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Original Article

Use of carbon nanoparticles to improve the dissection of lymph nodes and the identification of parathyroid glands during thyroidectomy for papillary thyroid cancer

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Abstract: Objective: This study aims to determine whether carbon nanoparticles (CN) can improve the dissection of lymph nodes and aid in the identification and protection of the parathyroid glands (PGs) during thyroidectomy for papillary thyroid cancer (PTC). Methods: PTC patients who underwent total thyroidectomy with ipsilateral or bilateral central lymph node dissection were recruited from April 2013 to March 2015. These patients were assigned to either the CN group or the control group. CN suspension was injected into the thyroid gland to stain this gland and the surrounding lymph nodes. In this manner, the PGs were identified and protected because only the stained thyroid gland and lymph nodes were dissected. The primary end points were the number of dissected lymph nodes, the identified and reimplanted PGs, and the postoperative hypoparathyroidism rate. Results: CN suspension injection was conducted in 195 of the 376 patients. The number of central lymph nodes dissected in the CN group was significantly higher than those dissected in the control group (9.51 ± 4.73 versus 5.36 ± 2.45, $P = 0.001$). The metastatic rates of the lymph nodes were similar between the two groups (25.7% versus 26.4%). More PGs were identified (3.62 ± 0.68 versus 3.29 ± 0.79, $P = 0.002$) and fewer were reimplanted (0.73 ± 0.75 versus 0.96 ± 0.84, $P = 0.048$) in the CN group. A significant difference between the two groups was observed in terms of transient hypoparathyroidism rate (43/195 versus 64/181, $P = 0.006$). No permanent hypoparathyroidism occurred in both groups. Conclusions: The use of CN effectively improves the dissection of central lymph nodes and the protection of the PGs, thereby reducing transient hypoparathyroidism.

Keywords: Papillary thyroid cancer, central lymph node, parathyroid gland, carbon nanoparticles, hypoparathyroidism

Introduction

Papillary thyroid cancer (PTC) is among the fastest growing groups of cancers in recent years [1-3]. Although the majority of PTC patients have excellent prognoses [4], this type of cancer involves cervical lymph nodes in 20%-90% of patients. Metastases of regional lymph nodes may be present even when the primary tumor is small and intrathyroidal [1, 5-8]. Several studies have indicated that central lymph nodes (level VI) are the most commonly involved in metastases [9, 10]. Although lymph node metastasis has been reported to have no clinical importance on the prognosis of low-risk PTC patients, at least two studies have found that such metastasis is an independent risk factor of decreased survival [11, 12]. In addition, recent studies have shown that total thyroidectomy (TT), in conjunction with prophylactic central lymph node dissection (CLND), can decrease locoregional recurrence among PTC patients [13, 14]. Central lymph node metastasis has an important prognostic value for accurate clinical staging and postoperative treatment. The completeness of CLND can improve PTC prognosis. Therefore, TT with CLND is a widely accepted procedure for PTC surgery [15].

However, this procedure is associated with a high incidence of transient or permanent hypoparathyroidism, particularly after bilateral CLND, because of accidental resections of the parathyroid glands (PGs) or the lack of glandu-

