The Effects of Preoperative Embolization on Carotid Body Paraganglioma Surgery: A Systematic Review and Meta-analysis

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Abstract

Objective. There is no definitive consensus on the impact of preoperative embolization on carotid body paraganglioma management. The purpose of this study was to assess the effects of preoperative embolization on carotid body paraganglioma excision.

Data Sources. A systematic search was conducted without limits, and it included studies published on or before July 2013 from PubMed, CINAHL, Web of Knowledge, and the Cochrane Library. Relevant synonyms for the search terms “paraganglioma,” “carotid body tumor,” and “embolization” were applied.

Review Methods. Studies evaluating patients undergoing surgical intervention with embolization for carotid body tumors were included. Two reviewers independently assessed the titles and abstracts for inclusion and extracted the data. The guidelines set forth by the Cochrane Collaboration were followed in the process of data extraction. Data were pooled with a fixed effects model, and standardized mean difference (SMD) and 95% confidence intervals (95% CIs) are reported.

Results. A total of 22 studies (15 nonrandomized studies with a comparator, 7 single-arm studies) were included, enrolling 578 patients with 607 tumors. Patients undergoing preoperative embolization had significantly less estimated blood loss compared with those of surgical excision only (12 studies; 295 tumors; SMD: –0.52; 95% CI: –0.77, –0.28). Patients undergoing preoperative embolization had less operative time compared with that of surgical excision only (6 studies; 174 tumors; SMD: –0.46; 95% CI: –0.77, –0.14).

Conclusion. Surgical excision with preoperative embolization appears to decrease estimated blood loss and operative time when compared with that without preoperative embolization for carotid body paragangliomas.

Keywords
paraganglioma, carotid body tumor, embolization, head and neck surgery, systematic review

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Paragangliomas of the head and neck are rare vascular tumors. Those that arise at the carotid bifurcation are commonly referred to as carotid body tumors (CBTs) and represent the most common paraganglioma of the head and neck. Early surgical excision has been recommended in CBTs to reduce the risk of perioperative complications and malignancy.1,2 Unfortunately, resection can prove difficult and be fraught with significant complications. In 1971, Shamblin classified CBTs into 3 classifications based on their relationship to the internal and external carotid arteries.3 Class I tumors are localized between the internal and external carotid arteries; class II tumors are adherent to or partially surrounding the carotid arteries; and class III encases 1 or both carotid arteries. Shamblin designed this classification in an attempt to predict the difficulty of surgical resection.

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The use of preoperative embolization has been advocated to aid in surgical resection by decreasing intraoperative blood loss and operative time. Other authors have assessed the implications of preoperative embolization on neurovascular complications. Despite these studies, there is no definitive consensus on the impact of preoperative embolization on carotid body paraganglioma management. In addition, most reports of CBT are small case series, making decisions on optimal treatment strategies difficult.

Therefore, we conducted a systematic review and meta-analysis to assess the implications of preoperative embolization on patients undergoing surgical excision of carotid body paragangliomas. The primary outcomes include estimated blood loss (EBL) and operative time.

**Methods**

**Eligibility Criteria**

Published studies were included if they enrolled patients undergoing surgical intervention for cervical paragangliomas and compared the effects of preoperative versus no preoperative vascular embolization on the operative time, total blood loss, and embolization-related mortality and morbidity. Studies that evaluated patients not undergoing surgical excision were excluded. Paragangliomas of sites other than the carotid body were excluded. All case reports and case series with <5 patients were excluded.

**Information Sources**

We searched electronic databases, including PubMed, CINAHL, Web of Knowledge, and the Cochrane Library.

**Search**

A systematic search was conducted without limits and included studies published on or before July 2013. Relevant synonyms were applied for the search terms “paraganglioma,” “carotid body tumor,” and “embolization.”

