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Review Article

Carbon nanoparticles improve lymph node dissection and parathyroid gland protection during thyroidectomy: a systematic review and meta-analysis

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Abstract: Objective: To assess whether carbon nanoparticles can effectively improve the quality of lymph node dissection and protect parathyroid glands during thyroidectomy. Methods: A systematic literature search (MEDLINE, OVID, EMBASE, Science Citation Index, and Cochrane Library Central) was performed to identify randomized controlled trials before July 31, 2017. Articles with comparison of use and non-use of carbon nanoparticles during thyroidectomy were included. The primary endpoints were the number of lymph nodes retrieved and the rates of inadvertent parathyroidectomy, hypoparathyroidism, and hypocalcemia. Results: Eight studies were included for analysis. Carbon nanoparticles were associated with more lymph nodes retrieved (mean difference [MD], 2.92; 95% confidence interval [CI], 0.29 to 5.56; $P = 0.03$) and lower rates of inadvertent parathyroidectomy (odds ratio [OR], 0.24; 95% CI, 0.13-0.43; $P < 0.00001$), transient hypoparathyroidism (OR, 0.39; 95% CI, 0.24-0.64; $P = 0.0002$), and hypocalcemia (OR, 0.39; 95% CI, 0.25-0.62; $P < 0.0001$). There was no significant difference of permanent hypoparathyroidism rates between the patients with use and non-use of carbon nanoparticles (OR, 0.34; 95% CI, 0.05-2.19; $P = 0.25$). Conclusions: Carbon nanoparticles potentially improve the completeness of lymph nodes dissection and protect parathyroid glands during thyroidectomy.

Keywords: Carbon nanoparticles, thyroidectomy, lymph nodes dissection, parathyroid gland, hypoparathyroidism

Introduction

The incidence of thyroid cancers has steadily increased over the last decade [1]. Although many patients have an excellent prognosis, there is involvement of cervical lymph nodes in 20 to 90% of cases [2-4]. Insufficient lymph node dissection can easily cause residual cancer or relapse after surgery, and re-operation may be required. Central lymph nodes are most commonly involved with metastasis. Lymph node metastasis not only has important prognostic value for accurate clinical staging, postoperative treatment, follow-up programs and assessment of recurrence risk [5, 6], but also is an independent risk of decreased survival [7, 8]. Therefore, lymph node dissection is widely used for the treatment of thyroid cancers. However, central lymph node dissection is always associated with higher incidence of transient or permanent hypoparathyroidism because of injury to the parathyroid glands from mechanical or thermal trauma, devascularization, or removal [9, 10]. The incidence of transient hypoparathyroidism is reported to be about 10 to 46%, while that of permanent hypoparathyroidism is as low as zero and as high as 43% [11]. Postoperative hypoparathyroidism can add the hospital cost, affect the quality of life, and increase the risk of medical disputes. Therefore, there is a contradiction between radical dissection of central lymph nodes and protection of parathyroid glands.

New technology is urgently needed to simultaneously ensure radical dissection of central lymph nodes and protection of parathyroid glands. Recently, a strong lymphatic tracer--carbon nanoparticle has been advocated to improve the dissection of lymph nodes and avoid injury of parathyroid glands during thyroidectomy and central lymph nodes dissection. Carbon nanoparticles can stain the thyroid gland and its surrounding lymph nodes black, without changing the anatomic color of the parathyroid glands. This promotes complete lymph node dissection and facilitates the ability of surgeons to identify and protect parathyroid glands [12, 13]. Although two studies of meta-analysis have confirmed the effectiveness of carbon nanoparticles, there are some limitations in the two studies, including: 1) many studies for meta-analysis are published in Chinese; 2) some studies are non-randomized controlled trials; and 3) most studies of randomized controlled trials are low in quality [14, 15]. These limitations make the conclusion in doubt. In addition, some recent studies reported that carbon nanoparticles could not effectively protect parathyroid glands and reduce the incidence of hypoparathyroidism [16, 17].

Up to now, the efficiency of carbon nanoparticles on lymph nodes dissection and parathyroid glands protection during thyroidectomy has remained a topic of debate. Therefore, a systematic and comprehensive analysis of the existing evidence for use and non-use of carbon nanoparticles must be conducted to determine whether carbon nanoparticles can effectively improve the completeness of lymph node dissection and protect parathyroid glands during thyroidectomy.