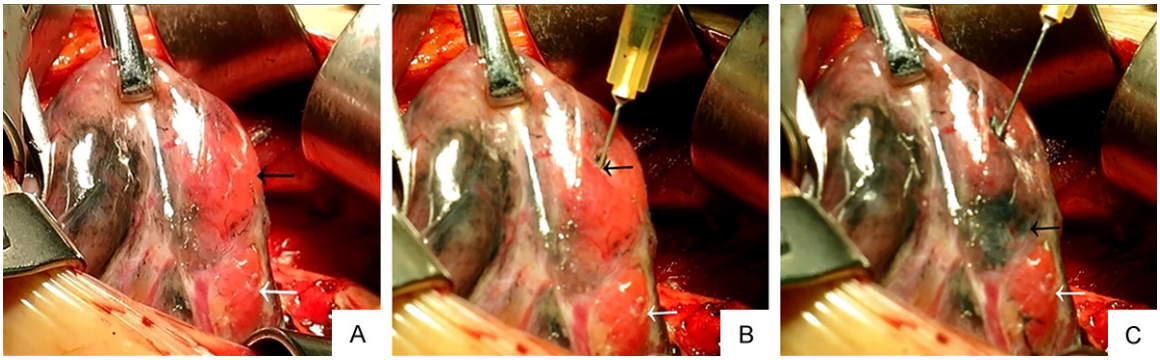

Figure 1. Additional injection. A: Suspicious parathyroid gland (white arrow) was closely related to thyroid gland (black arrow) and the part of thyroid gland was not stained black. B: An additional carbon nanoparticles suspension was injected into thyroid gland (black arrow) next to the suspicious parathyroid gland (white arrow). C: Suspicious parathyroid gland (white arrow) was confirmed because the thyroid gland next to it was stained black (black arrow) while it was not stained black.

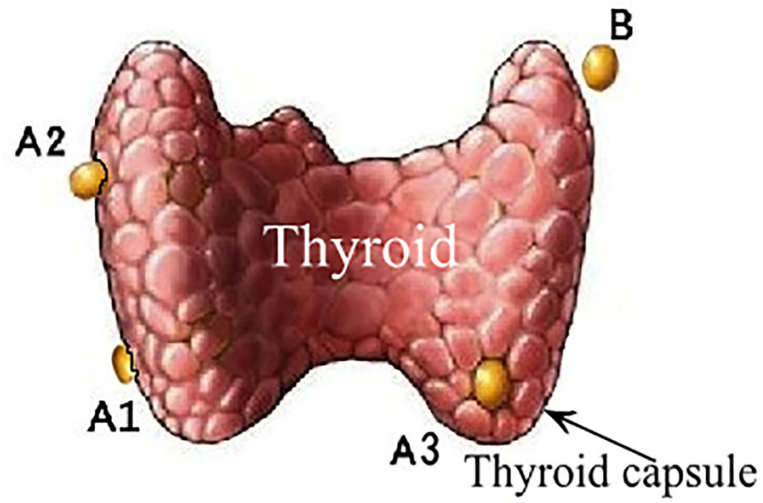

Figure 2. Schematic illustration of the types of parathyroid gland (type A1, A2, A3, and B).

lar blood supply [16, 17]. To protect the glandular blood supply of the PGs, several central lymph nodes may be omitted. Therefore, the clear identification of the PGs and the accurate dissection of central lymph nodes are essential to reduce hypoparathyroidism and locoregional recurrence after thyroidectomy.

Various methods have been applied to identify and protect the PGs, including methylene blue injection, parathyroid scintigraphy, and intraoperative frozen sections [18, 19]. However, the efficacies of these methods remain controversial [20]. The thyroid glands have a rich network of lymphatics, and thus, the lymphatic capillaries of the PGs do not receive thyroid lymph. Therefore, we assume that staining the thyroid gland and the surrounding lymph nodes using lymphatic tracer carbon nanoparticles (CN) is possible to achieve accurate dissection, and consequently, improve the dissection of central lymph nodes and the protection of the PGs during surgery.

Methods

Patients

PTC was diagnosed via histopathological examination after ultrasound-guided fine-needle aspiration biopsy. The patients were enrolled for TT with ipsilateral or bilateral CLND at the Department of Thyroid Surgery, West China Hospital from April 2013 to March 2015. The exclusion criteria included previous thyroid or parathyroid surgery, preoperative hypocalcemia or hypoparathyroidism, pregnancy, lactation, and lateral neck lymph node dissection. PTC patients assigned to the control group were those injected with normal saline solution into the thyroid gland between April 2013 and March 2014. Meanwhile, PTC patients assigned to the CN group were those injected with standard CN (Lai Mei Pharmaceutical Co., Chongqing, China) suspension (1 mL: 50 mg) into the thyroid gland. All the patients were informed and agreed to attend follow-up meetings at least 6 months

