EFFICACY OF CARBON NANOPARTICLES FOR PARATHYROID GLANDS PROTECTION DURING TOTAL THYROIDECTOMY AND BILATERAL CENTRAL LYMPH NODES DISSECTION FOR THYROID CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction*: Parathyroid injury is a common surgical complication of total thyroidectomy (TT) and bilateral central lymph nodes dissection (BCLND) for thyroid cancer (TC). Effects of carbon nanoparticles (CN) in protecting parathyroid during TT and BCLND were revealed by many studies, while ineffectiveness of CN was also reported. We conducted this meta-analysis to find out the potential effects of CN in protecting parathyroid during TT and BCLND for patients with TC.*

Methods*: This study was registered at PROSPERO (registration number CRD42020212973). Studies were searched from databases, including PubMed, EMBASE, Web of Science and Cochrane Library. Outcomes were extracted from studies coincident with predetermined criteria. The outcomes were then pooled and compared to find out the potential advantages of CN.*

Results*: A total of six studies were included into the final meta-analysis. Significantly lower rates of accidental parathyroid resection and transient hypoparathyroidism were found in CN group than control group [risk ratio (RR) = 0.35, 95% CI 0.19 to 0.63, P < 0.01; RR = 0.31, 95% CI 0.14 to 0.70, P < 0.01, respectively]. The permanent hypoparathyroidism rate of the CN group was lower than that of the control group, while the difference was not significant (RR = 0.59, 95% CI 0.22 to 1.59, P = 0.30).*

Conclusion*: CN can facilitate parathyroid protection from accidental resection in TC patients treated with TT and BCLND. Moreover, it is also helpful in significantly lowering the rate of transient hypoparathyroidism, rather than permanent hypoparathyroidism. More prospective studies are needed to confirm our findings.*

Keywords: *Carbon nanoparticles, Parathyroid protection, Thyroid cancer, Meta-analysis.*

DOI: 10.19193/0393-6384_2022_1_116

Received *March 15, 2021;* ***Accepted*** *October 20, 2021*

Backgrounds

Being rapidly rising during the past three decades, the incidence of thyroid cancer (TC) reached 10.1 per 100,000 in female and TC became the ninth most frequently-diagnosed cancer worldwide in 2020[(1)]. Surgical therapy is a crucial part of all-round treatments and recommended for primary TC, especially for the differentiated thyroid cancer[(2, 3)]. However, surgeries may also cause complications including recurrent laryngeal nerve injury, superior laryngeal nerve injury, hypoparathyroidism, bleeding, and wound infection. Among these complications, hypoparathyroidism occurs more frequently[(4)]. Postoperative hypoparathyroidism includes transient and persistent hypoparathyroidism, both of which could result in severe neuromuscular symptoms and influence the quality of life in these

patients. Postoperative hypoparathyroidism results from surgical injury to parathyroid, either or both of inadvertent resection and blood supply damage.

In previous literature, several systematic reviews emphasized the protective effects for parathyroid by carbon nanoparticles (CN) suspension injection during surgeries[5-8]. CN is a kind of stain composed of nanoparticles having an average diameter of 150 nanometers, which is smaller than the diameter of lymphatic vessels but larger than the diameter of blood capillaries[9]. Because of the suitable diameter of CN, it can be safely injected into thyroid, and then thyroid and surrounding lymphatic vessels would be quickly black-stained. Meanwhile, the parathyroid will not be stained and still preserve its natural color, which facilitates parathyroid identification and lymph nodes dissection during thyroid surgeries.

Although the advantages of CN in parathyroid protection were reported by previous meta-analysis, these studies did not confine patients treated with a certain surgical procedure. It is worth noting that the possibilities of parathyroid injury are diverse in variant surgical procedures. The rate of postoperative hypoparathyroidism is dependent on the surgical extent and increases when total thyroidectomy (TT) and bilateral central lymph node dissection (BCLND) is performed[10].

