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Application of carbon nanoparticles in localization of parathyroid glands during total parathyroidectomy for secondary hyperparathyroidism

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ABSTRACT

Background: Intraoperative imaging is used to address the challenges of parathyroidectomy, but no standard modality has been established. This study aimed to assess whether carbon nanoparticle injection is useful in localizing parathyroid glands (PGs) during parathyroidectomy.
Methods: Patients who underwent total parathyroidectomy (TPTX) between September 2015 and November 2018 were included. The operative duration and intact parathyroid hormones (iPTH) were analyzed.
Results: A total of 61 patients were included; of these, 32 with carbon nanoparticle injection (TPTX + CN group) and 29 without (TPTX group). The operative duration in the TPTX + CN group was significantly shorter (90.6 ± 21.2 vs 101.4 ± 19.4 min, P = 0.042), which is more apparent in those with normal sized PGs. For those with four enlarged PGs, iPTH levels on 1 day and 1 year postoperatively were significantly lower in the TPTX + CN group (P = 0.032 and P = 0.036, respectively).
Conclusion: Carbon nanoparticles are useful in the identification normal sized PGs and complete resection of enlarged PGs.

Introduction

Secondary hyperparathyroidism (SHPT) is a common severe complication of chronic kidney disease (CKD) that leads to osteodystrophy and vascular calcification.[1] The 2017 Kidney Disease Improving Global Outcomes guidelines stipulate that surgical treatment remains an effective treatment modality for those who fail to respond to pharmacological therapy and have a persistent high level of parathyroid hormone (PTH).[2] Recent meta-analyses have reported that total parathyroidectomy (TPTX) is the optimal option for the surgical treatment of SHPT with respect to minimizing the recurrence rate.[3] However, TPTX continues to have unsatisfactory surgical outcomes as the incidence of persistent or recurrent SHPT could be up to 20%.[4] Excessive residual parathyroid glands (PGs) due to incomplete excision, ectopic PGs, or supernumerary PGs are the main contributing factor for persistent SHPT or recurrence after surgery.[5]

The size of the PGs varies considerably in SHPT patients, with Li et al.[6] reporting a ranged of 0.4–3.5 cm, and the most common challenges during total parathyroidectomy (TPTX) include the localization of small PGs and complete resection of enlarged PGs due to hyperplasia.[7] Currently, there is no established method for accurate localization of PGs. Methylene blue has been reported to concurrently stain thyroid glands and lymph nodes,[8] while indocyanine green fluorescence imaging is expensive and could only be used in video-assisted surgeries.[9] In China, carbon nanoparticles (approved by China Food and Drug Administration, No.H20041829; Lai Mei Pharmaceutical CO, Chongqing, China) have been applied in thyroidectomy for the identification and in situ protection of PGs over 5 years.[10,11] Since its introduction, no injection-associated allergies, hematoma, or nerve injury have been reported.[12] Because of the special diameter of the granules, the nanoparticles could be

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captured by macrophages and enter the lymphatic ducts instead of blood capillaries.[13] Consequently, the thyroid gland and the lymph nodes are black stained, while PGs are unstained.[14] This "identification and protection" procedure has been proven to have the advantages of convenience and safety.[14] Carbon nanoparticle injection clearly distinguishes the border between the thyroid glands and the PGs, and this could be helpful in identifying the PGs and reducing the residual PGs in situ. However, a few studies have evaluated the use of carbon nanoparticles in parathyroidectomy.[15] In 2018, Chen et al.[16] reported combined use of carbon nanoparticles and 99mTc-MIBI in total parathyroidectomy, which was complex and challenging.

Therefore, this study aimed to retrospectively analyze if the utility of carbon nanoparticles is useful in shortening the duration of surgery and complete resection of the PGs.

Materials and methods

Ethics statement

The study was approved by the Ethics Committee of Shanghai Changzheng Hospital affiliated to the Naval medical university, and written informed consents were obtained from all patients.

Study design and subjects

A retrospectively cohort study was performed on patients who underwent TPTX by the same surgical team between September 2015 and November 2018 in our department. Patients with(1) sustained serum PTH over 800 pg/ml and medication failure; (2) at least one enlarged parathyroid gland measuring more than $8mm^3$; and (3) severe symptoms, such as bone pain, pruritus, and ectopic calcification were included. Meanwhile, the exclusion criteria were (1) previous history of neck surgery, (2) history of concurrent thyroidectomy and other surgery, and (3) missing data. The patients were then divided into two groups according to the use of carbon nanoparticle injection; the TPTX + CN group and the TPTX group comprised those who underwent TPTX with and without carbon nanoparticle injection, respectively. Allocation of patients was nonrandomized.