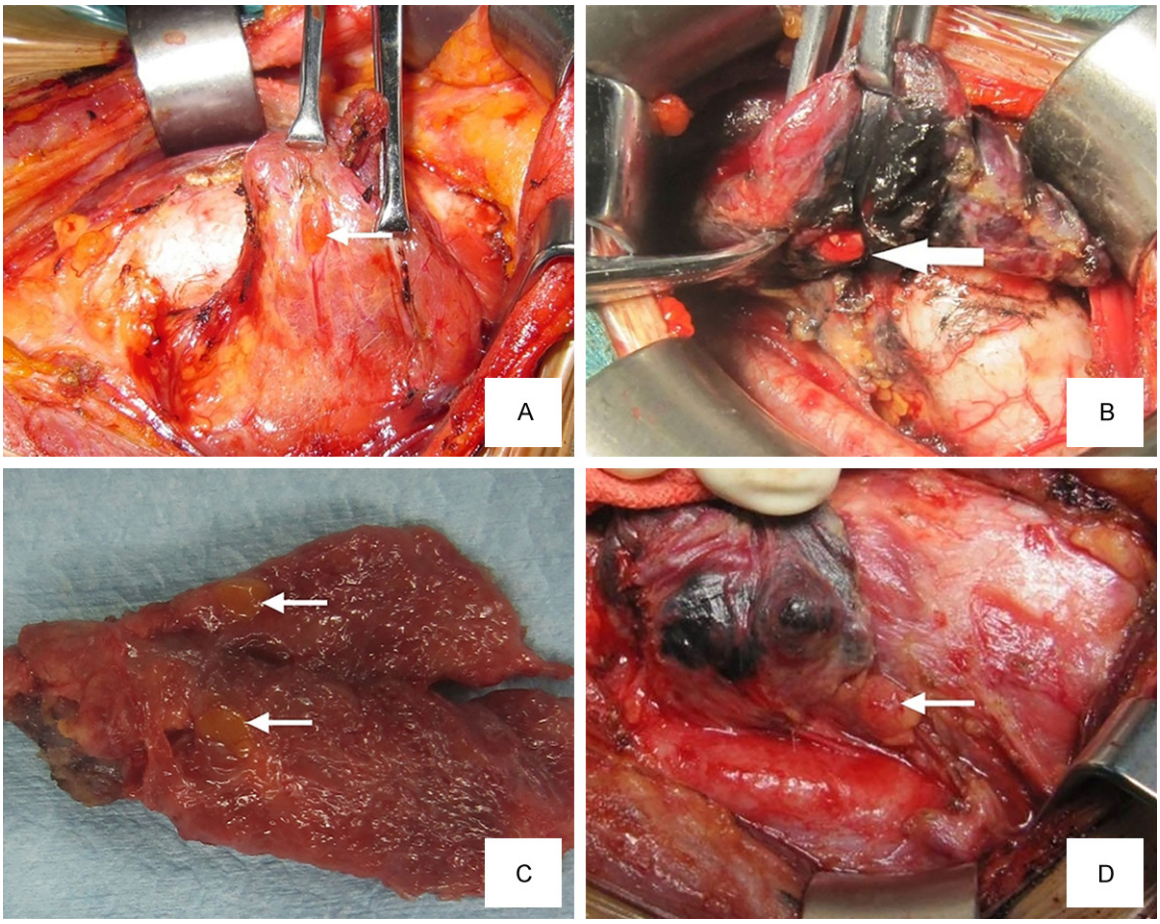

Figure 3. Intraoperative figures description of types of parathyroid gland (white arrow) after carbon nanoparticles suspension injection. A: Type A1 parathyroid gland locates next to thyroid gland and outside of thyroid capsule. B: Type A2 parathyroid gland is embedded in thyroid gland and locates outside of thyroid capsule. C: Type A3 parathyroid gland locates in the resected thyroid gland. D: Type B parathyroid gland had no close relationship with thyroid gland.

after surgery. The study was approved by the Medical Ethics Committee of West China Hospital, Sichuan University.