Hence, we conducted this meta-analysis, trying to find out the potential effects of parathyroid protection of CN in patients undergoing TT and BCLND. The comparison results using pooled data from relative studies where patients were treated with the same procedure convinces surgeons more firmly.

Search strategy

This study was registered at PROSPERO (registration number CRD42020212973). Articles were searched form PubMed, EMBASE, Web of Science and Cochrane Library from the inception to February 15, 2021 with the following key words or medical subject headings, ("Thyroid Cancer, Papillary" or "Thyroid cancer, follicular" or "Thyroid cancer, medullary" or "Thyroid Carcinoma, Anaplastic" or "Adenocarcinoma, Follicular" or "Carcinoma, Medullary" or "Thyroid Cancer" or "Thyroid Carcinoma") and ("Carbon Nanoparticle" or "Nano-Carbon" or "Nanoparticles"). The study design and publication languages were not specifically restricted in our search strategies. However, all searched articles than went through further selection manually.

Study selection

Study selection, data extraction and quality assessment were performed by two authors independently. Dissent was solved by discussion or consultation form another author.

Literature search results were screened by authors and all finally included articles were all published in English or Chinese. Additional articles from relevant reference lists were also eligible for inclusion. Both prospective and retrospective studies, comparing carbon nanoparticles (CN) with control in parathyroid protection during surgical treatments in patients with thyroid cancer (TC), were potentially included in our study. CN group included patients whose thyroids were injected with CN for parathyroid identification and lymph nodes tracing during surgeries. Patients who did not receive any staining tracer injection were enrolled into control group. All patients in both CN and control groups suffered from TC and underwent TT and BCLND in primarily conventional methods, rather than endoscopic or secondary operations. Before routine pathology after operation, TC should be diagnosed by aspiration biopsy before operation or frozen pathology during operation. At least one clinical outcome of interest designed in our study can be extracted from one study.

A study would be excluded if the CN or control group included less than ten patients. Editorials, abstracts, and letters were also excluded. In studies with overlapped patient populations in subsequent analyses, only the study with the more recent or largest population was included. To summarize the study selection process, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used.

Data extraction

Data regarding first author and publication year, study design, patients' characteristics, follow up duration, and the number of patients suffering from complications in CN and control group were extracted and recorded. These complications included transient and permanent hypoparathyroidism, and accidental parathyroid resection. In our study, hypoparathyroidism was regarded as transient or permanent if hypoparathyroidism did not recover at one month or six months after surgeries respectively. That parathyroid tissue was found in the surgical specimen was counted as accidental parathyroid resection.

Quality assessment

We used the Newcastle-Ottawa Scale (NOS) for assessing the methodological quality of cohort studies. The Cochrane Collaboration's tool was applied for the randomized controlled trial (RCT). Three major domains constitute NOS, including selection, comparability, and outcome. Each domain comprises relative scale items to facilitate potential risk appraisal, endowed with a maximum score of four, two and three points respectively. A study can earn a max score of nine points, and studies owning 7-9 scores are considered as high, 4-6 as moderate quality. Cochrane Collaboration's tool comprises six domains for assessing risk of bias, and each domain can be rated as low concern, high concern or unclear.

Data analysis and statistical methods

Analyses were performed using Review Manager (version 5.3) software from Cochrane Collaboration. Risk ratios (RRs) with 95% confidence intervals (CIs) of outcome variables were calculated and compared to find out potential difference between the CN group and control group. The random-effect model was applied to calculate the pooled RR and its 95% CI if significant heterogeneity among studies was found. Otherwise, the fixed-effect model was used. Heterogeneity among studies was assessed by Cochrane Q statistic and I2 test. A p-value < 0.1 for Q statistic test or I2 > 50 % was considered being significantly heterogeneous. Differences between pooled outcomes were considered statistically significant if the p value was less than 0.05.

