

## Peer Review File

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**Reviewer A:**

Comment 1: This is a well presented case series. I would like to see a comment on long-term follow up or the lack thereof

Reply: Thank you for your comment. Longer follow-up was not felt to be necessary for the patients analysed in this case series – three months was considered adequate to determine the efficacy of the surgery (resolution of pain) and the development of any complications.

Changes: ‘Methods’ page 5, lines 134-136:

“Three months was considered adequate time to assess the efficacy of the surgery (resolution of pain) and the development of any complications.”

**Reviewer B:**

Overall – this represents a case series of a condition which is not commonly treated surgically

Major comments:

1. Could the authors elaborate on how the diagnoses was made in the 29 patients who underwent styloidectomy? From Line 182 to Line 189 the authors state that patients had styloid process elongation and but it is unclear what Langais classification each patient had, In addition, Line 184 mentions that the important clinical findings were “flexible nasendoscopy” – what was the abnormal finding on nasendoscopy? In addition, only 5 patients had symptoms isolated to the shorter side – what abnormality did they have apart from the size of the styloid process which led to the decision for surgery

Reply: Thank you for your comment. Eagle’s syndrome is a diagnosis of exclusion, with the aim of clinical examination, FNE and MRI being to rule out other pathologies, such as dental disease or base of skull or tongue tumour. Nasendoscopy was utilized to exclude occult malignancy, particularly in the base of tongue, as a cause of pain. This has been clarified in the ‘Diagnosis’ section on page 9.

The Langais classification of each patient was not routinely recorded as the classification system is considered to be of anatomical interest only and does not relate to symptomatology.

The patients who had symptoms on the shorter side still had ipsilateral elongated styloid process as a cause for their symptoms. Given that only 4% of patients with elongated styloid processes have symptoms, it is possible to have bilateral styloid process elongation without having bilateral symptoms and symptoms do not necessarily occur on the longer side. Eagle (1949) similarly presents a case of bilateral elongation, with the symptomatic and therefore operative side being the “shorter” styloid process. This section of the ‘Diagnosis’ has been adjusted for clarity.

Changes:

‘Diagnosis’, page 8 Lines 266-278:

“Eagle’s syndrome is primarily a diagnosis of exclusion, with the main positive clinical finding being elicitation of pain on palpation of the styloid process in the tonsillar fossa. In order to exclude other pathologies, all patients underwent the routine pre-operative workup, including recognition of any dental disease via clinic examination and orthopantomogram (OPG) and flexible nasendoscopy and magnetic resonance imaging (MRI) to exclude an occult skull base or submucosal oropharyngeal lesions. Computered tomography with three-dimensional reconstruction (3D-CT) was utilised as a diagnostic adjunct to determine styloid process length (see Figure 3). All patients had bilateral styloid process elongation over 25mm. Five patients (26.3%) had symptoms isolated to the side with the radiologically shorter (but still elongated) styloid process and, given the frequency of bilateral elongation, the decision to operate was always based on lateralising symptoms.

2. The duration of follow up for this study is very short at 3 months – could the authors please elaborate on the reasons for this? In line 207- the authors state that the outcomes of surgery was “largely successful” – could the authors elaborate on what “largely successful” outcomes mean? Line 349 – for example, patients had relief of symptoms needs to be qualified given the extremely short duration of follow up.

Reply: Thank you for this comment. 3 months thought to be adequate follow up to determine resolution of pain and any complications- if symptoms are going to be improved with surgery or complications occur, they will do so within three months post-operatively. This has been clarified in ‘Methods’ on page 5 lines 110 – 112.

We agree that the phrase “largely successful” is a judgement and therefore probably not relevant to the ‘Results’ section. This has been

amended to simply state the outcomes from surgery.

Changes:

'Methods' page 5, lines 134-136: "Three months was considered adequate time to assess the efficacy of the surgery (resolution of pain) and the development of any complications."

'Results- Management and outcomes' on page 9, lines 309-311: "Sixteen patients (84.2%) reported resolution of pain, globus or neurovascular symptoms while three patients (15.8%) had ongoing symptoms despite styloidectomy."

3. The authors mention that a review of surgical approaches was undertaken, specifically comparing the transoral vs the transcervical route based upon a review of the literature. However, apart from assessing the odds ratio of complications, there is very little comparison between the two outcomes. Could the authors elaborate further on what appears to be at glance, a large literature review? For example, what were the indications for surgery, the outcomes of surgery, or even the demographics of the patients reviewed? Were these differences statistically significant? Line 315-321 needs to expand upon this.

Reply: Thank you for this comment. At your suggestion, we have performed a more extensive review of the literature.

Changes:

'Abstract- Results', page 3, lines 53 – 58.

