemia was similar in both groups ($P = 0.882$).

The case number of hypoparathyroidism was 20 (22.2%) in the CN group and 28 (19.9%) in the control group, which did not achieve statistical significance ($P = 0.667$). 20 patients with hypoparathyroidism in the CN group achieved clinical resolution in a mean time of 1.87 ± 1.16 weeks while 28 patients in the control group achieved in 5.33 ± 1.63 weeks.

3.4. Follow-up outcomes of serum Ca^{2+} and PTH

The median follow-up time was 19 months (range 12–24 months) for the CN group and 18 months (range 6–18 months) for the control group. The follow-up response rate was 94.5%.

The changes of serum Ca^{2+} during 1 year after surgery were shown in Fig. 3. The serum Ca^{2+} level transiently fell on postoperative day 1 in both groups and climbed gradually within 1 year postoperatively. From perioperative period to 1 month postoperatively, the serum Ca^{2+} levels were slightly higher in the control group than that of the CN group ($P > 0.05$). However, Ca^{2+} levels had recovered rapidly in the CN group. Ca^{2+} levels were slightly higher in the CN group when compared with the control group and this trend maintained 1 year after surgery. But there was no statistically significant differences regarding to Ca^{2+} levels during 1 year postoperatively ($P > 0.05$) (Fig. 3).

Both groups had a decreased serum PTH levels on postoperative day 1. The CN group had an earlier and faster recovery of serum PTH levels as compared to that of the control group. The CN group recovered rapidly within 1 week postoperatively, whereas the control group climbed quickly in three months postoperatively. At the end of 1 year postoperatively, the CN group had recovered almost to preoperative levels. While the control group reached to the normal range but was lower than preoperative levels. The serum PTH levels in the CN group were apparently higher than that of the control group at the first week ($P = 0.020$) and month ($P = 0.033$) postoperatively (Fig. 4).

4. Discussion

CLND is considered to be a necessary for detecting metastatic lymph nodes, providing more accurate information on staging of the disease and eradicating the potential sources of nodal recurrence are achieved [13–15]. But the long-standing discussion on CLND mainly centers on the increasing risk of injury to the PGs. Despite of the unpredictable ectopic thyroid glands [16], the key to minimizing permanent hypoparathyroidism is the preservation of as much functional parathyroidism tissue in situ as possible. In most studies, every attempt includes the procedure of meticulous dissection of the precarious blood supply and intracapsular dissection is made to identify and preserve PGs in situ and functioning [17,18]. However, preservation of PGs in situ and its functional integrity are still not easily achieved technically. Therefore, techniques to protect PGs during CNLD such as lymphatic tracers have been proposed.

CNs suspension injection has been applied recently to help

Table 2
Postoperative outcomes of patients.

	CN group	Control group	P value
Patients number(n)	90	141	
Incidental removed parathyroid %(n)	5.6% (5/90)	16.3% (23/141)	0.015
Central lymph node dissected (n)	7.11 ± 5.40	5.45 ± 3.53	0.010
Central lymph node metastases (n)	1.50 ± 2.62	1.27 ± 1.96	0.451
Lateral lymph node dissected (n)	11.63 ± 12.20(n = 8)	7.60 ± 4.60(n = 10)	0.401
Lateral lymph node metastases (n)	3.50 ± 4.60(n = 8)	3.00 ± 1.89(n = 10)	0.779
Vocal cord paralysis%(n)	6.7%(6/90)	4.3%(6/141)	0.545
Neuronmuscular symptoms %(n)	17.8% (16/90)	25.5% (36/141)	0.169
Hypocalcemia %(n)	17.8% (16/90)	17.0% (24/141)	0.882
Hypoparathyroidism %(n)	22.2% (20/90)	19.9% (28/141)	0.667