Results

Search results

A total of 533 studies were searched, 171 articles from PubMed, 68 from EMBASE, 273 from Web of Science and 21 from Cochrane Library. The process of selecting studies were summarized in Fig. 1. After removing duplications and further screening titles and abstracts, there were a total of 44 articles identified for full-text evaluation. After full-text articles review, 39 articles were excluded for the following reasons: letter (n = 1); other kinds of surgeries (n = 24); without reporting outcomes needed in our study (n = 4); without reporting detailed surgery methods or study design (n = 6); only abstracts (n = 4). Afterwards, the remaining five studies were deemed eligible according to the inclusion and exclusion criteria and were selected for further meta-analysis[9, 11-14].

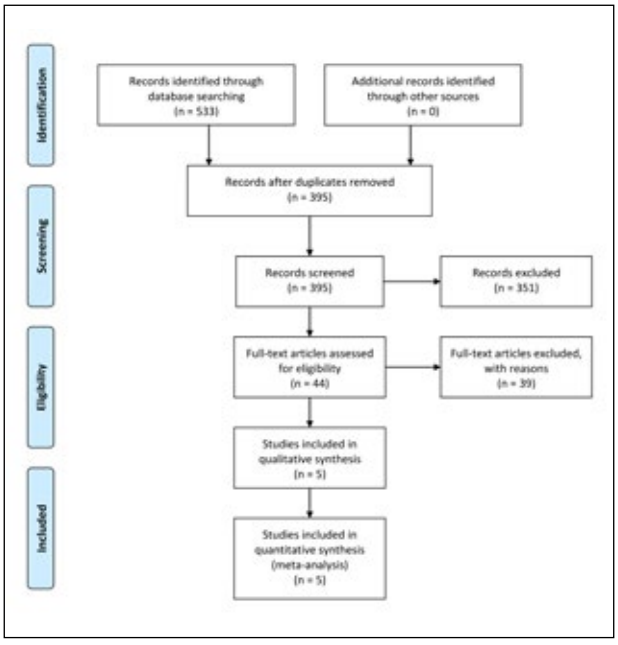

Figure 1: Study flow diagram.

Data extraction

Clinic characters and extracted results of outcome variables from included studies were summarized in Table 1. A total of 842 patients were divided into CN and control groups, with 330 and 512 patients in each group. There were 228 male and 614 female patients among these 842 patients. Four studies only include patients with papillary thyroid cancer (PTC), while the other one study also include patients suffering from other TC, including follicular thyroid cancer (FTC) and medullary thyroid cancer (MTC)[13].

Study ID	Group	Study design	n	Male/ Female	Mean age (years)	Follow-up duration	Transient hypopara-thyroidism	Permanent hypopara-thyroidism	Accidental parathyroid resection
Wang 2020	CN	RCT	32	14/18	43	As least 6 months	-	0/32	-
	Control		32	15/17	43		-	0/32	-
Qian 2019	CN	Retrospective cohort study	104	34/70	41.6	6 months	-	0/104	2/104
	Control		90	28/62	38.8		-	0/90	8/90
Xue 2018	CN	Retrospective cohort study	106	20/86	44.88	60 to 84 months	2/106	1/106	-
	Control		300	66/234	44.35		23/300	3/300	-
Liu 2018	CN	cohort study	45	17/28	46.17	at least 4 years	5/45	0/45	3/45
	Control		47	12/35	45.39		14/47	0/47	10/47
Wu 2015	CN	RCT	43	22/64	49(median)	As least 6 months	-	4/43	7/43
	Control		43				-	4/43	11 /43

Table 1: Characteristics of included studies.
CN carbon nanoparticles, NR not reported, RCT randomized controlled trial, PTC papillary thyroid cancer, FTC follicular thyroid cancer, MTC medullary thyroid cancer

Four studies reported that included patients underwent primary thyroid surgeries, while the other one study did not document this variant[9]. In this study, all enrolled patients had normal of parathyroid

hormone (PTH) and serum calcium levels before surgeries, so we also included this study.

One study just reported the rate of transient hypoparathyroidism, while did not define the duration from surgeries when diagnosing transient hypoparathyroidism[11]. Hence, we did not extract the data of transient hypoparathyroidism from this study.