Operative procedures

After general anesthesia, a 5-cm curved neck incision was performed, similar to that in thyroidectomy. The anterior capsule was carefully dissociated to expose each lobe of thyroid. For patients in TPTX + CN group, approximately 0.1–0.2 ml of carbon nanoparticles suspension (with a standard concentration of 50 mg/ml) was slowly injected into the middle points of each lobe, after which the whole thyroid gland turned dark rapidly (see Fig. 1A and B). The injection site was pressed by gauze for 10 seconds to avoid exosmosis. After injection, the middle thyroid veins were cut and the lateral of thyroid lobe was dissected to identify PGs. For patients in the TPTX group, routine exposure of the PGs was performed without any injection (see Fig. 1C). The excised PGs were analyzed via frozen section examination. Neck exploration and bilateral thymectomy were performed in both groups when less than four PGs were removed. The number of PGs resected, the maximal diameter of each PG, and the operative duration were recorded.

Perioperative management and definitions

Preoperative imaging including ultrasound and 99mTc-MIBI scintigraphy was conducted in both groups. Unfortunately, we didn't employ intraoperative parathyroid hormone (ioPTH) monitoring in both groups. Serum intact parathyroid hormone (iPTH), calcium and phosphate were routinely measured on day 1 after surgery. Intravenous supplementation of calcium gluconate was performed when patients complained of hypocalcemia symptoms or when the serum calcium was lower than the threshold value of 2.1 mmol/l.

Ectopic PGs were defined as those located in uncommon sites and required additional exploration or were missed.[17] Normal sized PGs were defined as glands with a maximal diameter of less than 8 mm, which is reported to be the maximal size of normal PGs.[18] Supernumerary PG was assumed when patients have more than 4 PGs confirmed by surgery and pathology. Transient and permanent hypoparathyroidism were defined as serum iPTH lower than 15 pg/ml within 6 months and 6 months post-surgery, respectively. Persistent SHPT was defined as a sustained rise in PTH levels that were five-fold greater than the upper threshold of normal value within a 6-month period following surgery. SHPT recurrence was defined as increased PTH levels that were five-fold greater than the upper threshold of normal value after the 6-month period following surgery.[19] Both persistent SHPT and recurrence were assumed as surgical failure.

The primary outcome was operative duration, while secondary outcomes included (1) the incidence of persistent SHPT as well as recurrence and (2) the incidence of complications such as vocal cord palsy and neck hematoma.

Statistical analysis

Measurement data were presented as mean ± standard deviation (mean ± SD) or median (interquartile range), and categorical data were expressed as frequencies (%). Data were analyzed using Student's *t*-test, Mann-Whitney *U* test, chi-squared test, and Fisher Exact test as appropriate. All statistical analyses were performed using the SPSS software version 19.0 (IBM-SPSS, Inc., Chicago, IL, USA), and a two-sided P value of <0.05 was considered significant.

Results

Patient characteristics

Of the 67 patients identified, one with a previous history of neck surgery (n = 1) and five with a history of combined thyroidectomy (n = 5) were excluded. Thus, 61 patients were included in the final analysis. Of these, 32 and 29 patients belonged to the TPTX + CN group and the TPTX group, respectively. No patients in both groups underwent parathyroid glands auto-transplantation. The clinical characteristics of the two groups are listed in Table 1. There were no significant differences in age, sex, BMI, dialysis duration, and preoperative serum iPTH, creatine and hospital stay between the two groups.

Characteristics of PGs

No ectopic or supernumerary PGs were found throughout preoperative imaging. A total of 9 cases were determined to have ectopic PGs, 4 in TPTX group and 5 in TPTX + CN group, respectively (Table 1). Characteristics of ectopic PGs could be divided as (1) intrathymic, 1 in TPTX group, (2) intrathyroidal, 1 in TPTX + CN group, (3) the descending superior PG, 1 in TPTX + CN group, (4) the descending inferior PG, 1 in TPTX group and 1 in TPTX + CN group, and (5) unknown, 2 in TPTX group and 2 in TPTX + CN group. Supernumerary PGs were identified by MIBI in 2 patients during follow-up, 1 was located in the right carotid sheath from TPTX group, and another one was located in the right supraclavicular fossae from TPTX + CN group. Both patients underwent reoperative

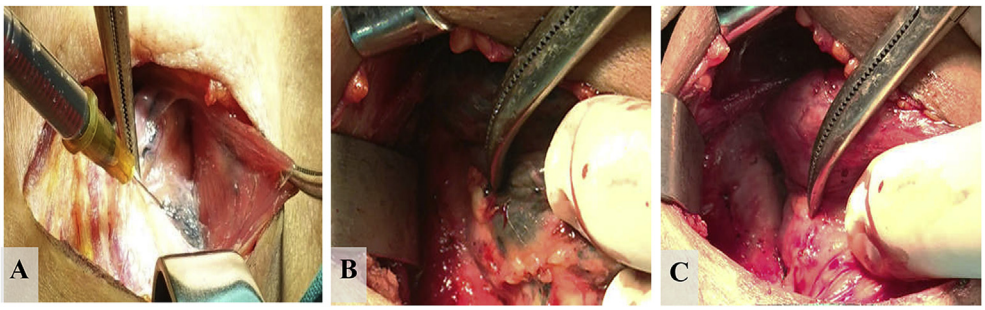

Fig. 1. Surgical procedures. **(A)** Approximately 0.1–0.2 ml carbon nano particles were injected into subcapsular area of the thyroid gland. **(B)**The whole thyroid gland turned dark rapidly while the parathyroid glands didn't. **(C)** Parathyroid glands in those without carbon nano particles injection. Abbreviations in Figures: PG, Parathyroid gland.

parathyroidectomy within the year that followed surgery.

Comparison of surgical outcomes

The operative duration was significantly shorter in the TPTX + CN group (101.4 ± 19.4 min in TPTX group and 90.6 ± 21.2 min in TPTX + CN group, P = 0.042) (Table 2). The occurrence of persistent SHPT and recurrence were not significantly different between the TPTX and TPTX + CN groups (p = 0.614 and p = 0.611, respectively). Detailed information regarding surgical failure is described in Supplementary Table S1. There were no significant differences in iPTH levels observed between the groups either 1 day or 1 year post-surgery.

No supernumerary PGs were found in patients assumed as surgical success. A subgroup analysis, investigating the potential role of carbon nanoparticles on detection of normal sized PGs, was conducted on those defined as successful surgery and had no ectopic PGs (Table 3). We found that among patients with 1 or 2 normal sized PGs, the mean operative duration was significantly shorter in the TPTX + CN group than that in the TPTX group (P = 0.033 and P = 0.026, respectively), while the difference did not reach statistical significance among patients with no normal sized PGs (P = 0.413). Notably, iPTH levels on 1 day and 1 year post-surgery of patients with no normal sized PGs in the TPTX + CN group were significantly lower than that in the TPTX group (P = 0.032 and P = 0.036).

Complications

There were also no significant differences in the incidence of hypoparathyroidism (12.5% vs 10.3%, P > 0.999) between the TPTX + CN and the TPTX groups. No permanent hypoparathyroidism and recurrent laryngeal nerve injury occurred in both groups. One patient in the TPTX + CN group underwent reoperation because of hematoma.

Table 1
The clinical characteristics of patients in both groups.

	TPTX group (n = 29)	TPTX + CN group (n = 32)	P value
Age (year)	50.6 ± 10.8	49.4 ± 12.8	0.708
Gender			0.481
Females (N, %)	11 (37.9)	15 (46.9)	
Males (N, %)	18 (62.1)	17 (53.1)	
BMI (kg/m^2)	22.3 ± 2.6	22.2 ± 3.2	0.882
Dialysis duration (year)	7.3 ± 3.6	7.4 ± 3.7	0.875
Preoperative Serum iPTH (pg/ml)	1624.2 ± 567.0	1600.0 ± 656.8	0.879
Preoperative serum creatine (μmol/L)	1061.7 ± 324.4	1012.9 ± 306.7	0.548
Hospitalization time (day)	5 (5-6)	6 (5-8)	0.231
Patients with 4 PGs resected	27 (93.1)	30 (93.8)	>0.999
Patients with ectopic PGs (N, %)	4 (13.8)	5 (15.6)	>0.999
Patients with normal sized PGs (N, %)			0.264
None (N, %)	17 (58.6)	24 (75.0)	
1 (N, %)	9 (31.0)	4 (12.5)	
2 (N, %)	3 (10.3)	4 (12.5)	

Data are presented as the means ± SD, median (interquartile range) or number (%). Abbreviations: *N*, number; *PGs*, Parathyroid glands.

Table 2
Surgical outcomes of TPTX and TPTX + CN patients.