Surgical procedures

All surgeries were performed by the same surgical team. The surgical procedures for exposing the thyroid gland were conducted according to the methods described by Huang et al. [21]. After the front part of the thyroid gland was exposed, CN suspension or normal saline solution was slowly injected into the upper, middle, and lower poles of the gland (0.1 mL each pole) using a skin test needle. Injection into lesions or blood vessels was avoided. After injection at each point, the site was gently pressed with sterile gauze for 1 min to prevent solution leakage. Then, surgical resection was initiated after 10 min. The thyroid gland and the surrounding lymph tissues (lymph vessels and lymph nodes) were stained black, whereas the PGs were not. When a suspicious PG clung to the thyroid gland or a part of the thyroid gland was not stained black during the surgery, additional CN suspension (0.1 mL) was injected into the thyroid gland beside the unstained part (i.e., additional injection) (**Figure 1**) [22]. A suspicious PG was routinely sent for intraoperative frozen biopsy in both groups. A recurrent laryngeal nerve was identified via intraoperative neuromonitoring (Medtronic NIM Response 2.0). The indications for TT were as follows: (1) high risk; (2) bilateral or multifocal PTC; (3) PTC>1 cm; (4) extrathyroidal invasion; (5) age >45 years with metastases of neck lymph nodes; (6) pathological variables, including tall cell, diffuse sclerosis, solid, and follicular variants; (7) distant

Table 1. Characteristics of the patients in the two groups

	CN group (n = 195)	Control group (n = 181)	*P* Value
Age (years)	43.38 ± 11.65	45.67 ± 13.50	0.202
Gender (male/female)	57/138	55/126	0.822
Thyroiditis	39	44	0.323
Hyperthyroidism	14	9	0.398
Calcium (mmol/L)	2.31 ± 0.13	2.30 ± 0.12	0.725
PTH (pmol/L)	5.19 ± 1.87	5.61 ± 2.16	0.139
Laryngoscope (abnomal)	5	7	0.563
TT + bilateral CLND	130	109	0.200
Tumor size (cm)	1.03 ± 0.61	1.04 ± 0.57	0.953
Multifocality (≥2)	39	34	0.795

CN: carbon nanoparticles; PTH: parathyroid hormone; TT: total thyroidectomy; CLND: central lymph node dissection.

metastases; and (8) BRAF (V600E)-positive mutation. The indications for bilateral CLND were as follows: (1) bilateral PTC, (2) PTC>1 cm and located in an isthmus, (3) PTC with stages T3 and T4, (4) prelaryngeal and pretracheal lymph node metastases, (5) metastases on opposite sides of central lymph nodes, and (6) BRAF (V600E)-positive mutation. The remaining patients underwent prophylactic or therapeutic ipsilateral CLND.

Perioperative management

Perioperative management was standardized. Serum calcium, parathyroid hormone (PTH), and thyroid function were tested. Thyroid ultrasound and laryngoscope were conducted in each patient before surgery. Postoperative hypoparathyroidism was defined as a PTH measurement <1.6 pmol/L (normal range: 1.6-6.9 pmol/L) after surgery. PTH was routinely tested 1 day, 3 days, 30 days, and 3 months after surgery. Oral calcium supplement or intravenous substitution of calcium therapy was conducted among patients with symptomatic hypocalcemia. A final PTH test was performed for these patients 6 months after surgery. If PTH still did not return to normal, then hypoparathyroidism was classified as permanent; otherwise, it would be classified as transient.