Quality assessment

The results of NOS for methodological quality evaluation were summarized in Table 2.

First author & Year	Selection				Comparability		Outcome			Total scores
	A	B	C	D	E		F	G	H	
Qian2019	1	1	1	1	1	1	1	1	1	9
Xue2018	1	1	1	1	1	1	1	1	1	9
Liu2018	1	1	1	1	1	0	1	1	1	8

Table 2: Results of quality assessment by NOS.
A. *Representativeness of the exposed cohort;* **B**. *Selection of the non-exposed cohort;* **C**. *Ascertainment of exposure;* ***D***. *Demonstration that outcome of interest was not present at start of study;* ***E***. *Comparability of cohorts on the basis of the design or analysis;* ***F***. *Assessment of outcome;* ***G***. *Was follow-up long enough for outcomes to occur;* ***H***. *Adequacy of follow up of cohorts*.

These studies owned high quality of methodology. The drawback of the study was lack of statement of comparability of CN and control groups in patients' baseline pathological characteristics[9]. The RCTs were deemed acceptable, although they did not report relative information about study design and implementation, such as allocation concealment and application of blind method (Table 3)[12, 13].

Comparison of transient hypoparathyroidism rate

Two studies reported the transient hypoparathyroidism rate (Fig. 2a)(9, 14). The results were pooled using a fixed model for the heterogeneity was not significant between these two studies (p = 0.62, I2 = 0). In the pooled results, there were 151 patients in the CN group and 347 patients in the control group. Seven patients went through transient hypoparathyroidism in CN groups (4.6%), and 37 patients experienced transient hypoparathyroidism in control groups (10.7%). The difference between these two groups was significant (RR = 0.31, 95% CI 0.14 to 0.70, P < 0.01).

First author & Year	Selection bias		Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
	Sequence Generation	Allocation Concealment					
Wang 2020	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Wu 2015	Low	Unclear	Unclear	Unclear	Low	Low	Low

Table 3: Results of quality assessment by the framework of Cochrane Collaboration's Tool for RCT.

Comparison of permanent hypoparahyroidism rate

Five studies with a total of 842 patients were included into the meta-analysis of permanent hypoparathyroidism rate, with 330 patients in the CN group and 512 patients in the control group (Fig. 2b)(9, 11-14). A fixed-model was applied for the heterogeneity was found insignificant (P = 0.97, I2 = 0). Five patients suffered from permanent hypoparathyroidism in the CN group (1.5%), and 7 patients in the control group (1.4%). The event rate of the CN group was higher than that of the control group, while the difference was not significant (RR = 0.98, 95% CI 0.31 to 3.08, P = 0.98).

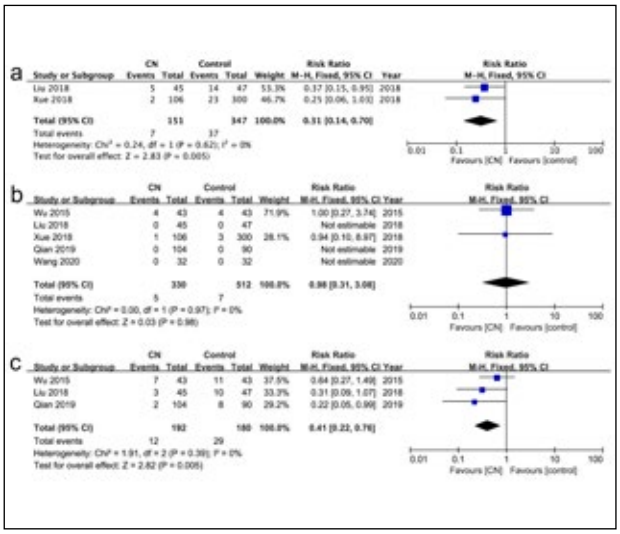

Figure 2: Results of the meta-analysis comparing the CN and control group for parathyroid protection: (**a**) transient hypoparathyroidism rate; (**b**) permanent hypoparathyroidism rate; (**c**) accidental parathyroid resection rate