"a total of 401 patients undergoing surgical management for Eagle's syndrome. The trans-oral approach was utilised in 60.4% of cases, compared 39.7% of patients undergoing trans-cervical access. Symptoms were completely relieved in 88.3% of cases, with no difference in success between approaches. There was no difference in complication rates between the trans-oral and trans-cervical groups (8.8% versus 4.1%,  $p = 0.06$ )."

'Methods', page 6, lines 145-147:

"Collected data included the age and sex of the patients, history of

tonsillectomy, indications for surgery, surgical approach, surgeon performing surgery, outcomes and complications.”

‘Literature review’, page 9, lines 314-378:

“Twenty-nine studies were included with a total of 401 patients undergoing surgical management for Eagle’s syndrome (see Table 1). The patients ranged in age from 17 to 78 years old. There was a female predominance, with 270 females (67.3%) compared to 115 males (28.9%), while the sex was not determinable in 16 cases. 212 (52.9%) patients had previously undergone tonsillectomy while 56 (14%) had no history of tonsillectomy (in 133 cases, prior tonsillectomy status could not be determined). In the great majority of patients, the indication for surgery was pain, dysphagia and/or globus sensation (397 patients, 99%). Four patients (1%) presented with carotid artery syndrome.

Overall, the trans-oral approach was preferred, being employed in 242 (60.4%) cases, while the other 159 (39.7%) underwent ... Seventy-nine (19.7%) of the studies were conducted by oromaxillofacial (OMFS) units, while the other 322 (80.3%) were written by otolaryngologists. Assuming that the same unit who conducted the studies also performed the surgeries, there was a statistically significant difference in surgical approaches- otolaryngologists performed trans-oral surgery in 66.8% of their cases, while OMFS performed trans-oral surgery in 34.2% ( $p < 0.001$ ).

Symptoms were relieved in 354 (88.3%) and partially improved in 30 (7.5%) cases. There was no change in symptoms in the remaining 17 cases (4.2%). There was no difference in success rates between trans-oral versus trans-cervical approach (88.9% vs 87.4%,  $p = 0.35$ ). Complications occurred in 24 cases- 14 in the trans-cervical group, an incidence of 8.8% of surgeries; and 10 in the trans-oral group, occurring in 4.1% of cases ( $p = 0.054$ ). The odds ratio for a complication in a patient undergoing trans-cervical compared to trans-oral access was 2.24 (95% CI 0.97 – 5.18,  $p = 0.06$ ) ... There were six cases of self-resolving subcutaneous emphysema, but we considered this to be an expected post-operative finding rather than a complication. Those complications related to open trans-cervical approach included eight cases of transient marginal nerve paresis, two cases of transient hypoglossal nerve paresis and three cases of greater auricular nerve paraesthesia.”

4. Could the authors reconcile the reasons for choosing the transcervical approach given the supposedly higher risks of complications on review of the literature? Surgical preference is once aspect but are there others?

Could the authors elaborate on why the transoral route is still the preferred option in the literature?

Reply: Thank you for your comment. The trans-cervical approach is the preferred access due to the senior surgeon's personal experience as a skull base surgeon, with low risk of attendant complications. Certainly, the only complications that occurred in our series were two great auricular nerve hypoesthesias among the trans-cervical group. Any risk to the marginal nerve is mitigated through use of the NIM. However, in the trans-oral group, there was a risk of procedure abandonment and need to return for open procedure at a later date. Moreover, there was a much lower rate of tonsillectomy among the 19 patients in our series compared to in the literature- the trans-oral approach relies on being able to palpate the styloid tip, which is often difficult access in the setting of tonsil tissue. The 'Discussion' section has been updated to discuss this in more depth.

Changes: 'Discussion,' page 12, lines 516-564:

"In our review of the literature, trans-cervical approach not was associated with a significantly increased rate of complications compared to the trans-oral approach. There are a number of suggested reasons why the trans-oral route is preferred in the literature. The number appears to be strongly influenced by the six studies from India, which account for 63.6% of the trans-oral surgeries in the literature. The predilection for this surgical approach in the Indian studies may be related to the risk of keloid scarring and the cephalometrics of this patient population. (34) The majority of the surgeries were conducted by otolaryngologists, who may be more comfortable operating through the tonsillar fossa, compared to OMFS, and patients in otolaryngology-conducted case series were more likely to undergo surgery via the trans-oral route. At least 52.9% of patients in the literature had a history of tonsillectomy, which affords trans-oral access and ability to palpate the styloid tip in the tonsillar fossa. In recent years, novel approaches to styloidectomy have been discussed in the literature, including trans-oral tonsil-sparing styloidectomy (35) and intra-operative navigation equipment. (36)

In our cohort of 19 patients, the trans-cervical approach was preferred over the trans-oral approach because the complications associated with trans-oral access (eg. difficult access, conversion, post-operative trismus and respiratory distress) could be considered more serious than the temporary neuropraxias associated with the trans-cervical approach. In the hands of an experienced skull base surgeon and with use of the NIM, the rate of motor neuropraxia in our series was zero. The rate of prior

tonsillectomy in our series (15.8%) was much lower than in the general literature, making trans-oral access and palpation of the styloid tip more difficult. Via the trans-cervical approach, all styloid tips can be palpated and clearly visualised, thereby mitigating the risk of parapharyngeal infection and neurovascular injury. Great auricular nerve hypoaesthesia can be minimised through identification and careful retraction.”