PG classification

Given the difficulty in preserving a PG in situ and based on *the positional relationship between the* thyroid gland and the PGs*,* the PGs were classified into two types (types A and B) in the department of the researchers (**Figure 2**) [22]. Type A PG has three subtypes, namely, A1, A2, and A3. Type A1 PG clings to the thyroid gland and is located outside the thyroid capsule (extracapsular). Thus, this type is difficult to separate from the thyroid gland (**Figure 3A**). Type A2 PG is embedded into the thyroid gland, but is also located outside the thyroid capsule (extracapsular). It is extremely difficult to separate from the thyroid gland (**Figure 3B**). Type A3 PG is located in the thyroid parenchyma (intrathyroidal) or within the thyroid capsule (subcapsular or intracapsular), and can only be found in resected thyroid specimens (**Figure 3C**). Type B PG has no close relationship with the thyroid gland (extracapsular), and thus, is easy to separate from it (**Figure 3D**).

Data collection

All the data were collected prospectively, including the general characteristics (age, sex, and comorbidities), preoperative examinations (laboratory examination, ultrasound, and laryngoscope), intraoperative factors (surgical procedure, operating time, number and type of PGs, and PG protection), pathologic examinations, number of central lymph nodes retrieved in resected specimens, black-stained central lymph nodes, metastatic central lymph nodes, postoperative laboratory examinations, morbidity, and mortality. The PG identification index (PII) was defined as the ratio between the number of times that a PG was confirmed via intraoperative frozen biopsy and the number of times that a suspicious PG was sent for intraoperative frozen biopsy. An accidental PG resection was defined as resection performed without finding a PG during surgery (including serial examination of the resected specimens) but finding one in the final pathological examination. The American Joint Committee on Cancer staging (seventh edition) was applied to all the PTC patients [23]. The primary end points were the number of dissected lymph nodes, the identified and reimplanted PGs, and the postoperative hypoparathyroidism rate.

Statistical analysis

Continuous variables were presented as mean ± standard deviation. Statistical analysis was

Table 2. The details of PG identification in the two groups

	CN group (n = 195)	Control group (n = 181)	*P* Value
Type A1 PG	239 (38.0)	177 (37.5)	0.004
Type A2 PG	28 (4.5)	5 (1.1)	0.001
Type A3 PG	6 (0.9)	1 (0.2)	0.123
Type B PG	356 (56.6)	289 (61.2)	0.001
PG identification	3.23 ± 0.68	2.61 ± 0.79	0.002

Data are no. (%) of total number of parathyroid gland identification. CN: carbon nanoparticles; PG: parathyroidgland.

Table 3. The details of PG re-implantation in the two groups

	CN group (n = 195)	Control group (n = 181)	*P* Value
Type A1 PG	105 (47.1)	98 (42.8)	0.023
Type A2 PG	15 (6.7)	4 (1.7)	0.106
Type A3 PG	6 (2.7)	1 (0.4)	0.123
Type B PG	97 (43.5)	126 (55.1)	0.001
PG re-implantation	1.14 ± 0.76	1.27 ± 0.84	0.017

Data are no. (%) of total number of parathyroid gland re-implantation. CN: carbon nanoparticles; PG: parathyroid gland.

performed using SPSS software (version 19.0). Statistical comparison was conducted between the CN group and the control group by using the χ^2 test or Student's *t*-test. $P<0.05$ was considered statistically significant.

Results

Patient characteristics

Among the 376 patients recruited for the study, 195 received CN suspension injections and 181 received saline solution injection (controls). Subsequently, 130 patients from the CN group and 109 from the control group underwent TT with bilateral CLND, whereas 65 patients from the CN group and 72 from the control group underwent TT with ipsilateral CLND. As shown in **Table 1**, no significant difference was noted for general characteristics, preoperative examinations, and surgical procedures between the two groups. Moreover, no significant difference was observed between the two groups in terms of PTC pathological stages. The mean operating time was significantly shorter in the CN group than in the control group (127.33 ± 25.06 min versus 144.86 ± 27.40 min, $P = 0.000$).

Dissection of central lymph nodes

In the CN group, 1854 central lymph nodes were dissected, with an average of 9.51 ± 4.73 per patient. Among these, 1359 central lymph nodes (73.3%) were stained black and 476 (25.7%) were confirmed to be metastatic lymph nodes. In particular, 353 (74.2%) were black-stained metastatic lymph nodes and 123 (25.8%) were unstained metastatic lymph nodes. The metastatic rates of black-stained and unstained metastatic lymph nodes were 30.0% (353/1359) and 24.8% (123/495), respectively, which did not amount to a statistically significant difference ($P = 0.674$). In the control group, 970 central lymph nodes were dissected, with an average of 5.36 ± 2.45 per patient. The difference in the number of lymph nodes dissected between the two groups was statistically significant ($P = 0.001$). The number of metastatic lymph nodes in the control group was 256 (26.4%). The metastatic rates of the lymph nodes were similar between the two groups ($P = 0.684$).

PG identification

In the CN and control groups (**Table 2**), 629 and 472 PGs were identified, respectively. The identified number of PGs and types A1, A2, and B PGs were significantly higher in the CN group than in the control group. No significant difference was noted between the two groups in the number of type A3 PG. However, type A3 PG was observed in 6 patients in the CN group, whereas only 1 was identified in the control group.

PG protection

The details of PG reimplantation in the two groups are presented in **Table 3**. In total, 223 PGs (35.5%) in the CN group and 229 PGs (48.5%) in the control group were reimplanted ($P = 0.000$). The reimplantation rates of types A1 and B PGs were significantly lower in the CN group than in the control group ($P = 0.023$ and $P = 0.000$, respectively). The two groups had comparable reimplantation rates for other types of PG. Nevertheless, a significant difference in terms of the mean number of PGs for reimplantation was observed between the CN

Table 4. The postoperative complications in the two groups

	CN group (n = 195)	Control group (n = 181)	*P* Value
Transient hypoparathyroidism	43 (22.1)	64 (35.4)	0.006
Transient hoarseness	21 (10.8)	28 (15.5)	0.220
Chylous fistula	3 (1.5)	1 (0.6)	0.624
Bleeding	2 (1.0)	2 (1.1)	1.000
Wound infection	4 (2.1)	6 (3.3)	0.531
Pneumonia	0 (0.0)	2 (1.1)	0.231
Permanent hoarseness	2 (1.0)	3 (1.7)	0.675

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

group and the control group (1.14 ± 0.76 versus 1.27 ± 0.84, $P = 0.017$).

The PIIs in the CN group and the control group were 82.3% (223/271) and 72.0% (229/318), respectively ($P = 0.003$). The final pathological examination presented 12 cases of accidental PG resection in the CN group, whereas 19 cases of accidental PG removal occurred in the control group. No statistically significant difference was observed between the two groups ($P = 0.137$).

Postoperative complications and follow-up

Table 4 summarizes the postoperative complications in the two groups. Transient hypoparathyroidism was documented in 43 of the 195 patients (22.1%) in the CN group and 64 of the 181 patients (35.4%) in the control group ($P = 0.006$). No significant difference was found between the two groups in terms of the occurrence of transient hoarseness, chylous fistula, bleeding, wound infection, and pneumonia. All the patients completed a 6-month follow-up period. No permanent hypoparathyroidism was found in both groups. Permanent hoarseness occurred in 2 patients in the CN group and 3 patients in the control group ($P = 0.675$).

Discussion

The crucial components for CN suspension injection are nanocarbon granules, which have a mean diameter of 150 nm and exhibit lymphatic tropism. The gap between capillary endothelial cells is 20-50 nm, whereas the gap between endothelial cells of lymph capillaries is 120-150 nm. Therefore, after being injected into thyroid tissue, CN enter lymphatic capillaries instead of blood capillaries and immediately enter into drainage lymph nodes. Finally, thyroid tissues and the surrounding lymph nodes are stained black, which facilitate completion of lymph node dissection.