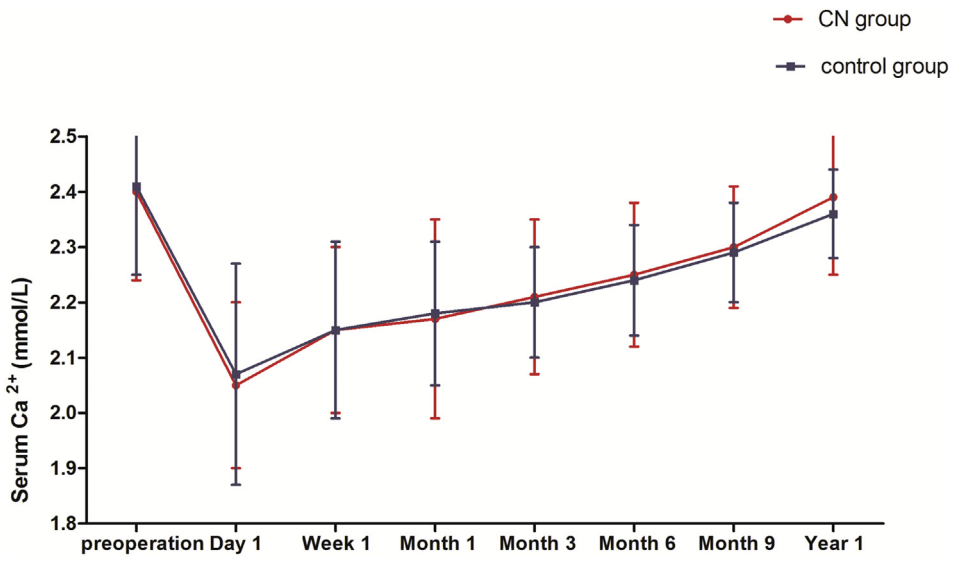

Fig. 3. Changes in serum Ca^{2+} in the two groups after surgery during postoperative year 1.

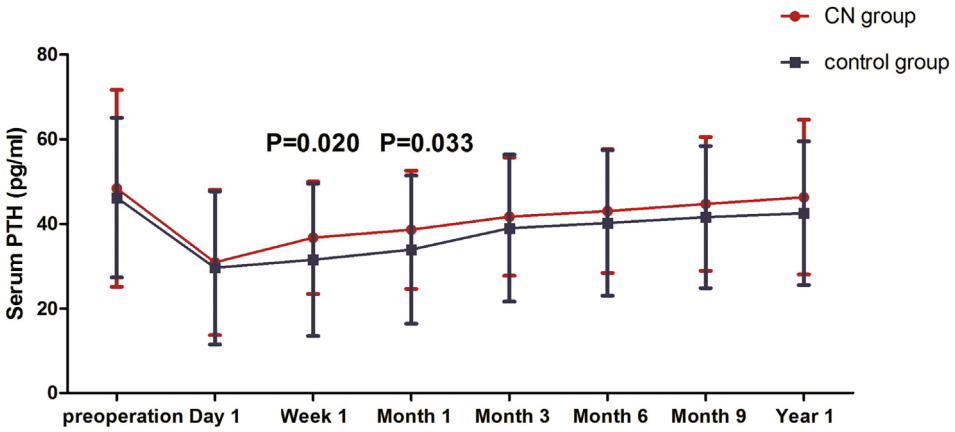

Fig. 4. Changes in serum PTH in the two groups after surgery during postoperative year 1.

identifying lymph nodes in lymph node dissection [9–11]. The CNs suspension comprises nanosized carbon particles (average diameter, 150 nm). These particles can enter into lymphatic vessel capillaries (diameter of 150–500 nm), but not blood vessel capillaries (diameter of 20–50 nm) [19]. After the injection of CNs suspension into thyroid parenchyma, the CNs will penetrate and diffuse the whole thyroid lobe, enter into the lymphatic vessels rapidly, accumulate in the lymph and stain them back thereby. However, the PGs have no lymph-vessel connections to the thyroid to be stained black. To put it into a nutshell, tracer function and PGs identification will be achieved.