Variables	TPTX group (n = 29)	TPTX + CN group (n = 32)	P value
Operative duration (min)	101.4 ± 19.4	90.6 ± 21.2	0.042
Persistent SHPT (N, %)	1 (3.4)	3 (9.4)	0.614
Recurrence (N, %)	2 (7.1)	1 (3.4)	0.611
POD1 iPTH (pg/ml)	27.9 (4.5–878.0)	23.5 (7.7–1216.0)	0.260
1-year iPTH (pg/ml)	46.1(19.6–567.0)	34.8 (16.8–765.0)	0.067

Data are presented as the means ± SD, number (%) or median (interquartile range). Abbreviations: *N*, number; *SHPT*, Secondary hyperparathyroidism; *POD1 PTH*, Serum iPTH on postoperative day 1; *1-year iPTH*, Serum iPTH on1 year after surgery.

Table 3
Analysis on those defined as surgical success and had no ectopic PGs.

Variables	TPTX group (n = 24)	TPTX + CN group (n = 25)	P value
Number of normal sized PGs (N = 0)			
Number of patients (n)	14 (58.3)	18 (72.0)	
Operation duration (min)	90.4 ± 17.5	84.4 ± 21.7	0.413
POD1 PTH (pg/ml)	29.8 ± 13.6	21.2 ± 8.0	0.032
1-year iPTH (pg/ml)	46.4 ± 22.3	32.5 ± 13.0	0.036
Number of normal sized PGs (N = 1)			
Number of patients (n)	8 (33.3)	3 (12.0)	
Operation duration (min)	103.1 ± 12.8	83.3 ± 5.8	0.033
POD1 PTH (pg/ml)	29.3 ± 18.3	28.7 ± 4.5	0.958
1-year iPTH (pg/ml)	46.3 ± 25.0	36.4 ± 7.2	0.528
Number of normal sized PGs (N = 2)			
Number of patients (n)	2 (8.3)	4 (16.0)	
Operation duration (min)	120.0 ± 14.1	87.5 ± 9.6	0.026
POD1 PTH (pg/ml)	41.6 ± 19.2	31.2 ± 10.6	0.415
1-year iPTH (pg/ml)	50.3 ± 22.3	37.9 ± 13.3	0.423

Data are presented as the means ± SD, number (%). Abbreviations: *PGs*, Parathyroid glands; *POD1 PTH*, Serum iPTH on postoperative day 1; *1-year iPTH*, Serum iPTH on1 year after surgery.

Discussion

TPTX is challenging due to the variability of parathyroid glands.[5] Several intraoperative imaging techniques have been applied in parathyroid surgery, of which carbon nanoparticles injection is cost-effective.[9,20] To our knowledge, this is the first retrospective study that thoroughly evaluated the effects of carbon nanoparticle injection in parathyroidectomy. We found that carbon nanoparticle injection could markedly shorten the operative duration, particularly for those with normal sized glands. Furthermore, patients with no normal sized PGs in the TPTX + CN group had a lower level of serum iPTH on 1 day and 1 year post-surgery, which may primarily be attributed to reduced residual PGs. These findings indicate that carbon nanoparticle injection is a promising technique in parathyroid surgery.

In our study, the PG borders were adequately distinct to confirm complete excision (Fig. 2A–C). Therefore, we believe that TPTX could be more standardized with the application of carbon nanoparticles. Serum iPTH levels on 1 year after surgery in the TPTX + CN group tended to be lower than those in the TPTX group, although differences were not significant [Median (interquartile range), 34.8 (25.8–48.7) vs 46.1(32.6–63.0), respectively; P = 0.067]. Subgroup analysis showed that the iPTH levels on postoperatively day one and year one of those with no normal sized PGs in the TPTX + CN group were significantly lower than the TPTX group, probably because of the decreased residual PG tissues in the TPTX + CN group. Theoretically, more distinctive differences in serum iPTH and incidence of recurrence are most likely to be observed throughout the long-term follow-up of patients. This is because the continuing proliferation of residual parathyroid tissues is likely to occur in CKD patients.

Generally, ectopic, small sized and supernumerary PGs are the major factors leading to prolonged surgical duration.[21] Patients with renal failure are at increased risk under general anesthesia, as a result of which, researches on preoperative and intraoperative imaging techniques are proposed to shorten surgical duration.[9,22] Neck ultrasound has been reported to be much less accurate for small glands (<10 mm).[23] Our findings suggest that application of carbon nanoparticles could significantly shorten surgical duration in general. Subgroup analysis showed that the operative duration of patients with 1 or 2 normal sized PGs was remarkably shorter in the TPTX + CN group (83.3 ± 5.8 vs 103.1 ± 12.8, P = 0.033 and 87.5 ± 9.6 vs 120.0 ± 14.1, P = 0.026, respectively). These findings suggested that carbon nanoparticle injection is effective for localizing PGs and is still useful for detection of normal sized PGs in situ. The contrast between thyroid and surrounding tissues provided by the use of carbon nanoparticles helps surgeons to identify PGs in situ quickly, which is the mechanism of most intraoperative imaging for localization of PGs. In this current study, the contrast formed by carbon nanoparticles was stable and dramatic (see Fig. 1B), suggesting that carbon nanoparticles injection is optimal for intraoperative imaging.