**Study Selection**

Two authors (R.S.J. and J.A.M.) independently assessed all titles and abstracts of the articles obtained from the electronic search according to a priori inclusion and exclusion criteria. All duplicate articles were removed. Conflicts were resolved with consensus discussion. Included studies were reviewed in entirety, and bibliographies were checked to identify any missing relevant articles. Inclusion and exclusion criteria were applied. Final included articles were then used for data extraction.

**Data Collection Process**

Data were extracted independently by 2 review authors (R.S.J. and J.A.M.). The guidelines set forth by the Cochrane Collaboration were followed in the process of data extraction.

**Data Items**

We extracted data on study characteristics—including study design, funding source, multicenter versus single-center study, number of male versus female participants, participants’ median age and range, primary tumor type, tumor size, laterality, tumor secretory function, embolization method, operative time, blood loss during the operation, and adverse events of embolization.

**Summary Measures**

We extracted the means and standard deviations from individual studies for the continuous outcomes. In cases where the data were reported as median and range, we converted these data into mean and standard deviation using the method by Hozol et al.

**Statistical Analysis**

Data were pooled with a fixed effects model, and standardized mean difference (SMD) and 95% confidence intervals are reported. For statistical analyses, data were entered into Review Manager Software (Revman 5.2). Heterogeneity was assessed with the $I^2$ statistic. Sensitivity analyses were conducted to investigate the impact of methodological quality of reporting on the treatment effects. This was performed to explore sources of statistical heterogeneity among studies. We assessed the risk of bias among included studies using the checklist by Wells et al, which addresses the methodological issues in nonrandomized studies.

**Additional Analysis**

We conducted subgroup analysis based on embolization type and tumor size. Secondary outcomes included length of hospital stay and complications of the embolization procedure and the surgical procedure.

**Results**

**Study Selection and Characteristics**

A total of 2405 studies were identified in the literature search. An additional 41 were identified through manually searching the bibliographies of the full-text articles assessed for eligibility. The flowchart in Figure 1 depicts the process of study selection and the reasons for exclusion. Therefore, a total of 22 studies enrolling 578 patients with 609 tumors met inclusion criteria and were included in the systematic review. All studies were retrospective reviews. There were no randomized control trials. Only 15 studies compared surgical excision with and without preoperative embolization. Included primary studies and characteristics of relevant data available for analysis are described in Table 1.

**Risk of Bias within Studies**

Overall, the methodological quality of included studies was moderate. Specifically, all the included studies provided the study design, but none provided the scientific background or why the given study design was chosen. Eighteen studies (82%) clearly defined the goals and subquestions. Seventeen studies (77%) compared ≥2 groups, while only 15 (68%) compared those who did or did not undergo preoperative embolization. No study compared the same group over time. No groups were formed by randomization or any other means in any of the included studies. As a result, there were no descriptions of group creation. Comparability between groups was not assessed on potential confounders in any of
the studies. No studies described the strengths and weaknesses of the data source. Adequate description was not provided regarding how treatment effects were measured or how to avoid classification bias. There was no description of confounding in any study. General interpretation of the results in the context of current evidence was presented in all studies.

**Primary Analysis**

*Estimated blood loss.* Of the 22 studies evaluated, only 15 had a control group. Of these, another 3 studies\(^4,\,7,\,11\) did not have sufficient data available to calculate standard deviation and therefore were not included in the analysis. Data were extracted from 12 studies with 295 tumors. The EBL was significantly lower in patients undergoing preoperative embolization than patients undergoing surgical excision alone (SMD = \(-0.52\); 95% CI: \(-0.77, -0.28\); \(P < .0001\)). There was no heterogeneity among these trials (\(I^2 = 7\%\), \(P = .37\); **Figure 2**).

*Operative time.* Only 6 of the included studies had sufficient data available for the outcome of operative time.\(^{15,\,16,\,19,\,21,\,22}\) Data were extracted from 6 studies with 174 tumors. Operative time was significantly lower in patients undergoing preoperative embolization than patients undergoing surgical excision alone (SMD = \(-0.46\); 95% CI: \(-0.77, -0.14\); \(P = .004\)). There was significant heterogeneity among these trials (\(I^2 = 58\%\), \(P = .03\); **Figure 3**).