Materials and methods

Search strategy

Major databases including MEDLINE, OVID, EMBASE, Science Citation Index, and Cochrane Library Central were searched for relevant articles. Randomized controlled trials that compared the use and non-use of carbon nanoparticles during thyroidectomy published before July 31, 2017, were included in the meta-analysis. The following medical search headings were used: carbon nanoparticles, parathyroid gland, hypoparathyroidism, lymph nodes dissection, and thyroidectomy. The combination of these headings and similar other headings were also searched, including nano-carbon, parathyroid, lymph nodes resection, thyroid resection, and thyroid surgery. The reference list of articles identified were examined to find relevant studies that had not been identified by the database searches. Two researchers (Wei T and Gong YP) independently screened the title and abstract of each publication to identify eligible trails. Full articles of eligible studies were then obtained for detailed evaluation. A discussion was conducted to resolve any disagreement in the selection process. If the procedure failed, a third person (Zhu JQ) adjudicated.

Inclusion and exclusion criteria

To be included in the analysis, randomized controlled studies had to fit the following criteria: (1) publish on humans in English; (2) be the first surgery of traditional thyroidectomy; (3) report the indication of thyroidectomy; (4) provide a clear documentation of the injection method of carbon nanoparticles suspension; (5) report the outcomes after thyroidectomy, including lymph node dissection, inadvertent parathyroidectomy, hypoparathyroidism, and hypocalcemia; and (6) when two or multiple studies were reported by the same authors and/or institution, either the most recent study or the higher quality study was included in the analysis. Letters, abstracts, commentaries, case reports, studies lacking control groups, re-operations, endoscopic surgeries, and reviews without original data or appropriate data for extraction were excluded.

Data extraction

Two researchers (Wei T and Gong YP) independently extracted data from all eligible trails, and then cross-checked the data. Data extracted from each trial included the following parameters: first author, study period, participant characteristics, surgical extent, injection method of carbon nanoparticles suspension, lymph node dissection, inadvertent parathyroidectomy, hypo-parathyroidism and hypocalcemia. Any disagreements were resolved by the same method as mentioned previously.

Quality assessment

The randomized controlled trials were scored using the Jadad scoring system, which evaluates studies based on appropriate randomization, proper blinding, and an adequate description of withdrawals and dropouts [18]. A study was considered high in quality if the quality score is equal to or greater than 3.

Statistical analysis

Meta-analyses were performed in line with the recommendations of the Cochrane Collabora-

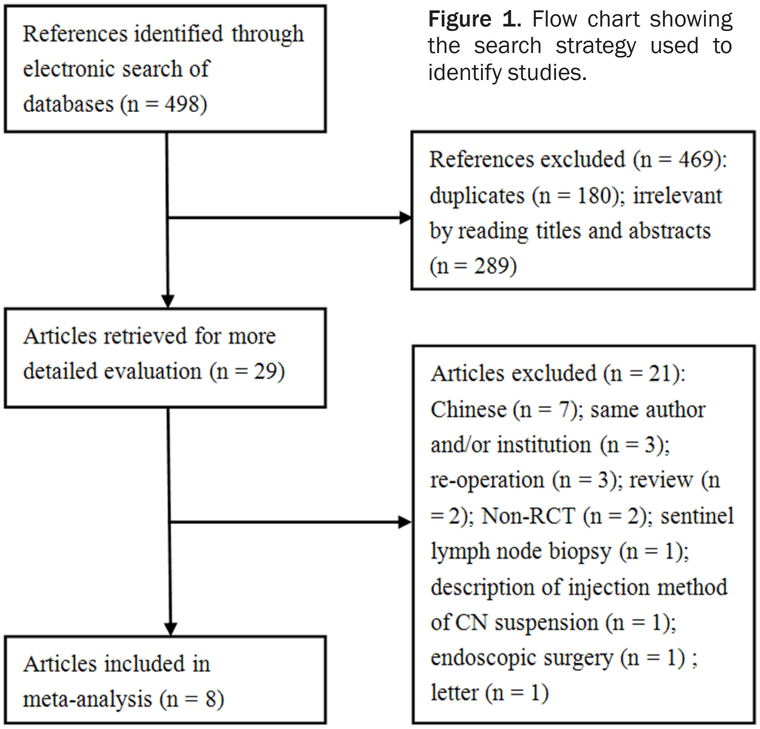

Figure 1. Flow chart showing the search strategy used to identify studies.

