Cholesterol Granulomas: A Comparative Meta-Analysis of Endonasal Endoscopic versus Open Approaches to the Petrous Apex

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INTRODUCTION

Petrous apex cholesterol granulomas (PACG) are rare disorders that can lead to patient morbidity and must, occasionally, be drained by either endoscopic endonasal (EN) or open procedures (OP). The objective of our study was to complete a review of the literature to compare the EN and OP approaches on multiple levels, notably on safety and effectiveness. Ovid MEDLINE and Embase were used to perform a thorough literature review of all cases of PACG treated by either EN or OP dating from January 1948 to August 2017. In total, 49 articles were selected including 23 for EN (n=76) and 26 for OP (n=210). Differences were found in the incidence of preoperative hearing loss (HL) (EN 18.4%, OP 57.3%; p<0.001), headache (EN 48.7%, OP 31.2%; p=0.007), and disequilibrium (EN: 14.5%, OP 26.1%; p=0.04). Differences in lesion proximity to the sphenoid sinus (EN 23.6%, OP: 1.0%; p<0.001), clivus (EN 11.8%, OP 4.7%; p=0.03), otic capsule (EN 0.0%, OP 5.2%; p=0.03), internal auditory canal (EN 2.6%, OP 10.9%; p=0.01), and internal carotid artery (ICA) (EN 9.2%, OP 2.8%; p=0.02) were found on preoperative imaging. The EN procedure had better hearing improvement rates (EN 85.7%, OP 23.4%; p<0.001), lower complication rates (EN 7.9%, OP 17.6%; p=0.04), shorter median follow-up (EN:13.5 months, OP:37.2 months; p<0.001), and shorter time to recurrence (EN 3 months, OP 22.6 months; p=0.002) than the known OP. No differences were found in age, preoperative size, recurrence rate, operative time, stent placement, or improvement of other symptoms. Endoscopic nasal approaches, when feasible, should be favored to open procedures for PACG drainage given their better hearing improvement and less complication rates.

KEYWORDS: Petrous apex, cholesterol granuloma, infralabyrinthine, infracochlear, middle fossa, suboccipital, translabyrinthine, endonal
Stenting has been used to theoretically diminish the risks of recurrence. However, their benefit remains unproven and controversial. Of note, an alternative to stenting, proposed by Paluzzi et al. [10], is the nasoseptal mucoperiosteal miniflap.

In a cadaver dissection study, Scopel et al. [11] demonstrated that EN approaches were able to reach the posterior-inferior PA in 90% and the superior and anterior-inferior PA in all specimens. With this in mind, EN approaches may not be limited to lesions approximating the sphenoid sinus.

The objective of our study was to complete a review of the literature of all the aforementioned approaches to compare the EN and OP approaches on multiple levels, notably on safety and effectiveness.

MATERIALS AND METHODS

Literature Review
The systematic review was completed according to Preferred Reporting Items for Systematic Reviews guidelines. Pubmed, Ovid MEDLINE, and EMBASE databases were used to perform a literature review of English language publications from January 1948 to August 2017. The keyword combinations included the following: petrous apex cholesterol granuloma AND infralabyrinthine OR infracochlear OR middle fossa OR suboccipital OR translabyrinthine OR transsphenoid OR transclival OR transpterygoid. An outline of our review methodology can be seen in Figure 1.

Selection Criteria
Articles explicitly reporting patients with histologically proven PACG were reviewed. The lesion had to have been either drained or excised via either EN or OP approaches. Each study was analyzed to extract all available data and assure eligibility for inclusion of all patients. Patients were separated into two groups according to the operative procedure they underwent (EN or OP). Age, preoperative symptoms, size and location of the lesion, operative times, follow-up times, postoperative symptom improvement, surgical complications, and recurrence rates with or without the use of stent placement were compared. The pediatric population was excluded. Articles describing only revision surgery were also excluded.

Titles and abstracts were reviewed by two authors (P. T. and N. S.) to discard irrelevant studies. All of these were then analyzed to include any additional articles of interest. Relevant studies were independently determined by P. T. and N. S., based on the inclusion criteria.