Comparison of accidental parathyroid resection rate

Three studies reported the results of the rates of accidental parathyroid resection[9, 11, 13]. The rates of accidental parathyroid resection in these studies varied from 1.9% to 16.3% in patients with CN injection and from 8.9% to 25.6% in patients without CN injection. The heterogeneity was detected insignificant (P = 0.39, I2 = 0) and a fixed-model

was performed. 12 patients underwent inadvertent parathyroid resection in CN group (6.3 %), while 37 events happened in control group (16.1 %) (Fig. 2c). A significantly higher rate of accidental parathyroid resection was found in control group than CN group (RR = 0.41, 95% CI 0.22 to 0.76, P < 0.01).

Publication bias assessment

On account of limited number of included studies, publication bias was not performed.

Discussion

The rapidly rising incidence of TC attracts widespread attention. In US, the incidence of TC in 2013 was almost 2.5 times as much as the incidence in 2000[15]. In China, it even increased by 4.7 times from 2003 to 2012[16]. TT and BCLND is a commonly used surgical approach for TC. Hypoparathyroidism is the most frequent complication after TT and BCLND, which is directly on account of iatrogenic parathyroid injury, including accidental parathyroid resection or blood supply damage during surgeries[17]. Previous systematic reviews revealed the advantages of CN in protecting parathyroid[5-8]. However, the lack of same resection extent confined in inclusion standards in these reviews may enroll patients with diverse levels of risks of parathyroid injure[18]. Therefore, we performed this meta-analysis including patients all undergoing TT and BCLND to decrease the potential effects from diverse surgical methods.

A total of five studies were included into the final meta-analysis. The pooled results showed that the use of CN during operation significantly lowered the rates of transient hypoparathyroidism and accidental parathyroid resection.

Accidental parathyroid resection

In literature, several risk factors were reported associated with the increasing rate of accidental parathyroid resection, including thyroid cancer, central neck dissection, total thyroidectomy and reoperation[19]. In our study, we focus on the TC patients treated with TT and BCLND who are considered as high-risk population complicated by accidental parathyroid resection. The rate of accidental parathyroid resection in CN group, with a pooled rate of 6.3%, was significantly lower than the control group. This pooled rate was similar to the reported rate in literature, 7.3% in PTC patients with CN injection[20].

To a large extent, the anatomic relationship between thyroid and parathyroid influence the rate of accidental parathyroid resection during TT and BCLND. The study by Taterra et al. revealed that the anatomic distribution of 94.7% of parathyroid glands in patients with normal parathyroid functions were based on the posterior surface of thyroid[21]. This anatomic relationship makes it easier to identify non-stained parathyroid under the background of black-stained thyroid by CN injection. Our results confirmed the significant effects of CN for lowering accidental parathyroid resection, which is accord with previous systematic studies[5-8]).

Transient hypoparathyroidism

Transient hypoparathyroidism is the most common complication after TT and BCLND, and the rate of transient hypoparathyroidism can influence up to 55% patients after TT with or without BCLND(22). Accidental parathyroid resection is considered as an independent risk factor for transient hypoparathyroidism(22). It is confirmed in our study that the rate of transient hypoparathyroidism significantly decreases in CN group accompanying the significantly lower rate of accidental parathyroid resection in CN group.

Permanent hypoparathyroidism

Compared with nerve damage, permanent hypoparathyroidism is a more frequent long-term complication after TT and BCLND. The role of CN in reducing permanent hypoparathyroidism rate was controversial between previous systematic reviews[5, 6, 8]. In our study, although the usage of CN significantly decreased the rate of accidental parathyroid resection in CN group, the rates of permanent hypothyroidism between CN and control groups were comparable. This result is opposite to the traditional understanding, identifying and preserving as many parathyroid glands as possible to prevent postoperative complications[23]. We think, to some extent, accidental parathyroid resection can be an important but not a determinant factor in permanent hypoparathyroidism taking place. In a previous study including 454 PTC patients undergoing TT with or without lymph nodes dissection, patients were found preserved one to four parathyroid glands. Insignificant association was found between the number of preserved parathyroid glands and the occurrence of permanent hypoparathyroidism[22]. Hence, although with significantly increased rate of accidental parathyroid resection in control group,

the rate of permanent hypoparathyroidism can still be similar to the CN group as long as preserving at least one intact parathyroid gland.