Minor comments:

1. Line 291- 297 – unnecessary and should be included as part of the introduction rather than discussion

Reply: Thank you for your suggestion- this paragraph has been moved to the introduction.

Changes: Introduction, pages 4, lines 102-108: “Clinical examination and radiology are performed with the aim to exclude other pathologies, such as otitis media, trigeminal or glossopharyngeal neuralgia, masticatory muscle disorders, dental or salivary gland disease and head and neck cancer. MRI is essential in excluding occult soft tissue pathologies. Head and neck CT with 1mm slices and 3D reconstruction is the imaging modality of choice in Eagle’s syndrome in identifying the extent and orientation of the stylohyoid ligament ossification.[19,28]”

2. Line 299 -306 – consider rewriting this paragraph as it is confusing as to which cohorts are being discussed – the literature review cohort or this current cohort?

Reply: Thank you for this comment. We have amended this paragraph by changing the first sentence and re-ordering the paragraphs to improve the clarity and flow of the discussion section.

Changes: 'Discussion, pages 12-13, lines 425-453:

"Our case series of 19 patients with Eagle's syndrome treated surgically represents a large cohort. Although the literature suggests that there is a predominance in female patients and the syndrome is most common in the 30 – 50-year-old age range, our study's patients were mostly male. Patient symptoms are frequently bilateral, with two of our patients requiring bilateral styloidectomy. The majority of our patients suffered from the 'classic syndrome symptom cluster,' although one patient experienced the 'carotid artery syndrome,' presenting with a constellation of cerebrovascular and neurological symptoms due to compression of the internal carotid artery. The diagnosis..."

3. Line 323 – 330 - consider removing as this is repetitive

Reply: Thank you for your comment. We do not think this section is particularly repetitive as it mentions other possible complications of both approaches not previously identified in the literature review and discusses other issues (eg. difficult access exacerbating factors and the importance of total styloidectomy). However, we have shortened and adjusted this section to be less repetitive.

Changes: 'Discussion,' page 14, lines 507-511:

"The trans-oral approach avoids an external incision, is a shorter procedure and can be done under local anaesthetic. However, it relies on the ability to palpate the styloid tip; concurrent tonsillectomy has associated risks of post-operative haemorrhage; and the possibility of neurological and infective complications or abandonment of procedure."

4. Line 336 – 341 – consider removing as this is repetitive

Reply: Thank you for this comment, we agree and have removed this section.

Changes: Removed from 'Discussion':

"However, these complications generally consisted of transient marginal or hypoglossal nerve palsies and three complications related to paraesthesia of the greater auricular nerve. The complications experienced by the patients undergoing trans-oral approach included

difficult access, post-operative trismus, pain and respiratory distress and transient lingual nerve paraesthesia.”

5. Line 370 – what do the authors mean by “perceived” decreased risk of complications ?

Reply: Thank you for your comment. We agree that this statement is vague and have adjusted the Conclusion.

Changes: ‘Conclusion’, page 16, lines 618-625:

“Although trans-oral surgery is preferred in the literature, there is no significant difference in complications and the authors of this paper prefer the trans-cervical approach, with our series of 19 patients demonstrating a low rate of associated complications.”

6. Line 373 – could the authors offer reasons for why there are lower risks of complications in their series compared to the literature?

Reply: Thank you for the suggestion- we have expanded on this point in the Discussion section. We offer a number of reasons for the low complication rate in our series, including skull base surgery experience, use of the NIM and identification and gentle retraction of the GAN.

Changes:

‘Trans-cervical approach’, page 7, lines 177-178:

“...hyperextension and placement of a facial nerve integrity monitor (NIM)”

‘Discussion,’ page 15, lines 557-564:

“In the hands of an experienced skull base surgeon and with use of the NIM, the rate of motor neuropraxia in our series was zero ... Great auricular nerve hypoaesthesia can be minimised through identification and careful retraction.”

7. Line 375 – could the authors clarify what they mean by a “simple but successful” procedure especially given the 15.8% failure rate as well as the other risks reported in the literature?



Reply: Thank you for this comment. Our success rate of 84.2% is similar to that in the literature of 88.3% in the literature. Of the three patients who had persistent pain despite surgery, one was subsequently discovered to have an occult base of tongue tumour and the other two had ongoing, ill-defined pain due to thyrohyoid pain syndrome or cervicofacial neuralgia. We agree that the statement “simple but successful” is vague and have updated the Conclusion.

Changes: ‘Conclusion’, page 16, line 624:  
“styloidectomy can be a beneficial procedure...”