**Subgroup Analysis**

*Embolization method.* The majority of studies with data available for analysis of EBL indicated transarterial embolization
performed within 24 to 48 hours preoperatively, and the pooled analysis was in favor of embolization (SMD = –0.55; 95% CI: –0.81, –0.30). Wang et al\textsuperscript{20} did not differentiate by embolization technique, and they showed no difference between embolization and no embolization for the outcome of EBL (SMD = –0.24; 95% CI: –1.00, 0.52; test of interaction, \(P = .45\)). All 6 studies with useful data for operative time were based on transarterial embolization; thus, no comparison could be made between transarterial and transcatheter techniques.

Table 1. Included Primary Studies and Characteristics of Relevant Data Available for Analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients (Tumors), n</th>
<th>Patients (Tumors), n</th>
<th>EBL, mL\textsuperscript{a}</th>
<th>Operative Time, min\textsuperscript{a}</th>
<th>Patients (Tumors), n</th>
<th>EBL, mL\textsuperscript{a}</th>
<th>Operative Time, min\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ward et al\textsuperscript{22}</td>
<td>1988</td>
<td>16 (17)</td>
<td>6 (6)</td>
<td>397 (100-800)</td>
<td>105 (45-210)</td>
<td>10 (11)</td>
<td>1375 (250-3500)</td>
<td>280.2 (150-420)</td>
</tr>
<tr>
<td>Lamuraglia et al\textsuperscript{14}</td>
<td>1991</td>
<td>17 (17)</td>
<td>11 (11)</td>
<td>373 ± 213</td>
<td>—</td>
<td>6 (6)</td>
<td>609 ± 564</td>
<td>—</td>
</tr>
<tr>
<td>Little et al\textsuperscript{6}</td>
<td>1996</td>
<td>21 (22)</td>
<td>11 (11)</td>
<td>1123 ± 1450</td>
<td>306 ± 150</td>
<td>10 (11)</td>
<td>764 ± 588</td>
<td>234 ± 96</td>
</tr>
<tr>
<td>Tikkakoski et al\textsuperscript{19}</td>
<td>1997</td>
<td>20 (27)</td>
<td>9 (12)</td>
<td>588 (65-1800)</td>
<td>204 (100-330)</td>
<td>11 (15)</td>
<td>1374 (100-4500)</td>
<td>288 (80-545)</td>
</tr>
<tr>
<td>Wang et al\textsuperscript{20}</td>
<td>2000</td>
<td>28 (28)</td>
<td>17 (17)</td>
<td>625 (50-3200)</td>
<td>—</td>
<td>11 (11)</td>
<td>855 (100-3500)</td>
<td>—</td>
</tr>
<tr>
<td>Plukker et al\textsuperscript{29}</td>
<td>2001</td>
<td>39 (39)</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>39 (39)</td>
<td>750 (50-4600)</td>
<td>174 (90-450)</td>
</tr>
<tr>
<td>Kasper et al\textsuperscript{13}</td>
<td>2007</td>
<td>20 (25)</td>
<td>10 (13)</td>
<td>365 ± 180</td>
<td>—</td>
<td>10 (12)</td>
<td>360 ± 101</td>
<td>—</td>
</tr>
<tr>
<td>Liu et al\textsuperscript{17}</td>
<td>2006</td>
<td>17 (17)</td>
<td>6 (6)</td>
<td>238 (80-400)</td>
<td>—</td>
<td>11 (11)</td>
<td>600 (100-1000)</td>
<td>—</td>
</tr>
<tr>
<td>Makeieff et al\textsuperscript{30}</td>
<td>2008</td>
<td>52 (57)</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>52 (57)</td>
<td>174 (100-248)</td>
<td>—</td>
</tr>
<tr>