The study was approved by our institutional research ethics board and follows the standards of our institutional ethics committee.

Statistical Analysis
Statistical analysis was done using the Microsoft Excel software (Redmond, Washington, USA). Chi-square test was used to analyze categorical data. Fisher’s exact test was used to analyze categorical data when one of the tested groups was composed of ≤5 patients. Student’s t-test was used to analyze all continuous data. Homogeneity among studies in each group was also undertaken.

Figure 1. Study methodology.
RESULTS
A total of 49 articles were included in our review: 23 described endonasal approaches [5, 10, 12-34] and 26 described open approaches [4, 6, 34-57]. Reports of 286 patients were included, 76 of whom underwent EN approaches and 210 OP approaches. The most commonly used surgical approaches are listed in Table 1.

The mean age was similar between both EN and OP groups (EN: 38.6±15 years; OP: 39.7±11.6 years; p=0.6). The most common presenting symptom was hearing loss, followed by headaches and vestibular symptoms (Table 2). Differences in preoperative symptoms between each group are shown in Table 3. No difference was found in the preoperative lesion size between both EN and OP groups (EN: 3.15±0.83 cm; OP: 2.75±0.57 cm; p=0.19). Differences in lesion proximity to important anatomic structures are shown in Table 4.

As shown in Table 5, symptom improvement was similar between EN and OP groups, except for hearing loss which responded better to EN than hearing-sparing OP (EN 85.7%, OP 23.4%; p<0.001). Table 6 demonstrates symptom improvement among the most frequently used approaches. All patients who underwent the MF approach showed complete resolution of their symptoms. The IL approach showed better hearing improvement than the IC approach (41% vs 17%; p=0.03).

Stenting was used in 51 patients (17.8%). Sixteen patients among the EN group (21%) underwent stent placement, including five TS, three TC, and eight the combined TC+IP approaches. Of the 35 stents placed within the OP group (16.7%), 21 used the IC approach, 12 the IL approach, and two MF approaches. Stents were specifically de-
scribed as being made with Silastic in only six patients\textsuperscript{40, 41, 42, 51}. Specific stent manufacturers were mentioned in only two articles. One article among the EN group described the stent as a 4-mm Xomed frontal sinus stent (Medtronic Inc., Jacksonville, Florida, USA)\textsuperscript{23}, and another among the OP group described it as fashioned from an angiocath (Becton, Dickinson and Co.)\textsuperscript{48}. Furthermore, two articles mentioned T-shaped stents in the EN group\textsuperscript{29, 30}. Graham et al.\textsuperscript{51} described an MF approach which necessitated stent placement into the anterior tympanic cavity, and Balachandran et al.\textsuperscript{35} described a double-barrel stenting approach which required two drilling tracts to the lesion. Finally, two articles mentioned postoperative removal of stents under general anesthesia because of granulation tissue formation\textsuperscript{10}. No articles in our review mentioned anticoagulant therapy or its effect on patient quality of life.

EN approaches showed similar recurrence rates as OP approaches when stent placement was used (6% vs 17%; \(p=0.22\)). When comparing the recurrence rate of nonstented patient, EN approaches had a significantly higher recurrence rate (16% vs 7%; \(p=0.03\)). No difference was found in recurrence rates between stented and nonstented EN approaches (6% vs 16%; \(p=0.20\)). A trend was seen toward a significantly higher recurrence rate in stented OP approaches than nonstented ones (17% vs 7%; \(p=0.07\)).

Among all collected articles, only two in the EN group\textsuperscript{15, 24} and four in the OP group\textsuperscript{42, 43, 53} were described as excised and not drained, all of which had positive postoperative outcomes. Given the rarity of excision, comparison between drainage and excision between groups was difficult to make.

