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, post-operative 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,
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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, reoperations, 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, hypoparathyroidism 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-
碳纳米颗粒在甲状腺手术中的应用

图1. 流程图显示用于识别研究的搜索策略。

结果

合格研究

图1详细说明了初始搜索和后续选择相关文献的结果。在初始搜索中，498篇文献被识别为相关文献。其中，306篇来自MEDLINE，148篇来自Ovid，11篇来自EMBASE，33篇来自Science Citation Index，0篇来自Cochrane Library Central。总共排除了289篇无关文献和180篇重复文献。进一步评估了29篇文献，21篇[14-17, 20-36]被排除，原因如图1所示。2014年和2016年共有8篇文献被纳入。

研究和患者特征

研究特征、患者人口学、病因、手术程序和质量评估如表1所示。共有844名患者被纳入，其中420名患者参与了碳纳米颗粒组，424名患者参与了对照组。研究中描述了手术程序，但只有两篇文献[40, 41]详细描述了单侧和双侧中央淋巴结摘除。双侧中央淋巴结摘除的百分比为100%。还考虑了肿瘤大小（MD, -0.07; 95% CI, -1.30 to 2.86; P = 0.51）性（OR, 0.86; 95% CI, 0.60-1.25; P = 0.44）和病因（OR, 1.90; 95% CI, 0.51-7.12; P = 0.34）。所有研究描述了手术程序，但只有两篇文献[40, 41]详细描述了单侧和双侧中央淋巴结摘除。双侧中央淋巴结摘除的百分比为100%。此外，还有其他原因导致的甲状腺手术。

文献被纳入篮选过程，原因如图1所示。八篇文献[12, 13, 37-42]于2014年至2016年间出版，符合选择标准，因此被纳入。
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### Table 1. General characteristics of the included studies

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

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

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

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 (I² = 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 (I² = 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).
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
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
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, 37-39, 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
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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 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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