<td>Ozay et al\textsuperscript{18}</td>
<td>2008</td>
<td>14 (14)</td>
<td>5 (5)</td>
<td>372 ± 150</td>
<td>—</td>
<td>9 (9)</td>
<td>411 ± 344</td>
<td>—</td>
</tr>
<tr>
<td>Arnold et al\textsuperscript{11}</td>
<td>2009</td>
<td>9 (9)</td>
<td>4 (4)</td>
<td>150</td>
<td>127</td>
<td>5 (5)</td>
<td>700</td>
<td>180</td>
</tr>
<tr>
<td>Gemmene et al\textsuperscript{24}</td>
<td>2010</td>
<td>8 (8)</td>
<td>8 (8)</td>
<td>406 (50-1650)</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Li et al\textsuperscript{15}</td>
<td>2010</td>
<td>62 (66)</td>
<td>33 (36)</td>
<td>354.8 ± 334.4</td>
<td>170.3 ± 75.4</td>
<td>29 (30)</td>
<td>656.4 ± 497.4</td>
<td>224.6 ± 114</td>
</tr>
<tr>
<td>Lim et al\textsuperscript{16}</td>
<td>2010</td>
<td>13 (13)</td>
<td>7 (7)</td>
<td>400 (200-1200)</td>
<td>360 (180-540)</td>
<td>6 (6)</td>
<td>550 (200-1400)</td>
<td>360 (220-480)</td>
</tr>
<tr>
<td>Zeiter et al\textsuperscript{4}</td>
<td>2010</td>
<td>25 (25)</td>
<td>10 (10)</td>
<td>305 (50-1000)</td>
<td>—</td>
<td>15 (15)</td>
<td>265.6 (40-90)</td>
<td>—</td>
</tr>
<tr>
<td>Avgerinos et al\textsuperscript{12}</td>
<td>2011</td>
<td>20 (20)</td>
<td>4 (4)</td>
<td>415 (230-850)</td>
<td>—</td>
<td>16 (16)</td>
<td>710 (250-1650)</td>
<td>—</td>
</tr>
<tr>
<td>Power et al\textsuperscript{7}</td>
<td>2012</td>
<td>98 (104)</td>
<td>29 (33)</td>
<td>263 ± 250</td>
<td>69 (71)</td>
<td>599 ± 265</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Shah et al\textsuperscript{16}</td>
<td>2012</td>
<td>7 (7)</td>
<td>7 (7)</td>
<td>55 (15-80)</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Zeng et al\textsuperscript{31}</td>
<td>2012</td>
<td>46 (48)</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>5 (5)</td>
<td>1260 ± 1256</td>
<td>255 ± 69</td>
</tr>
<tr>
<td>Zeng et al\textsuperscript{31}</td>
<td>2012</td>
<td>46 (48)</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>41 (43)</td>
<td>773 ± 727</td>
<td>227 ± 91</td>
</tr>
<tr>
<td>Zhang et al\textsuperscript{21}</td>
<td>2012</td>
<td>29 (29)</td>
<td>21 (21)</td>
<td>280 (50-850)</td>
<td>180 (160-220)</td>
<td>8 (8)</td>
<td>450 (100-1000)</td>
<td>220 (170-260)</td>
</tr>
<tr>
<td>Abdel-Aziz et al\textsuperscript{23}</td>
<td>2013</td>
<td>5 (5)</td>
<td>5 (5)</td>
<td>327 (40-1400)</td>
<td>148 (35-289)</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kalani et al\textsuperscript{25}</td>
<td>2013</td>
<td>12 (12)</td>
<td>12 (12)</td>
<td>191.6 (25-600)</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviation: EBL, estimated blood loss.

\textsuperscript{a}Mean ± SD or mean (range).

\textsuperscript{b}Zeng et al\textsuperscript{31} divided their study into functional (F) and nonfunctional (NF) tumors based on catecholamine secretion. Therefore, their study represents 2 rows, since they did not provide data for the overall study population.