### Table 6. Cholesterol granuloma symptom improvement by surgical approaches

<table>
<thead>
<tr>
<th>Symptom</th>
<th>EN (TS n=39)</th>
<th>EN (TC n=18)</th>
<th>EN (IP n=8)</th>
<th>OP (IC n=62)</th>
<th>OP (IL n=78)</th>
<th>OP (MF n=33)</th>
<th>OP (TL n=16)</th>
<th>OP (SO n=6)</th>
<th>OP (Other n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss</td>
<td>6/7 (86%)</td>
<td>2/2 (100%)</td>
<td>3/3 (100%)</td>
<td>5/30 (17%)</td>
<td>17/41 (41%)</td>
<td>N/A</td>
<td>0/5 (0%)</td>
<td>0/4 (0%)</td>
<td>3/8 (38%)</td>
</tr>
<tr>
<td>Headache</td>
<td>15/16 (94%)</td>
<td>6/7 (86%)</td>
<td>4/4 (100%)</td>
<td>1/1 (100%)</td>
<td>6/7 (86%)</td>
<td>4/4 (100%)</td>
<td>N/A</td>
<td>N/A</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>Vertigo/dissequilibrium</td>
<td>4/4 (100%)</td>
<td>3/4 (75%)</td>
<td>N/A</td>
<td>2/2 (100%)</td>
<td>5/5 (100%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0/2 (0%)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>6/7 (86%)</td>
<td>1/1 (100%)</td>
<td>2/2 (100%)</td>
<td>2/4 (50%)</td>
<td>5/5 (100%)</td>
<td>10/10 (100%)</td>
<td>N/A</td>
<td>N/A</td>
<td>2/3 (67%)</td>
</tr>
<tr>
<td>Paresis / paralysis</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0/1 (0%)</td>
</tr>
<tr>
<td>Paresthesia / pain</td>
<td>N/A</td>
<td>N/A</td>
<td>2/3 (67%)</td>
<td>N/A</td>
<td>1/1 (100%)</td>
<td>4/4 (100%)</td>
<td>N/A</td>
<td>N/A</td>
<td>2/2 (100%)</td>
</tr>
</tbody>
</table>

**Notes:** EN: Endoscopic endonasal; OP: open; TS: Transsphenoid; TC: Transphenoid transclival; IP: Infrapetrous; IC: Infracochlear; IL: Infracochlear; TM: Transmastooid; TL: Translabyrinthine; SO: Suboccipital; N/A: not applicable.

### Table 7. Recurrence and complications rate comparison between EN and open approaches

<table>
<thead>
<tr>
<th>Approach</th>
<th>Reported complications</th>
<th>Complication rate (%)</th>
<th>Complications</th>
<th>Reported recurrences</th>
<th>Recurrence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>65/76 (85.5%)</td>
<td>5/55 (9.1%)</td>
<td>Hearing loss, Epistaxis; Pneumocephalus</td>
<td>57/76 (75.0%)</td>
<td>7/57 (12.3%)</td>
</tr>
<tr>
<td>TS</td>
<td>30/39 (76.9%)</td>
<td>2/30 (6.6%)</td>
<td>Hearing loss, Epistaxis; Pneumocephalus</td>
<td>28/39 (71.8%)</td>
<td>6/28 (21.4%)</td>
</tr>
<tr>
<td>TC</td>
<td>17/18 (94.4%)</td>
<td>1/17 (5.8%)</td>
<td>Hearing loss, Epistaxis; Pneumocephalus</td>
<td>13/18 (72.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IP</td>
<td>10/11 (90.9%)</td>
<td>0 (0%)</td>
<td>Hearing loss, Epistaxis; Pneumocephalus</td>
<td>9/11 (81.8%)</td>
<td>1/9 (11.1%)</td>
</tr>
<tr>
<td>TC+IP</td>
<td>8/8 (100%)</td>
<td>2/8 (25%)</td>
<td>Hearing loss, Epistaxis; Pneumocephalus</td>
<td>7/8 (87.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>160/210 (76.1%)</td>
<td>36/160 (22.5%)</td>
<td>Hearing loss, Epistaxis; Pneumocephalus</td>
<td>151/210 (71.9%)</td>
<td>16/151 (10.6%)</td>
</tr>
<tr>
<td>IC</td>
<td>48/62 (77.4%)</td>
<td>7/48 (14.5%)</td>
<td>Hearing loss, Epistaxis; Pneumocephalus</td>
<td>47/62 (75.8%)</td>
<td>9/47 (19.1%)</td>
</tr>
<tr>
<td>IL</td>
<td>58/78 (74.4%)</td>
<td>18/58 (31%)</td>
<td>Facial paralysis, CSF leak, meningitis, SNHL</td>
<td>58/78 (74.4%)</td>
<td>4/58 (6.9%)</td>
</tr>
<tr>
<td>MF</td>
<td>26/33 (78.8%)</td>
<td>5/26 (19.2%)</td>
<td>CSF leak, meningitis, seizures</td>
<td>24/33 (72.7%)</td>
<td>2/24 (8.3%)</td>
</tr>
<tr>
<td>TL</td>
<td>10/16 (62.5%)</td>
<td>0*</td>
<td>CSF leak, meningitis, seizures</td>
<td>8/16 (50.0%)</td>
<td>0/8 (0%)</td>
</tr>
<tr>
<td>SO</td>
<td>5/6 (83.3%)</td>
<td>3/5 (60%)</td>
<td>Facial nerve palsy, abdominal hematoma, swallowing dysfunction</td>
<td>5/6 (83.3%)</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>13/15 (86.6%)</td>
<td>3/13 (23.0%)</td>
<td>Facial nerve paralysis, Carotid artery injury</td>
<td>9/15 (60%)</td>
<td>1/9 (11.1%)</td>
</tr>
</tbody>
</table>