tion using the software package Revman 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) [19]. For dichotomous outcomes, the odds ratio (OR) was calculated with a 95% confidence interval (CI). For continuous outcomes, the mean difference (MD) was calculated with its 95% CI. The OR value represented the odds of an adverse event occurring in the carbon nanoparticle group (or black-staining lymph nodes in the carbon nanoparticles group) compared with the control group (or non-black staining lymph nodes in the carbon nanoparticles group) and it was considered statistically significant at a *P* level of less than 0.05 if the 95% CI did not include the value 1. The MD value represented the difference between the two groups in the continuous variables and it was considered statistically significant at a *P* level of less than 0.05 if 95% CI did not cross the value 0. Heterogeneity was assessed using the χ^2 and I^2, and I^2 value of more than 50% was considered statistically significant. Either the random-effects model or fixed-effects model was used to calculate the pooled effect based on the heterogeneity but it was evaluated first with random-effects model. A funnel plot was constructed to evaluate potential publication bias based on the metastatic lymph nodes and inadvertent parathyroidectomy.

Results

Eligible studies

Figure 1 details the results of the initial search and the subsequent selection of relevant articles. In the initial search, 498 references were identified through electronic search in MEDLINE (n = 306), Ovid (n = 148), EMBASE (n = 11), Science Citation Index (n = 33) and Cochrane Library Central (n = 0). A total of 289 clearly irrelevant references and 180 duplicates were excluded. Twenty-nine studies were retrieved for further assessment. No relevant studies were identified by scanning the reference lists of the retrieved relevant articles and reviews. Of the 29 studies, 21 [14-17, 20-36] were excluded for various reasons as shown in **Figure 1**. Eight studies [12, 13, 37-42] published between 2014 and 2016 matched the selection criteria and were therefore included.

Study and patient characteristics

The study characteristics, patient demography, etiology, surgical procedure, and the quality assessments are shown in **Table 1**. A total of 844 patients were included in all publications, with 420 in the carbon nanoparticle group and 424 in the control group. The sample size of the studies ranged from 60 to 162 patients and the mean age of the patients varied between 36 and 49 years. The proportion of females varied between 71% and 92%. All the studies looked at malignant lesions. The proportion of papillary thyroid cancer varied between 95% and 100%. The two groups had no significant difference in age (MD, -1.43; 95% CI, -5.72 to 2.86; *P* = 0.51), sex (OR, 0.86; 95% CI, 0.60-1.25; *P* = 0.44) or etiology (OR, 1.90; 95% CI, 0.51-7.12; *P* = 0.34). All studies described the surgical procedure but only two studies [40, 41] revealed the details of unilateral and bilateral central lymph node dissection. The proportion of bilateral central lymph node dissection was 100%. In addition, there was also no significant difference of tumor size (MD, -0.07; 95% CI, -1.30 to

Table 1. General characteristics of the included studies

Author	Study period	Group	Patients (n)	Age	M/F	Etiology (n)	Procedure (n)	Quality score
Tian et al. [12]	2012.4-2013.10	CN	50	36.4 ± 2.5	5/45	PTC	CND	3
		Control	50	44.5 ± 5.8	11/39	PTC46, FTC4		
Sun et al. [13]	2011.6-2012.8	CN	40	43 (25-71)*	23/57	PTC, FTC	CND	3
		Control	40					
Gu et al. [37]	2012.6-2014.8	CN	50	46.98 ± 9.027	10/40	PTC47, FTC1, MTC2	CND36, CND+LND14	2
		Control	50	47.76 ± 13.912	6/44	PTC48, FTC1, MTC1	CND31, CND+LND19	
Zhu et al. [38]	2010.4-2011.4	CN	81	46.75 ± 12.09	14/67	PTC	CND, CND+LND	3
		Control	81	44.31 ± 10.73	16/65			
Xu et al. [39]	2013.9-2014.8	CN	57	45.37 ± 10.71	5/52	PTC	CND	2
		Control	57	42.68 ± 14.43	4/53			
Liu et al. [40]	2012.5-2015.5	CN	30	42.87 ± 15.02	7/23	PTC	CND	3
		Control	30	48.70 ± 11.28	8/22			
Yu et al. [41]	2012.1-2013.6	CN	70	44.5 ± 17.4	14/56	PTC	CND	4
		Control	70	45.5 ± 19.0	17/53			
Long et al. [42]	2012.1-2013.5	CN	42	44.5 ± 9.6	9/33	PTC	CND35, CND+LND7	4
		Control	46	43.8 ± 10.3	11/35		CND37, CND+LND9	