Figure 2. Forest plot comparing estimated blood loss for patients embolized and not embolized preoperatively, favoring preoperative embolization to decrease estimated blood loss during carotid body paraganglioma excision. CI, confidence interval; IV, inverse variance.
The difference between preoperative embolization and no embolization for outcome of EBL in studies with tumor size ≤4 cm (SMD = –0.30; 95% CI: –0.69, 0.09) and >4 cm (SMD = –0.20; 95% CI: –0.80, 0.39). Of the 6 studies included for the outcome of operative time, 4 reported tumor size. There was no significant difference between preoperative embolization and no embolization for outcome of operative time in studies with tumor size ≤4 cm (SMD = –0.34; 95% CI: –0.97, 0.29) and >4 cm (SMD = –0.06; 95% CI: –0.66, 0.53).

**Shamblin classification.** We attempted to stratify EBL and operative time by Shamblin classification. Unfortunately, most studies did not report these values; therefore, there are not enough data to stratify by Shamblin classification.

**Length of hospital stay.** Comparative data for length of hospital stay are available in only 4 studies. The data are limited because of variation in reporting, as only 1 of these studies reported standard deviation. Two were found to have significant differences while the remaining 2 did not show difference.

**Complications.** Complications were identified in 41 of 118 (34.7%) embolized patients and 70 of 160 (43.7%) nonembolized patients without significant difference between the 2 groups. Although included studies did not uniformly report complications in a standardized fashion, 8 studies compared complications between those embolized or not embolized preoperatively (Table 2). The most common complications in both groups were related to neurovascular injuries.

**Complications of the embolization procedure.** Of the 22 studies, 19 evaluated patients undergoing preoperative embolization. Of these, 11 reported complication data specifically related to the preoperative embolization procedure. There were 4 complications in 160 embolization procedures (2.5%). Complications included cranial nerve XII palsy (n = 1), temporary aphasial (n = 1), permanent vocal cord paralysis (n = 1), and arterial dissection (n = 1).

**Sensitivity Analyses**

The estimates of EBL and operative time were not influenced by the methodological quality of reporting included studies. That is, there were no significant differences in the pooled outcomes of EBL and operative time based on the level of methodological quality of reporting of the included studies.
Discussion

Carotid body paragangliomas are rare vascular tumors of the head and neck. Early surgical excision is recommended in an effort to reduce the potential complications of large tumors.1,2 The potential benefits of preoperative embolization in patients undergoing surgical excision of CBT have led to its widespread use, but the overall impact remains unclear. In a large series, Power et al concluded that large carotid body paragangliomas can safely be resected with or without preoperative embolization, but preoperative embolization may simplify the surgical excision and reduce blood loss.3 They added that, in their series, preoperative embolization did not have an impact on the rate of cranial nerve injury.

This systematic review and meta-analysis of published studies suggest that preoperative embolization leads to a decrease in intraoperative blood loss and operative time. The mean EBL among the patients who received embolization was 0.52 standard deviations lower (0.77 to 0.28 lower) than that of patients who were not embolized. The mean operative time among the patients who received embolization was 0.46 standard deviations lower (0.77 to 0.14 lower) than that of patients who were not embolized. There was not enough information available to determine the impact of the method of embolization—mainly, the percutaneous approach compared with the transfemoral transarterial approach.

Many papers acknowledged the importance of Shamblin classification and tumor size but then did not stratify the data for EBL and operative time based on this information. Power et al reported a correlation of the level of difficulty, operative time, blood loss, and nerve injuries to higher Shamblin-class tumors but recognized the subjectivity of this system.4 Yet, Ozay et al compared Shamblin I and II with Shamblin III and found increased blood loss, cranial nerve injury, and hospital stay for Shamblin III tumors, but their experience was limited to only 14 patients.5 Lim et al also compared Shamblin I and II with Shamblin III tumors in 13 patients and found increased operative time, blood loss, and cranial nerve deficit in patients with Shamblin III tumors.6 In the current review, studies that reported tumor size did not favor embolization to decrease EBL or operative time. Therefore, whether embolization is beneficial based on these parameters remains unclear.