There may be another explanation for comparable rates of permanent hypoparathyroidism between two groups. Protective effects of CN for parathyroid may lie more in the aspect of structural integrality, other than enough blood supply. Meanwhile, iatrogenic injury to parathyroid blood supply during surgeries also plays a crucial role in postoperative permanent hypoparathyroidism happening.

In the study by Su et al., 537 PTC patients were divided into two groups according to a new parathyroid classification system. The new classification method replaced preservation in situ with auto-transplantation for the parathyroid vulnerable for ischemic damage from surgical manipulations, mostly for inferior parathyroid glands. All two groups patients received CN injection and were treated with TT and BCLND. Although two groups had similar rates of accidental resection of parathyroid glands, the group undergoing significantly more parathyroid glands autotransplantation showed significantly lower rate of permanent hypoparathyroidism[20]. Therefore, Preservation in situ cannot insure the function of the parathyroid glands during TT and BCLND. Furthermore, for inferior parathyroid glands, 48.4% of which are surrounded by central lymph nodes, surgeons need to distinguish parathyroid from fat and lymph tissue when performing BCLND[20]. However, fat tissue is not black-stained by CN and only partial lymph nodes can be stained by CN[9], which increases the difficulty of parathyroid identification and risk of blood supply injury of parathyroid. The reported rate of permanent hypoparathyroidism in patients undergoing TT and BCLND can be as high as 16.2%, which was significantly higher than that in patients only received TT (6.3%), revealing the important role of extensive lymph nodes dissection in inducing permanent hypoparathyroidism[10].

Hence, although CN effectively prevent accidental parathyroid resection, prudent manipulation is still required in protecting the blood supply of parathyroid during TT and BCLND, especially for preserving blood supply for parathyroid glands.

Limitations

Several limitations of our study need to be noted by readers. Firstly, limited number of studies were included into our final meta-analysis, due to relatively strict inclusion criteria. A lack of study number then leaded to the failure of publication bias assessment and subgroup analysis based on variant study designs. Secondly, the definition of hypoparathyroidism is lack or discrepant in the included studies. Our study regarded the parathyroid hormone lower than normal value at 1 or 6 months after surgeries as transient or permanent hypoparathyroidism respectively. However, in one study, the numbers of patients suffering from hypoparathyroidism at 1 or 6 months were reported but the definition of hypoparathyroidism is lack[9]. The discrepancy of definition among studies may generate heterogeneity. Thirdly, the usage methods of CN during surgeries were variant among included studies. Both sides of thyroid were injected with CN in four studies, except one studies without report[9]. The reported number of inject spots ranged from two to six[13, 14], and the amount of injected CN suspension was also diverse. The time intervals from CN injection to TT and BCLND in these included studies ranged from 5 to 30 minutes[13, 14]. These factors may potentially influence the effect of the stain of thyroid and lymph nodes, which can also induce heterogeneity and bias.

Conclusions

Although these limitations, this systematic review explored the efficacy of CN in protecting parathyroid and decreasing the rate of hypoparathyroidism in patients with TT and BCLND. Based on the existing data, our study revealed that the usage of CN can significantly decrease the rate of accidental parathyroid resection and transient hypoparathyroidism. While, the significant effect in avoiding permanent hypoparathyroidism occurrence was not found. Furthermore, the results are based on the follow-up data from patients treated with TT and BCLND, but whether the results are available in patients undergoing other kinds of surgeries is still unknown. As more and more compelling studies come out, the efficacy of CN can be further explored and confirmed.

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Acknowledgments
This study was funded by the research fund at the hospital level from jiangsu taizhou people's hospital (ZL202001).

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