Our findings demonstrated that CNs played a key role in accurately identifying lymph nodes during CLND. Undoubtedly, thorough lymph node dissection was based on a surgeon's experience and techniques. However, CNs could be applied to detect exact numbers of lymph nodes dissected intraoperative and histopathological examination postoperative, and thus provide more accurate information on staging of the disease and eradicating the potential sources of nodal recurrence. Three following reasons were listed to justify these differences: First, in order to protect PGs and their blood supply, PGs and surrounding tissues will be preserved together in situ. However, some tiny lymph nodes (1–2 mm in diameter) that lurk in surrounding tissues may not be easily identified and dissected. On the contrary, with the CNs staining the lymph nodes black, they can easily be identified, which provides a condition to perform a meticulous and thorough dissection during the surgery. Second, it is also not easy to identify them from surrounding tissues in pathological tests even if some tiny lymph nodes are dissected. Therefore, if these tiny lymph nodes are stained black, the number of lymph nodes detected will increase. Third, more extensive lateral lymph node dissection is associated with cosmetic concerns such as the potential for nerve injury (accessory, vagus, phrenic, brachial plexus), hemorrhage and chyle leakage [20]. Therefore, some surgeons advocate selective lateral compartment neck dissection for the sake of decreasing the risk of complications. With the application of CNs tracer technique, lymph nodes and lymphatic vessels in III, IV and V regions are stained black and can be easily identified. The presence of black-stained lymph nodes and lymphatic vessels will allow surgeons to expand the scope of operation and dissect the black-stained lymph nodes with ease, which makes more lymph nodes to be dissected and complications to be prevented.

In the present study, serum PTH levels dropped markedly in each group on postoperative day 1. The rates of neuromuscular

symptoms were rather similar between 2 groups. But the rate of incidental removed PGs was higher in the control group than that of the CN group, which implies that, to some extent, CNs can easily distinguish the anatomical boundaries among lymphoid tissue, thyroid tissue, and PGs.

With regard to the long-term results, the PTH levels of the CN group were close to preoperative levels while the control group was lower than preoperative levels at the end of postoperative year 1. The reason to the rapid recovery of PGs function in the CN group may attribute to CN's function in identifying the PGs and their blood supply, which then minimized the risk of incidental removal or devascularization of the PGs. It was noteworthy that the decreased levels of serum Ca^{2+} did not recover along with the increase in serum PTH levels. Supplementation of calcium may significantly impact the levels of serum Ca^{2+} but may not be helpful in recovering PGs function [6]. Patients belong to the control group demanded calcium supplementation more frequently. Therefore, the difference of the serum Ca^{2+} levels between the 2 groups were not statistically significant, but the serum PTH levels were.

The technique of CN suspension injection to the thyroid parenchyma is crucial to lymph node and lymphatic vessels staining. In our opinion, the following skills should be required: (1) the dose of CN is no more than 0.1 ml administered for each area, and the total amount injected will be no more than 0.4 ml per lobe. If lateral lymph node dissection is to be performed, the dose of CN can be up to 0.5 ml per lobe. (2) Injection into lesions is avoided. (3) The injection speed must be slowly. (4) When injecting or withdrawing from the thyroid, the syringe is pumped back to avoid mistakenly injecting CNs into any blood vessels. In this study, 12 events of solution leakage occurred. Among them, 5 events were caused by the injection depth being too shallow. Four events were caused by the high dose of CNs to be injected and other 3 events were owing to pressing the injection site too late.

Although the results of this retrospective study are not convincing enough because of limitations in sample size and the rate of drop-out, our results demonstrated that CNs do play a key role in accurately identifying lymph nodes and promoting rapid recovery of parathyroid function in thyroid carcinoma surgery with CLND. This can be of great benefit to patients, meanwhile, further prospective studies should be performed to determine whether CNs have a prognostic contribute to lymph node dissection and long-term PGs function after thyroid carcinoma surgery combined CLND.

5. Conclusion

In summary, our findings suggest that the CNs should be used in thyroidectomy with CLND, therefore, to protect PGs, to promote more rapid recovery of parathyroid function, and to dissect lymph nodes accurately.

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