The impact of preoperative embolization on length of hospital stay also remains unclear based on the available data. In this systematic review, 1 study showed a significantly decreased length of hospital stay for those embolized;1; 1 study showed a significantly increased length of hospital stay;13; and 2 did not demonstrate a significant difference.15,16 In addition, there was heterogeneity among the duration of hospital stay among studies, which could be due to differences in embolization protocols, patient factors, or surgeon preferences. Larger studies with standardized reporting will need to be completed to evaluate if embolization has an effect on length of hospital stay.

In this meta-analysis, complications were found in 39.9% of patients with no significant difference between those embolized and not. Serious complications of surgical resection of CBT include cranial nerve injury and vascular injury. Such complications may lead to hoarseness, dysphagia, aspiration, stroke, or death. Power et al compared the neurovascular complications of patients treated with surgical resection with or without preoperative embolization.7 In their series, they found no difference in complications between the 2 groups and concluded that preoperative embolization does not decrease perioperative complications. In addition to surgical complications, complications may arise from the embolization procedure itself.7 These are believed to be uncommon based on available data reported. Although there does not appear to be a difference in complications between preoperative embolization and no preoperative embolization, no conclusions can be made regarding the implications of preoperative embolization on perioperative complications secondary to the heterogeneity in reporting.

The current study has several limitations. First, it is limited by the variances in reporting among the included studies. The level of evidence in the studies available for review also limits this study. There were no randomized control trials comparing embolization with no embolization prior to surgical excision of carotid body paragangliomas. Hence, we have to rely on the observational study designs, which are inherently a lower class of evidence. The methodological quality of the included studies was moderate to low. Last, many of the included studies are relatively recent publications, despite having no restrictions on publication date prior to July 2013. There is no clear explanation for this, but it could be explained by the increased accessibility of embolization, which made it a more common practice in later studies. Despite these limitations, several quality assurance measures were implemented, including the limitations employed during the study selection process as described.

As this is a review of retrospective studies, there is a risk of bias for determining who was selected to receive preoperative embolization, which could be due to patient factors or surgeon preference. Duration of surgery and EBL are dependent on patient factors and surgeon experience, which are not possible to address in the evaluation of retrospective and nonrandomized studies. These factors may explain the variance of operative time and blood loss between studies. Also, EBL is not a definitive number and relies on intraoperative reporting, the accuracy of which has been brought into question.27,28 Despite this, subjective assessment of EBL continues to be reported in the literature, and until reporting of this metric is improved, we must rely on the accuracy of such data in the original reports.

Conclusions

Based on the findings of this systematic review and meta-analysis, preoperative embolization appears to decrease intraoperative blood loss and operative time when compared with that of patients who undergo surgical excision without preoperative embolization for carotid body paragangliomas.
In addition, the embolization procedure itself had few complications and did not appear to decrease perioperative complications. Given the relative rarity of these tumors, randomized control trials will be difficult to perform. Therefore, future research should focus on standardization of reporting as well as performance of prospective comparative studies.

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Author Contributions

Ryan S. Jackson, conception of design, acquisition and interpretation of data, drafting the work and revising it critically, final approval of the manuscript and agreement to be accountable for all aspects of the work; Jeffrey A. Myhill, acquisition and of data, drafting the work and revising it critically, final approval of the manuscript and agreement to be accountable for all aspects of the work; Tapan A. Padhya, conception of design, interpretation of data, revising the manuscript critically, final approval of the manuscript and agreement to be accountable for all aspects of the work; Judith C. McCaffrey, conception of design, interpretation of data, revising the manuscript critically, final approval of the manuscript and agreement to be accountable for all aspects of the work; Jeffrey A. Myhill, acquisition and of data, drafting the work and revising it critically, final approval of the manuscript and agreement to be accountable for all aspects of the work; Rahul S. Mhaskar, conception of design, analysis and interpretation of data, drafting the work and revising it critically, final approval of the manuscript and agreement to be accountable for all aspects of the work.

Disclosures

Competing interests: Tapan A. Padhya, Inspire Sleep Medical (Minneapolis, Minnesota), surgical education consultant.

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