The current study determined a significantly higher number of central lymph nodes dissected in the CN group than in the control group. The potential reasons for this result are as follows: (1) more smaller lymph nodes are dissected in the CN group, (2) more lymph nodes in the VII region are dissected in the CN group, and (3) identification of black-stained lymph nodes by pathologists is easier. Similar rates of lymph node metastasis were found in the two groups, and CN could effectively improve the dissection of metastatic lymph nodes. Nevertheless, similar rates of lymph node metastasis were observed when lymph nodes were either stained black or unstained in the CN group. Therefore, black-stained lymph nodes were not associated with metastasis, and CN could not be used to identify the presence or absence of metastasis.

Hypoparathyroidism is a major and severe complication of thyroidectomy. The incidence of transient hypoparathyroidism after thyroidectomy was reported to be 14%-60%, whereas that of permanent hypoparathyroidism was 4%-11% [24-27]. Different surgical procedures and the inconsistent definition of postoperative hypoparathyroidism are the main causes of the considerable differences. In the current study, the transient hypoparathyroidism rate was 28.5%, which was in line with previous studies. However, no permanent hypoparathyroidism occurred in the two groups.

To avoid hypoparathyroidism, preserving the PGs in situ during thyroidectomy with CLND is important. An experienced surgeon in thyroid surgery and cautious dissection are considered major factors that can protect the PGs [28]. Nevertheless, injury may not be avoided and the PGs are sometimes found in surgical specimens. Such consequences are largely attributed to their locations. One study reported that 50%, 31%, and 22% PGs were found in the intrathyroidal, extracapsular, and central node compartment sites, respectively [29]. The descriptions of the location cannot accurately reflect the anatomy of the PGs and *the difficulty*

in preserving the PGs in situ. To date, no study on PG classification has yet been reported. In the department of the researchers, the PGs are initially classified into two types to accurately record their locations and reflect *the difficulty in preserving the PGs in situ.* These type are types A (A1, A2, and A3) and B. The effectiveness of numerous methods used to identify and protect the PGs can be accurately evaluated given the unified classification.

Emerging evidence has shown that the thyroid gland is rich lymphatics and lymphatic capillaries, whereas nearly none of these components are present in the PGs. Therefore, CN suspension is applied to identify and protect the PGs. After CN suspension injection, the thyroid tissues and the surrounding lymph nodes are stained black, whereas the PGs maintain their original color. Consequently, the adjacent black-stained thyroid tissues and the surrounding lymph nodes are remarkably distinguished. In the present study, CN could not only effectively aid in identifying the PGs, but could also significantly preserve the PGs in situ. Accordingly, the reimplantation rates during TT and CLND were reduced, which resulted in the significantly lower incidence of transient hypoparathyroidism. A recent study investigated the relationship between hypoparathyroidism and the number of PGs preserved during thyroidectomy. This study also concluded that preserving all the PGs could decrease transient hypoparathyroidism compared with when only three or less glands were preserved; however, this procedure did not affect permanent hypoparathyroidism [30].

In theory, black-stained thyroid tissues help identify type A PG, whereas black-stained lymph nodes help identify type B PG. However, type A3 PG appears to gain no benefit from CN suspension injection. Although no significant difference was observed in terms of the incidence of accidental PG resections between the two groups, the PII was significantly higher in the CN group than in the control group, which further confirmed that CN could effectively aid in identifying the PGs. The main causes of the aforementioned results may be the small sample size and the experienced surgeons. Therefore, future multicenter, randomized trials of large sample sizes will generate more convincing data concerning the advantage of CN suspension injection.

In summary, the current study showed that CN could be used to effectively identify the thyroid gland and central lymph nodes for dissection, thereby protecting the PGs and reducing the occurrence of transient hypoparathyroidism.

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Disclosure of conflict of interest

None.

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