Approximately 66% of missed PGs in reoperative parathyroidectomy are comprised of ectopic PGs.[24] In this current study, ectopic PGs were observed in 9 patients, of which 1 was intrathymic PG, 1 was intrathyroidal PG, 3 were descending PGs and 4 were missed PGs. Carbon nanoparticles injection could be helpful for detecting intrathyroidal PGs as well as distinguishing between

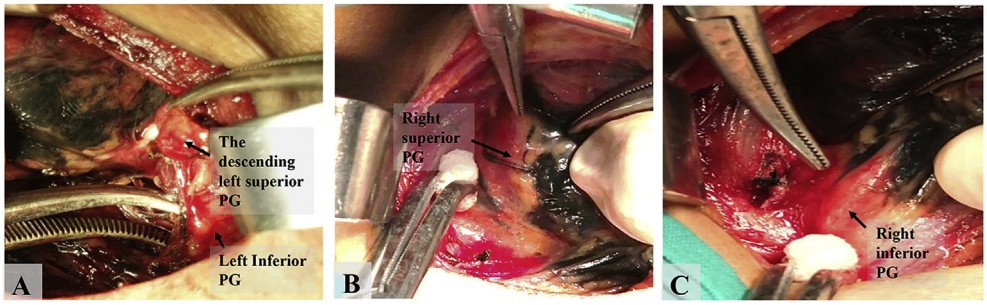

Fig. 2. Parathyroid glands in those with carbon nanoparticles injection. **(A)** The left superior parathyroid gland was ectopic due to gravity. **(B) and (C)** The PG borders were adequately distinct after the injection of carbon nano particles. Abbreviations in Figures: PG, Parathyroid gland.

lymph nodes and PGs, thus shortening the duration needed for neck exploration. It has been reported that missed ectopic PGs are mostly likely to locate in the mediastinum and thymic tongue.[5,25] In another retrospective study, approximately 18% of patients that underwent subtotal parathyroidectomy with prophylactic bilateral thymectomy had thymic supernumerary glands.[26] In this current study, bilateral thymectomy was performed only when the 4th PG failed to be found and an intrathymic PG was found in one patient. This fact favors that bilateral thymectomy could partly prevent recurrence through improving the detection of intrathymic PGs. In general, application of carbon nanoparticles will likely accelerate neck exploration but will not be as useful for identifying ectopic or supernumerary PGs located in the mediastinum and thymus. For these patients, preoperative imaging as well as bilateral thymectomy could enhance rates of surgical success and compensate for the inadequacy of carbon nanoparticles injection to a certain extent.

This study has some limitations. First, long-term follow-up was not performed. Serum iPTH levels on 1 year postoperatively in the TPTX + CN group tended to be lower although differences were not significant. Theoretically, these differences would likely be more pronounced in the long-term because of the proliferation of residual PGs. Second, ioPTH monitoring was not applied in this study, since it was not widely used in China during the study period. Instead, the iPTH on post-operative day one as well as the number of PGs confirmed by pathology were used to predict the surgical success, which is in accordance with the concept described by Schneider et al.[27] Third, the study population, particularly those with ectopic PGs, was small.

Conclusions

The present study highlights that application of carbon nanoparticles plays an important role in detection of normal sized PGs and complete excision of enlarged PGs via visual contrast among thyroid glands, lymph nodes and PGs. Similarly, carbon nanoparticles injection could accelerate cervical exploration for identifying ectopic or supernumerary PGs, but will not be as useful when PGs located outside of central cervical compartment. In general, carbon nanoparticle injection is effective and convenient as an assistive modality for TPTX.

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Data statement

Data of this article will be made available on request.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2020.04.034.

Abbreviation list

CKD	chronic kidney disease
PGs	parathyroid glands
POD1	postoperative day 1
1-year iPTH	Serum iPTH on1 year after surgery
PTH	parathyroid hormone
SHPT	secondary hyperparathyroidism
TPTX	total parathyroidectomy

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