**Notes:** EN: Endoscopic endonasal; OP: open; TS: Transsphenoid; TC: Transphenoid transclival; IP: Infrapetrous; IC: Infracochlear; IL: Infracochlear; MF: Middle fossa; TL: Translabyrinthine; SO: Suboccipital; CSF: Cerebrospinal fluid; SNHL: Sensorineural hearing loss.

*Postoperative hearing loss in TL was not considered a complication.
A trend toward a significantly shorter OR time was noted between EN and OP approaches (1 h vs 2.25 h, respectively; p=0.09); however, it must be mentioned that very few operative times were reported in the literature according to our review (n=9).

Table 7 shows symptom recurrence and surgical complication rates for the most commonly used approaches. Among all patients, the presence of recurrences and complications was reported in 208/286 (72.7%) and 225/286 (78.7%), respectively. When comparing EN and OP approaches, the symptom recurrence rates were similar (12.3% vs 10.6%; p=0.57) and the complications rates were significantly higher in the OP approach group than in the EN approach group (22.5% vs 9.1%; p=0.03).

The EN approach was also found to have shorter median follow-up (EN: 13.5 months, OP: 37.2 months; p<0.001) and shorter time to recurrence (EN: 3 months, OP: 22.6 months; p=0.002).

A study of homogeneity was attempted but was determined to be unreliable given the low sample size within each case series.

**DISCUSSION**

The indications for a given approach were rarely explicitly expressed within each article; however, the differences in preoperative symptoms and lesion location may explain why a certain procedure was favored over another. Of note, hearing loss and proximity to the internal auditory canal (IAC) and otic capsule seemed to favor the OP approach. Extension to the internal auditory canal has previously been stated as a contraindication to EN procedures [47]; nonetheless, two patients in our review underwent EN resection of PACG extending to IAC [23, 29]. Interestingly, they did not present any postoperative complications and were symptom-free at 3- and 10-month follow-ups. Of the 11 patients with PACG approximating to the otic capsule, one had no reported symptom improvement, and of the remaining 10 patients, 7 (70%) had improved hearing after an OP approach. This entails that the approximation to the otic capsule does not entail the lack of hearing improvement postoperatively and that these patients should be included in the hearing outcome comparison.