M/F = male/female; CN = carbon nanoparticles; PTC = papillary thyroid cancer; FTC = follicular thyroid cancer; MTC = medullary thyroid cancer; CND = central lymph nodes dissection; LND = lateral lymph nodes dissection. *Medians with ranges in parentheses.

Table 2. The injection details of carbon nanoparticles suspension

Author	Injection point (n)	Injection amount (mL)	Interval (min)
Tian et al. [12]	3	0.2 per point	10
Sun et al. [13]	2-4	0.1-0.2 per point	NM
Gu et al. [37]	2	0.1-0.15 per point	NM
Zhu et al. [38]	1-2	0.1 per point	NM
Xu et al. [39]	NM	0.5 total	5-10
Liu et al. [40]	3-6	0.4-0.8 per point	NM
Yu et al. [41]	2-3	0.1 per point	5
Long et al. [42]	3	0.05 per point	20

NM = not mentioned.

1.15; P = 0.91), preoperative parathyroid hormone (PTH) (MD, -0.37; 95% CI, -2.44 to 1.70; P = 0.73) and calcium (MD, -0.01; 95% CI, -0.06 to 0.04; P = 0.58) between the two groups. Of the eight studies, six [12, 13, 38, 40-42] were high in quality. Carbon nanoparticle suspension was provided by Chongqing LUMMY Pharmaceutical Co., Ltd. The details of the injection method are shown in **Table 2**. All studies revealed that carbon nanoparticle suspension was intraoperatively injected into the thyroid gland. The main difference among the studies were injection point, injection amount, and the interval between injection and thyroidectomy.

Lymph nodes dissection

All results regarding lymph node dissection are showed in **Figure 2**. Seven studies [12, 13, 37-39, 41, 42] reported on the total number of lymph nodes resected during thyroidectomy. However, three [12, 13, 42] of them did not provide sufficient information for analysis. Meta-analysis of the residual studies with the random-effects model (I^2 = 96%) showed that the total number of lymph nodes retrieved in the carbon nanoparticles group was significantly higher than those retrieved in the control group (MD, 2.92; 95% CI, 0.29 to 5.56; P = 0.03) (**Figure 2A**). Data on the number of black-staining lymph nodes was available in three studies [13, 38, 41]. The black-staining rate varied between 69.9% and 92.8%. Two studies [13, 38] reported the number of lymph nodes with less than 2 mm. The summarized effect with the fixed-effects model (I^2 = 0%) revealed that carbon nanoparticles could significantly improve the dissection of lymph nodes with less than 2 mm (OR, 1.89; 95% CI, 1.42-2.52; P < 0.0001) (**Figure 2B**). Yu et al. [41] also demonstrated that more lymph nodes and metastatic lymph nodes with less than 5 mm in length were detected in the carbon nanoparticles group than in the control group (279 vs 54, P = 0.0001; 78 vs 17, P = 0.0001, respectively).

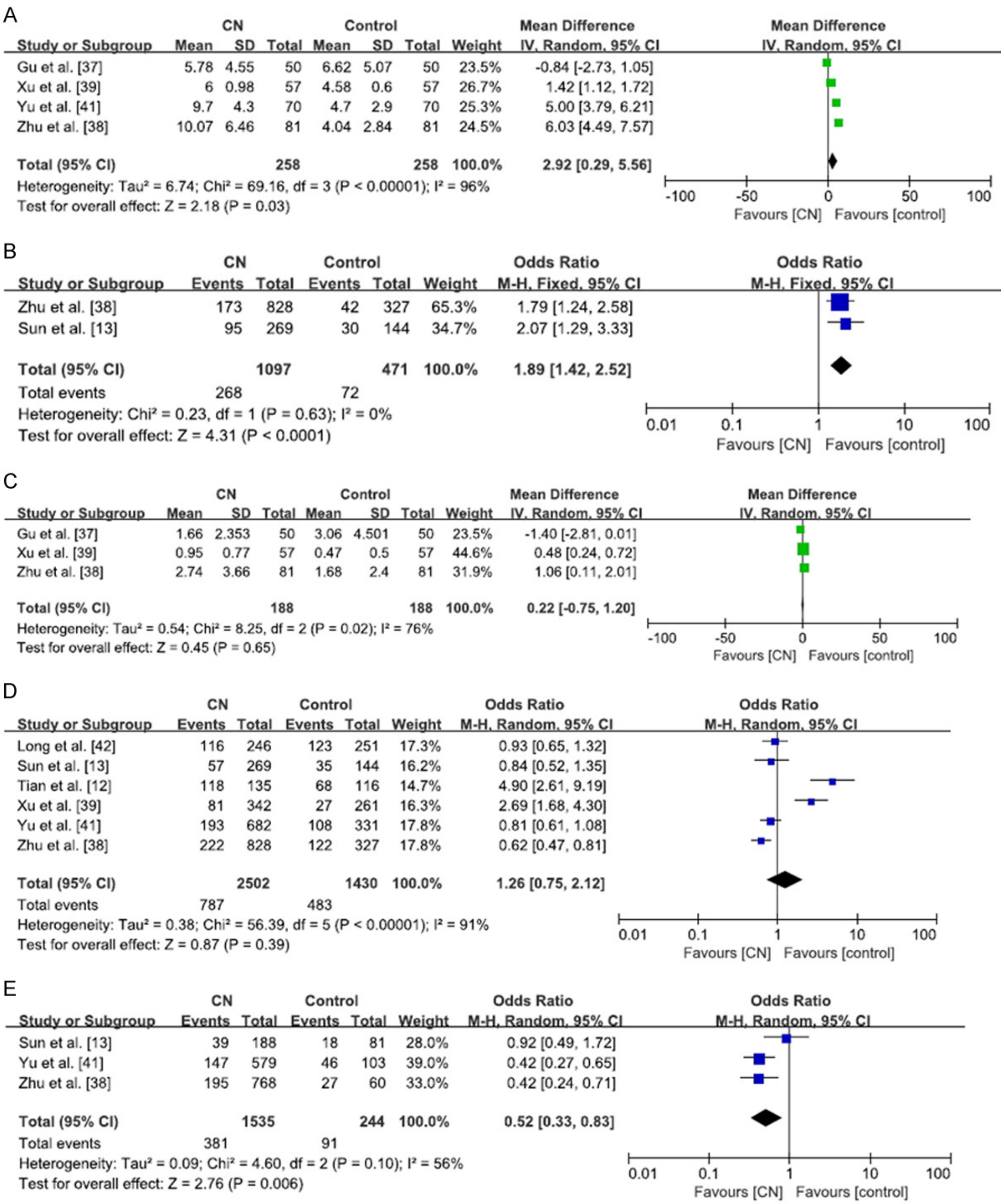

Figure 2. Forest plots illustrating results of meta-analyses comparing the carbon nanoparticle group versus control group for the outcomes of lymph node dissection: (A) total number of lymph nodes, (B) number of lymph nodes with less than 2 mm, (C) number of metastatic lymph nodes, (D) metastatic rate of all the lymph nodes and (E) metastatic rate of black-staining lymph nodes. CN = carbon nanoparticles; CI = confidence interval.

Three studies [37-39] provided information on the number of metastatic lymph nodes. Pooled analysis with the random-effects model (I^2 = 79%) showed that no statistically significant difference exists between the two groups (MD, 0.22; 95% CI, -0.75 to 1.20; *P* = 0.65) (**Figure 2C**). Data on the total number of metastatic lymph nodes was also available in six studies [12, 13, 38, 39, 41, 42]. The lymph node metastasis rate varied between 21.2% and 87.4% in

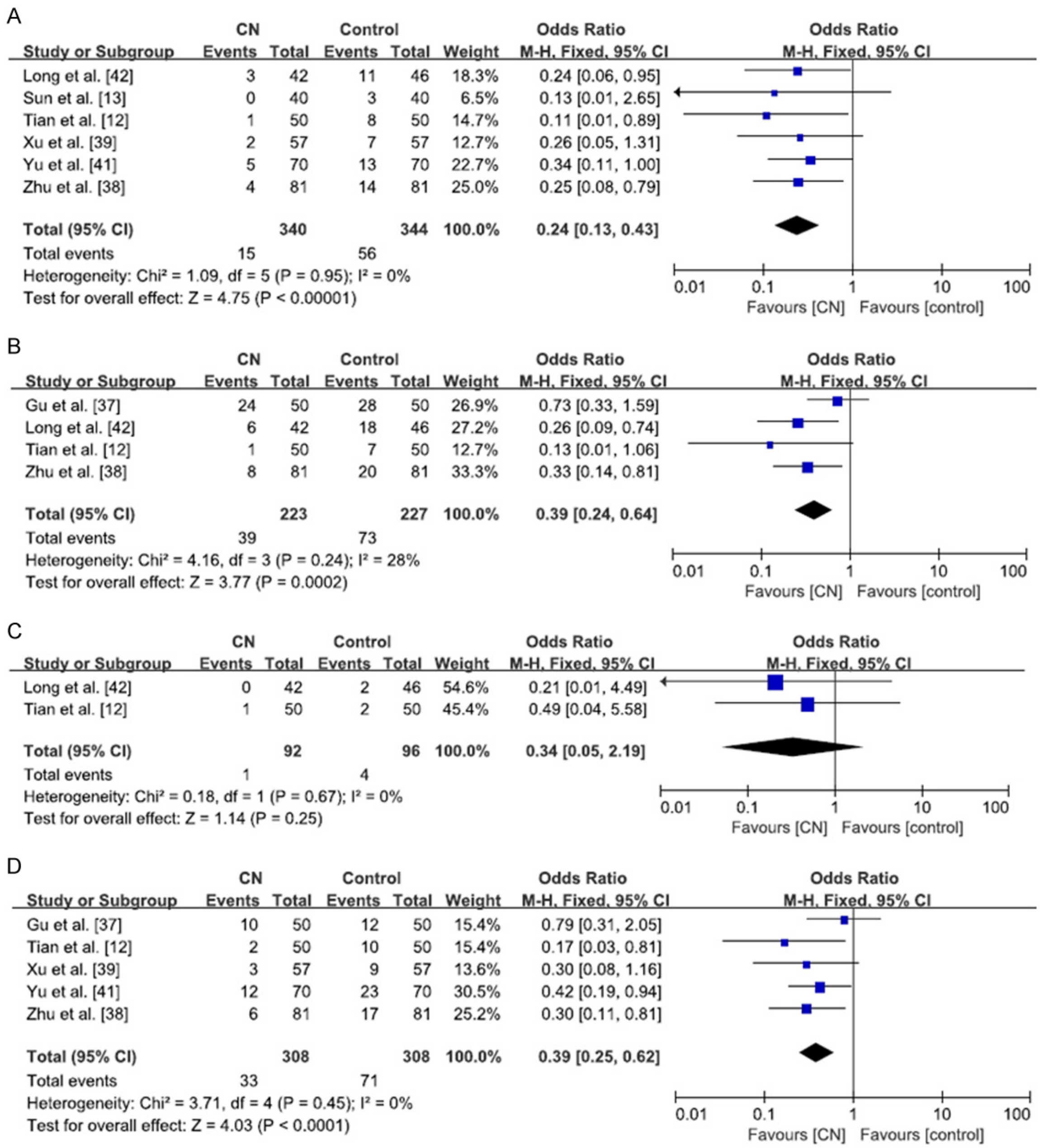

Figure 3. Forest plots illustrating results of meta-analyses comparing carbon nanoparticle group versus control group for the outcomes of parathyroid glands protection: (A) inadvertent parathyroidectomy, (B) transient hypoparathyroidism, (C) permanent hypoparathyroidism and (D) hypocalcemia. CN = carbon nanoparticles; CI = confidence interval.

the carbon nanoparticles group, while it ranged from 10.3% to 58.6% in the control group. The summarized effect with the random-effects model (I^2 = 91%) revealed no significant difference of lymph node metastasis rate between the two groups (31.5% vs 33.8%) (OR, 1.26; 95% CI, 0.75-2.12; P = 0.39) (**Figure 2D**).

Among the eight studies, three [13, 38, 41] reported on the number of black-staining metastatic lymph nodes with the positive rate varying between 20.7% to 25.4%. Meta-analysis of the three studies with the random-effects model (I^2 = 56%) showed that the lymph node metastasis rate was significantly lower when

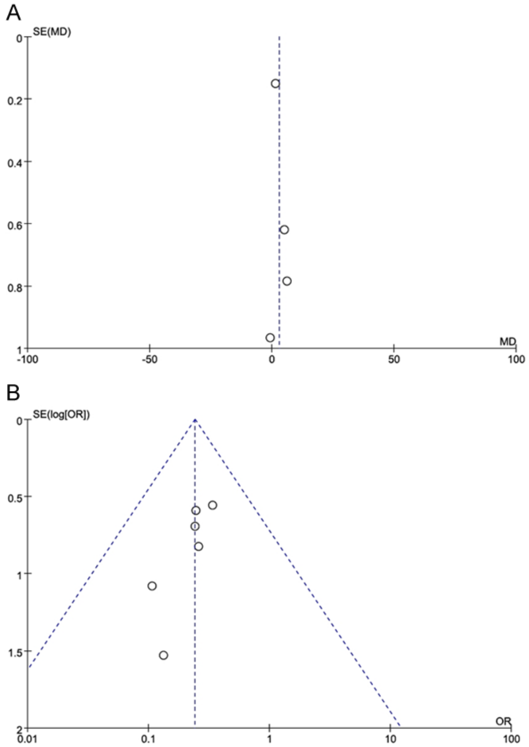

Figure 4. Funnel plot of carbon nanoparticle group versus control group in terms of total number of lymph nodes (A) and inadvertent parathyroidectomy (B). MD = mean difference; OR = odds ratio; SE = standard error.

lymph nodes were stained black (24.8% vs 37.3%) (OR, 0.52; 95% CI, 0.33-0.83; P = 0.006) (**Figure 2E**).

Parathyroid glands protection

All results of parathyroid gland protection are summarized in **Figure 3**. Six studies [12, 13, 38, 39, 41, 42] provided information regarding inadvertent parathyroidectomy. The fixed-effects model was used because of non-significant heterogeneity (I^2 = 0%) between studies. Significantly lower incidence of inadvertent parathyroidectomy was found in the carbon nanoparticles group than in the control group (OR, 0.24; 95% CI, 0.13-0.43; P < 0.00001) (**Figure 3A**). The postoperative levels of PTH were noted in three studies [12, 37, 40]. Tian et al. [12] reported that the difference between the two groups in serum PTH level was statistically significant at 48 h after surgery (29.66 ± 4.27 versus 23.21 ± 3.61 pg/ml, P < 0.05). However, Gu et al. [37] reported similar PTH levels in the two groups one day after surgery (18.01 ± 12.00 versus 16.67 ± 13.62 pg/ml, P = 0.410). Liu et al. [40] also reported the PTH levels in the carbon nanoparticles group and control group were 14.62 ± 12.33 pg/mL and 21.14 ± 13.35 pg/mL at 2 h after surgery (P = 0.06). The incidence of transient hypoparathyroidism and permanent hypoparathyroidism were recorded in four [12, 37, 38, 42] and two [12, 42] studies, respectively. Transient hypoparathyroidism was found in 17.5% patients (39/223) in the carbon nanoparticles group and 32.2% patients (73/227) in the control group (OR, 0.39; 95% CI, 0.24-0.64; P = 0.0002) (**Figure 3B**), while permanent hypoparathyroidism was found in 1.1% patients (1/92) in the carbon nanoparticles group and 4.2% patients (4/96) in the control group (OR, 0.34; 95% CI, 0.05-2.19; P = 0.25) (**Figure 3C**). Five studies [12, 37-39, 41], including 616 patients, were analyzed for the postoperative hypocalcemia rate. The summarized effect with fixed-effects model (I^2 = 0%) revealed a statistically significant result favoring the carbon nanoparticles group with a hypocalcemia incidence of 10.7% (33/308) compared with a hypocalcemia rate of 23.1% (71/308) in the control group (OR, 0.39; 95% CI, 0.25-0.62; P < 0.0001) (**Figure 3D**).

Publication bias

Funnel plots of the studies that reported on total number of lymph nodes and inadvertent parathyroidectomy are shown in **Figure 4**. None of the studies exceed the 95% CI and all of them were almost equally distributed around the vertical axis. Therefore, no strong evidence of publication bias existed in the meta-analysis.

Discussion

Carbon nanoparticles of about 150 nm in diameter have strong lymphatic tropism. The gap between capillary endothelial cells ranges from 20 to 50 nm, whereas the gap between endothelial cells of lymph capillaries ranges from 120 to 150 nm, along with the hypoplastic basement membrane. Therefore, carbon nanoparticles can enter lymphatic capillaries rather than blood vessel capillaries and then gather in the corresponding lymph nodes through macrophage pinocytosis. Finally, they lead to the black-staining of the lymph nodes. Based on these features, carbon nanoparticles have been used to assist lymph node dissection for gastric cancer and breast cancer, and good results have been achieved [43, 44]. Recently, carbon nanoparticles have been applied to trace lymph nodes in thyroid cancer. They can be preoperatively or intraoperatively injected into thyroid gland. However, there are two obvious disadvantages with preoperative injection. Firstly, ultrasound must be used for guidance to avoid injection into lesions. Secondly, carbon nanoparticles may stain cervical skin black. Although intraoperative injection is widely used, some attention should be paid for the method. When exposing the surgical site, the side and rear parts of the thyroid gland should not be separated to reduce damage to the thyroid capsule and surrounding thyroid lymphatic network. In addition, an appropriate amount of carbon nanoparticle suspension should be injected to prevent the possibility that the extravasation of the solution affects the surgical field. In most studies, 0.1 to 0.2 ml per point and two to three points were selected for injection.

The results of the current meta-analysis are in favor of carbon nanoparticles with regard to the total number of lymph nodes resected during thyroidectomy, which is consistent with the previous studies [14, 15]. Application of carbon nanoparticles brings convenience to complete lymph nodes dissection for the following reasons: 1) more lymph nodes less than 2 mm in length can be detected intraoperatively; 2) more lymph nodes in the VII region can be detected intraoperatively; and 3) permits easier identification of black-staining lymph nodes by pathologists. Because similar numbers of metastatic lymph nodes were found in the two groups, carbon nanoparticles could not effectively improve the detection of metastatic lymph nodes. The result may be attributed to the surgeon's experience, which is an important factor for the clearance of metastatic lymph nodes.

The meta-analysis showed a lower metastasis rate when lymph nodes were stained black. Lymphatic capillaries around the metastatic lymph nodes may be blocked by tumor cells. However, many studies found similar metastasis rates when lymph nodes were stained black or maintained the original color in the carbon nanoparticles group. The lower metastasis rates of black staining lymph nodes as reported by Zhu et al. [38] and Yu et al. [41] contributed greatly to the result. Because many metastatic lymph nodes are still stained black, carbon nanoparticles cannot be used to identify the presence or absence of metastasis.

Emerging evidence has shown that there are rich lymphatics and lymphatic capillaries in the thyroid gland, but almost none within the parathyroid glands [20]. Carbon nanoparticles could stain thyroid gland and lymph nodes black without staining the parathyroid, which would make it easy to distinguish parathyroid glands from thyroid nodules (Zuckerkandl nodules) and lymph nodes. The present study demonstrated that carbon nanoparticles could reduce the risk of inadvertent parathyroidectomy, leading to a lower incidence of transient hypoparathyroidism and hypocalcemia. However, carbon nanoparticles did not affect the incidence of permanent hypoparathyroidism. The number of parathyroid glands accidentally resected or preserved *in situ* may be attributed to the result because preserving at least one parathyroid gland with an intact blood supply is sufficient to prevent permanent hypoparathyroidism [11]. The incidence of permanent hypoparathyroidism after thyroidectomy is also similar whether a parathyroid gland is inadvertently excised or autotransplanted [45].

The current meta-analysis has some limitations and the results should be interpreted with caution. First, all the studies were published from China. Second, a test for heterogeneity was significant for many outcomes analyzed. The differences between the studies have led to heterogeneity, including differences in the injection method of carbon nanoparticles suspension, etiology and surgical extent.

A comprehensive review of the outcomes of carbon nanoparticles for thyroidectomy was performed in this study. The results indicate that carbon nanoparticles potentially improve the completeness of lymph node dissection and protect parathyroid glands during thyroidectomy. However, further standardized randomized controlled trials with a general injection method of carbon nanoparticle suspension, etiology, and surgical extent are required to draw a more definitive conclusion.

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Disclosure of conflict of interest

None.

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