Furthermore, many authors have limited the use of EN approaches to medial lesions either protruding or abutting the sphenoid sinus; however, the use of ICA lateralization or a transpterygoid infrapetrous approach has made a more deep and lateral dissection possible [11]. Paluzzi et al. [10] reported five patients necessitating ICA lateralization and no recurrences of their lesions secondary to complete resection. Although the use of ISF is strongly advocated, the MF approach unfortunately has the downfall of having a high complication rate. This approach unfortunately has the downfall of having a high complication rate. Complications were relatively severe and included CSF leak, meningitis [36], and seizures [53].

All patients operated via the TL approach had nonserviceable hearing and no recurrences of their lesions secondary to complete resection of the disease. In fact, given the wide exposure of the PA, a complete resection of the granuloma is possible, and therefore, a low recurrence rate is to be expected.

Of the six patients who underwent a suboccipital approach (SO) compared to the PA approach, postoperative symptom outcomes were reported only in four patients who initially presented with hearing loss and none showed postsurgical improvement. Two patients had postoperative complications; one developed a facial nerve palsy and an abdominal wound hematoma [34] and the second reported swallowing dysfunction [49]. The proximity to the brainstem origin of cranial nerves VII, IX, and X could explain these findings [58].

Interestingly, when comparing nonstented EN and OP approaches, a significantly higher recurrence rate was observed in EN which may
indicate a higher necessity for stenting in these cases. In fact, the larger dissected space in the OP techniques may explain the limited usefulness of stents in these procedures. Another interesting finding is the trend toward a higher recurrence rate in stented OP patients than non-stented ones. This may be secondary to stent blockage and subsequent narrowing of the open dissected space. Therefore, we conclude that stenting is an advantageous intervention only in EN cases and may increase the risk of recurrence in OP cases.

Finally, the shorter median follow-up and time to recurrence after EN approaches may represent another advantage of such procedures. Since disease recurrence presents earlier with EN, cure from PACG may be established more quickly in these patients than in those having undergone OP procedures. The timing of complications and hearing improvement were not reported in the reviewed articles. However, most described complications can be considered acute complications normally occurring within a year of surgery. Similarly, postoperative hearing assessment is usually done within a year of surgery as well. Therefore, the shorter follow-up time in EN approaches (13.5 month) should not invalidate the differences found between the EN and OP groups.

It is important to note, however, that regardless of these different outcomes between the EN and OP approaches, we do emphasize the value of observing patients with tolerable symptoms given the possibility of spontaneous resolution and the risks involved in surgery.

Limitations
First, our study is limited by the reported data within the above cited articles. As previously noted, postoperative outcomes were not systematically mentioned in every article. Furthermore, no distinction was made between symptom improvement and resolution. Also, if any authors brought subtle variations of known surgical approaches when excising or draining the cholesterol granuloma, these variations were not taken into account given their high number in variability. For example, the Brackmann’s method for the infracochlear approach is not identical to the one described by Golofsky et al. [41] No articles in the EN group and 18 articles in the OP group mentioned pure-tone audiometry (PTA) scores. Ten of the 18 articles in the OP group mentioned pre- and post-operative PTA scores. Given the limitations of quantitative data in literature, we opted to use only the mention of the presence, improvement, stability, or worsening of hearing loss. A specific threshold was not used given the lack of PTA scores in the EN group. Finally, homogeneity testing was not possible given the low sample size of each study, multiple case reports and series had to be included given the lack of literature on the topic. This permits an early interpretation of data in literature and more studies, including randomized studies, must be undertaken to further understand this topic. However, to do so, endoscopic endonasal approaches should be attempted in greater numbers and this study in an introduction to its safety and efficacy.

CONCLUSION
While the recurrence rates are similar between EN and OP procedures, the EN approach has lower complication rates as well as better hearing improvement outcomes. Also, stent placement seems to be more useful in the EN approach than in the OP approach. Given these results, we encourage to always consider EN approaches, when feasible, in patients with PACG. If an OP approach in chosen however, one should be aware of the lower recurrence rates and better hearing outcomes of the IL approach than the IC approach which has, on the other hand, less complications.

Peer-review: Externally peer-reviewed.


Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES