



Beyond the Learning Curve: Comparison of Microscopic and Endoscopic Incidences of Internal Carotid Injury in a Series of Highly Experienced Operators

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■ **BACKGROUND:** As the endoscopic endonasal approach (EEA) has gained popularity as an alternative to microsurgery (MS) for transsphenoidal resection (TSR), numerous studies have attempted to assess the differential risk of internal carotid artery (ICA) injury between the techniques, yet results have been equivocal and contradictory. The aim of this study was to evaluate ICA injury in MS versus EEA among highly experienced neurosurgeons.

■ **METHODS:** We performed a systematic literature review of publications from 2002–2017 reporting ICA injury outcomes in ≥ 250 cases using MS or EEA.

■ **RESULTS:** Seventeen series reporting 11,149 patients were included: 3 MS series, 13 EEA series, and 1 series with adequate samples for each. ICA injury incidences were 0.0%–1.6% in cohorts of 275–3000. MS series documented 5 ICA injuries in 2672 operations, for an overall incidence of 0.2% (range, 0.0%–0.4%), and EEA series reported 30 ICA injuries in 8477 operations, for a 0.4% injury rate (range, 0.0%–1.6%); the difference was nonsignificant ($P = 0.25$). Increased operative experience was associated with decreased incidence of ICA injury, a finding preserved in the overall study cohort and within discretely examined MS and EEA subgroups (overall $r^2 = 0.08$, MS $r^2 = 0.23$, EEA $r^2 = 0.07$).

■ **CONCLUSIONS:** ICA injury is the most serious complication of TSR of pituitary neoplasms. Operator inexperience may be a more important risk factor than choice of surgical technique, given the comparably low rates of

injury obtained by highly experienced surgeons independent of technique. This emphasizes the need for consolidated care in pituitary centers of excellence, improvement of high-fidelity simulators, and skull base mentorship between senior and junior staff.

INTRODUCTION

Transsphenoidal resection (TSR) has evolved into the standard of care for most pituitary adenoma operations over several decades of clinical practice, providing excellent outcomes for tumor control and safety, as reported in many retrospective series, prospective trials, and review articles.^{1–6} More recently, the endoscopic endonasal approach (EEA) has been developed as an alternative to microsurgery (MS) and has similarly been studied in numerous analyses, both in isolation and in comparison with MS.^{7–22} To date, despite the increasing number of large series and systematic reviews that have examined differences in outcomes between the MS and EEA techniques, results have been equivocal, with various publications suggesting diverse benefits in favor of each technique.^{23–35} In parallel, several analyses have demonstrated a learning curve pertinent to the early adoption of surgical skills in general (e.g., during residency or after graduation) and specifically in EEA training.^{36–45} This observation of a loosely defined learning curve is preserved at the individual and institutional levels and has been noted in the adoption of EEA into the field of skull base surgery at large, which has noted a dramatic decrease in adverse outcomes as EEA practitioners have become more proficient and their experience more extensive.^{38,46}

With these findings in mind, the aim this study was to conduct a systematic review comparing MS and EEA with respect to

Key words

- Cerebrovascular
- Complications
- Internal carotid artery
- Transsphenoidal resection
- Vascular injury

Abbreviations and Acronyms

EEA: Endoscopic endonasal approach

ICA: Internal carotid artery

MS: Microsurgery

TSR: Transsphenoidal resection

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internal carotid artery (ICA) injury in the modern era of TSR with an exclusive focus on the most experienced practitioners of each technique. In doing so, we looked beyond the learning curve, with the goal of providing a more accurate and clinically meaningful perspective on the relative safety of MS and EEA for pituitary adenoma resection.

MATERIALS AND METHODS

A systematic review was conducted by searching Medline, Embase, and Google Scholar databases during the years 2002–2017 using Medical Subject Headings/keywords pituitar*, hypophys*, or adenoma, together with transsphe* or endoscop* (Figure 1). Non-English publications and articles not reporting primary data (e.g., isolated reviews, meta-analyses, national database projects) were excluded, yielding 59 candidate citations. These were reviewed in detail to confirm that included patients underwent TSR for pituitary adenoma, that reported complications data included ICA injury, and

that the operator experience included >250 cases, yielding the final study population (Table 1). These publications were reviewed in detail, with data points abstracted including total sample size, operative approach, and incidence of ICA injury.

ICA injury rates abstracted from prior series were analyzed with respect to approach in a pooled fashion (MS vs. EEA) (Table 2). Meta-analyses or publications derived from national databases that had been excluded from the primary analysis were separately reviewed in a descriptive fashion to provide additional contextualizing data (Table 3). Pertinent study components were approved and overseen by the institutional review board (#15–003098). Statistical tests were 2-sided and included Student t test for continuous data and either Fisher exact or χ^2 test for continuous or categorical data, respectively, with statistical significance defined using the α threshold $P < 0.05$. Univariate linear regression was used to assess the strength of correlation between ICA injury incidence and operative experience.

RESULTS

The systematic literature review identified 17 series that met inclusion criteria during the study period, documenting a total of

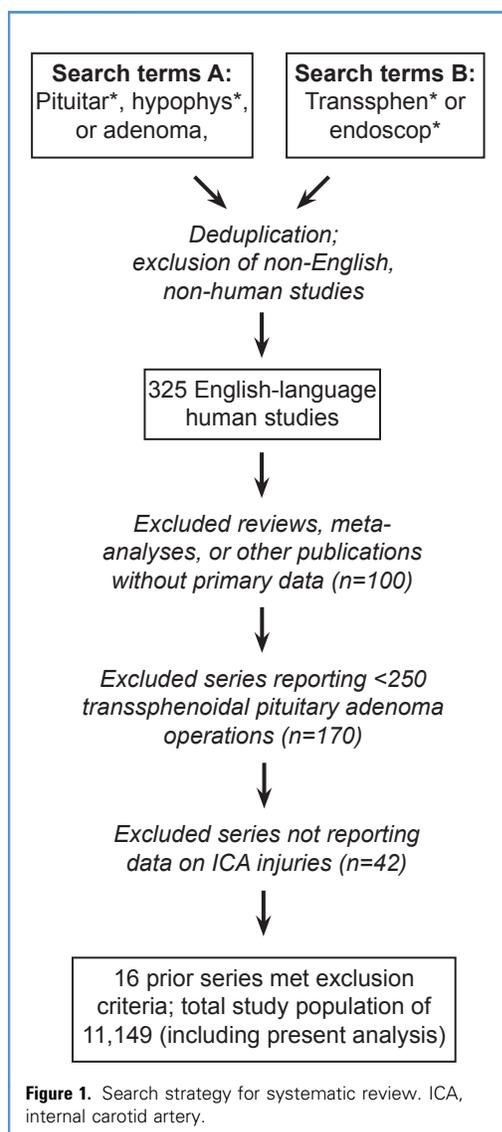


Table 1. Internal Carotid Artery Injury Incidence in Prior Case Series With Experience >250 Patients

Author, Year	Number of Cases	ICA Injury Incidence	Operative Approach
Kabil et al., 2005 ¹⁵	300	0/300 (0.0%)	EEA
Mortini et al., 2005 ⁵	1140	0/1140 (0.0%)	MS
Dusick et al., 2007 ¹	447	2/447 (0.4%)	MS
Frank et al., 2006 ⁹	381	4/381 (1.0%)	EEA
Han et al., 2008 ¹²	592	0/592 (0.0%)	EEA
Gondim et al., 2011 ¹¹	301	5/301 (1.7%)	EEA
Berker et al., 2012 ⁷	570	1/570 (0.2%)	EEA
Gardner et al., 2013 ¹⁰	660	2/660 (0.3%)	EEA
Kalinin et al., 2013 ¹⁶	3000	4/3000 (0.1%)	EEA
Halvorsen et al., 2014 ^{3,*}	268	1/268 (0.4%)	MS
	238	1/238 (0.4%)	EEA
Paluzzi et al., 2014 ¹⁹	555	3/555 (0.3%)	EEA
Jang et al., 2016 ¹³	331	1/331 (0.3%)	EEA
Magro et al., 2016 ¹⁸	300	1/300 (0.3%)	EEA
Sylvester et al., 2016 ²²	576	5/576 (0.9%)	EEA
Eseonu et al., 2017 ⁸	275	1/275 (0.4%)	EEA
Romero et al., 2017 ²¹	398	2/398 (0.5%)	EEA
Meyer et al., 2019 ⁴⁷	817	2/817 (0.2%)	MS

ICA, internal carotid artery; EEA, endoscopic endonasal approach; MS, microsurgery.
*Both EEA and MS groups included, given total and MS experiences were both >250 cases.

Table 2. Summary Statistics for Pooled Analysis of all Cases by Approach, 2002–2017

	MS	EEA	P Value
All studies	5/2672 (0.2%)	30/8477 (0.4%)	0.25
Range	0.0%–0.4%	0.0%–1.6%	
SD	0.2%	0.5%	

MS, microsurgery; EEA, endoscopic endonasal approach.

11,149 patients (Figure 1 and Table 1).^{1,3,5,7-13,15,16,18,19,21,22,47} Three studies documented MS outcomes, 13 studies focused on EEA, and 1 study included an adequate sample for each technique. Individual study populations comprised 275–3000 patients, with reported ICA injury incidences of 0.0%–1.6%. In MS series, 5 ICA injuries were reported in 2672 operations, for an overall incidence of 0.2% (range, 0.0%–0.4%); this was not significantly different than the 0.4% injury rate after EEA (range, 0.0%–1.6%), which was based on 30 injuries in 8477 operations ($P = 0.25$) (Table 2). Linear regression demonstrated a strong, inverse correlation between the variables: increasing operative experience associated with decreased ICA injury incidence, a finding that was preserved in the overall study population as well as the discretely examined MS and EEA populations (overall $r^2 = 0.08$, MS $r^2 = 0.23$, EEA $r^2 = 0.07$) (Figure 2A–C).

Three preceding meta-analyses comparing MS and EEA in large populations of patients with pituitary adenoma undergoing TSR explicitly reported vascular injury incidences and outcomes (Table 3).^{23,25,28} As these articles were analyzed descriptively, any study of vascular injury was included (as opposed to the stipulation regarding ICA injury specificity in the above-mentioned comparative analysis). In 2 series by Ammirati et al.²³ and Esquenazi et al.,²⁵ small but statistically significant increases in vascular injuries after EEA were noted (0.5% vs. 1.4%, $P < 0.0001$; 0.7% vs. 0.9%, $P = 0.01$). By contrast, Goudakos et al.²⁸ did not detect a significant difference between the rates of vascular injury (0.5% vs. 0.0%, $P = 0.55$). One national database analysis comparing MS and EEA with respect to vascular injury, reported by Asemota et al.⁴⁸ in 2017, failed to identify a significant difference between the groups (0.5% vs. 0.3%, $P = 0.34$).

DISCUSSION

We report the first systematic review comparing MS and EEA for TSR during the modern era. A focus on highly experienced neurosurgeons discloses their differential risk of ICA injury, which we consider to be the most critical complication of transsphenoidal pituitary surgery. Within this population, we noted a dramatic decrease in the overall rate of cerebrovascular complications, with a consistently reproduced improvement in safety correlated with increasing operator experience. At the high experience threshold used for our analysis, we also observed a de facto parity between MS and EEA, with most surgeons reporting $<0.5\%$ incidence of ICA injury. Correspondingly, the key finding of our analysis is that, in the current surgical age, choice of MS versus EEA has little or no impact on risk of catastrophic complications; rather, the surgeon's overall experience and specific comfort level with the selected technique is much more likely to be predictive of a safe outcome.

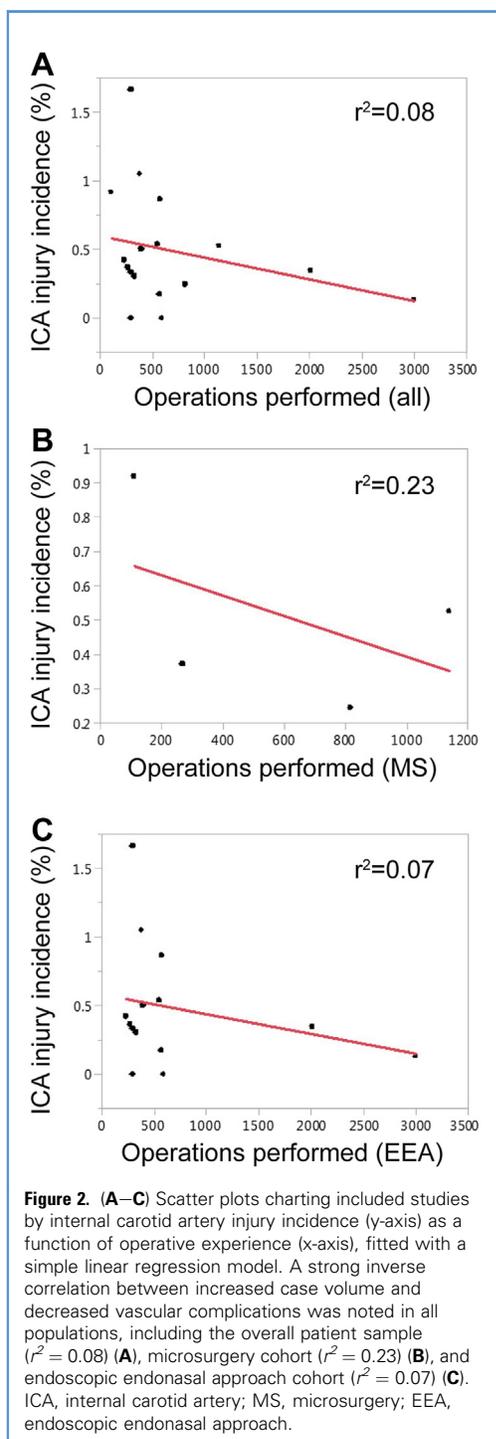
Our work is in dialogue with a large volume of neurosurgical research directed toward comparing the evolving EEA technique against its transsphenoidal forerunner and established gold standard for routine pituitary adenoma surgery, MS. Countless retrospective series, prospective registries, and randomized trials have presented their data and associated perspective on the issue.^{8,45,48-60} Early analyses were obliged to justify the continued development of EEA despite the clear learning curve associated with transition from MS, whereas several more recent publications are given to a nuanced selection process and scrupulous probing of complications, as though searching for an advantage with which the technical supremacy of EEA might be claimed. In our view, these approaches perhaps reflect a less enlightened tack, which may marginalize the needs of the patient to promote those of the surgeon.

Perhaps the most salient points of comparison for our work are the preceding meta-analyses, which similarly synthesized data from a large number of primary articles in an attempt to present a more nuanced, less unbiased perspective on the relative advantages of MS and EEA. Ammirati et al.²³ reviewed 38 series of at least 10 patients comparing MS and EEA published from 1990 to 2011, which included 22 MS and 24 EEA cohorts (3023 and 1887 patients, respectively). The specific focus of their analysis was short-term adverse events, including death, cerebrospinal fluid leak, meningitis, vascular injury, endocrine dysfunction including

Table 3. Meta-Analyses and National Database Studies Comparing Vascular Injury in Microsurgery Versus Endoscopic Endonasal Approach for Transsphenoidal Resection

Author, Year	MS Vascular Injury	EEA Vascular Injury	P Value	Favored
Ammirati et al., 2013 ²³	14/3023 (0.5%)	26/1887 (1.4%)	0.0001	MS
Goudakos et al., 2011 ²⁸	2/384 (0.5%)	0/326 (0%)	0.55	—
Esquenazi et al., 2017 ^{25,*}	7/648 (0.7%)	11/292 (0.9%)	0.01	MS
Asemota et al., 2017 ^{48,†}	16/3207 (0.5%)	9/2679 (0.3%)	0.34	—

MS, microsurgery; EEA, endoscopic endonasal approach.
 *Series included recurrent/residual tumors only.
 †Retrospective national database review derived from Truven MarketScan data.



diabetes insipidus or anterior hormone deficit, visual system complication, or other cranial nerve injury. No evidence of a significant difference was identified in association with any outcome except for vascular injury, which was increased nearly 3-fold in EEA operations (0.5% vs. 1.4%, $P < 0.0001$).

Although their methodology is based on relatively rigorous exclusion criteria that they explain clearly, it has several key

shortcomings, which are well described by Laws⁶¹ in his critical follow-up editorial. Chiefly, they included only articles in which both the primary pathology and the nature of the cerebrovascular injury were explicitly documented in the study. Consequently, the seminal review by Laws and Thapar⁵⁷ of vascular complications in 3061 MS transphenoidal operations was excluded, because although they reported that 87% of the patients were treated for pituitary adenoma ($n = 2664$), it was not clear how many of the 18 major vascular injuries were among those patients, as opposed to the other pathologies included, such as Rathke cleft cyst, meningioma, or craniopharyngioma. This is particularly important given that pituitary adenoma has been established as the lowest risk for vascular injury among the major sellar pathologies. Notwithstanding, even in the unlikely event that all 18 injuries were among patients with adenoma, and the results of Laws and Thapar⁵⁷ had been included in the meta-analysis, their individual event rate would have been 0.7%, and the differences between the groups would have remained significant (0.6% vs. 1.4%, $P = 0.0008$).

Another critique lodged against the results published by Ammirati et al.²³ is that, again owing to their relatively stringent inclusion criteria, a large fraction of the vascular complications are consolidated in a small number of reports, which may present an unaddressed source of confounding. Although this is certainly an important point for consideration, at least 1 complication was reported in 4 of 22 MS series compared with 10 of 24 EEA series; therefore, if 1 outlier were skewing the results, it would be more likely to adversely affect overall performance in the MS group. In reality, although 2 MS studies represented 71% of the vascular injuries, both were very large series, and so the overall incidence was kept low by their inclusion; by contrast, 7 of the 10 EEA articles with vascular complications included <200 patients, 3 of which reported <100 patients. As such, the net effect of inexperience weighed more heavily in the EEA group, which is not surprising considering that the study period 1990–2011 incorporated the true infancy of transphenoidal endoscopy.

In a parallel analysis that looked specifically at repeat TSR operations, Esquenazi et al.²⁵ identified a small but statistically significant increase in vascular injuries after EEA (0.7% vs. 0.9%, $P = 0.01$) based on a sample of 21 articles—8 addressing MS and 13 addressing EEA, capturing 648 and 292 patients, respectively. Similar to Ammirati et al.,²³ the most significant weakness of their analysis is the small sample sizes. Although the included cohorts appear relatively robust when considering how infrequently results are reported in repeat pituitary surgery, the expected event rate for vascular injury is still exceedingly low in the reoperation population, hampering the statistical power of their analysis and rendering an assessment of surgeon experience more ambiguous.

Goudakos et al.²⁸ performed a meta-analysis based on highly stringent criteria, ultimately excluding all but 11 of the highest graded randomized, quasirandomized, or grade I–II retrospective analyses. This approach captured 437 patients receiving MS and 369 patients receiving EEA, based on which they concluded that tumor control and cerebrospinal fluid leak outcomes were comparable, whereas EEA was significantly associated with shorter hospitalizations, lower rates of diabetes insipidus, and fewer

complications when analyzed in a pooled fashion. Intraoperative cerebrovascular events were not explicitly documented, but even when the indirect metrics hemiplegia and stroke were considered stand-ins for vascular injury (a dubious assumption), the rates of vascular injury were still not significantly different between the groups (0.5% vs. 0.0%, $P = 0.55$).

In addition to these meta-analyses, 1 publication by Asemota et al.⁴⁸ used big data techniques to address the question of MS and EEA and included vascular injury among the reported outcomes. The authors based their analysis on patient data extrapolated from the Truven MarketScan database, a national repository derived from insurer and payer information. They compared outcomes after 3207 MS and 2679 EEA operations, all of which were completed during the most contemporary treatment window defined by any publication included within our study, 2010–2014. Overall, the authors noted that EEA was significantly associated with several of the complications studied, but the difference in vascular injury rates was not significant (0.5% vs. 0.3%, $P = 0.34$).

Although the national database format limited the authors' ability to conduct any individual case reviews or confirm details surrounding key complications, such as ICA injury, their analysis demonstrates a particular strength of big data techniques in that it allowed accurate subselection of both diagnoses and complications in a way that is relatively standardized across a large number of centers and surgeons, empowering precise analysis of a large sample. That a significant difference was not observed between the MS and EEA cohorts with respect to vascular complications provides an interesting counterpoint to our own results: whereas we observed that among highly experienced surgeons the contested differences between MS and EEA resolve, the composite national data also failed to find significant differences in vascular outcomes between the techniques. Therefore, the prior reports describing competing advantages in association with either technique may ultimately reflect biased reporting of results on both sides of the debate—or, more concerning still, an equal distribution of underexperienced surgeons among practitioners of both MS and EEA.

In our view, the summative conclusion of the individual series and meta-analyses supports the same fundamental, intuitive principle: transsphenoidal pituitary adenoma surgery is a fundamentally safe operation in the hands of a skilled neurosurgeon, whose experience with his or her preferred technique ultimately has far more bearing on the risk of a catastrophic outcome than can be attributed to inherent differences between the techniques. As we have described previously, each technique offers the neurosurgeon a host of potential advantages.⁴⁷ MS is efficient, relies on simple instrumentation and a congruent skill set with other microneurosurgical operations, and affords true three-dimensional depth perception within a narrow field that many consider to be relatively protective in terms of reducing the risk of inadvertent lateral excursion and ICA exposure or injury. EEA offers a wide, detailed look that, despite the two-dimensional field, leverages endoscopic optics to provide a much higher resolution perspective, while simultaneously making use of a variety of newer and more purpose-specific instruments and allowing 3-hand and 4-hand techniques that are not ergonomically feasible with the operating microscope. Considered in the context of our

present findings, we have come to understand these inherent differences less as strict limitations on the techniques, but rather as indications of the ways in which experience will allow the operator to transcend either and stretch the tools to meet the challenges of an unpredicted clinical circumstance.

Perhaps the most important unanswered question invited by our findings is how to balance the need for a highly experienced surgeon to minimize the risk of catastrophic vascular injury against the need to train resident surgeons and, even more importantly, establish the careers of the next generation of pituitary surgeons, such that future patients will not be exposed to severe risk during a debilitating shortfall of surgeon experience. Certainly, residency programs that emphasize operative experience and early, integrated, hands-on training are more likely to produce skilled, safe graduates. Furthermore, the emergence of three-dimensional printing, cadaver perfusion, and other high-fidelity simulation technologies promises an avenue for zero-risk training supplementation.^{62–67}

Although operative experience is clearly irreplaceable, the goal should be to establish curriculums for postgraduate year 1 residents built around thorough, integrated, advanced simulations that would cover the breadth of neurosurgery, ensuring that once a trainee begins to carry out the critical portion of a particular operation, they have already encountered the full gamut of standard teaching cases, common anatomic variants, uncommon complications, and rare emergencies for that module many times over in the laboratory. Snyderman et al.,⁶⁸ Zada et al.,⁶⁷ and several other groups have already developed robust simulation models that are specific to the development of an EEA skill set, and we look forward to witnessing the patient safety and resident education benefits of more widespread dissemination and embrace of these practices throughout the neurosurgical training sphere.^{67,68}

The question of safely closing the experience gap between junior staff and senior surgeons is at once more challenging and higher stakes, as these individuals are well beyond the stage where available simulation technologies are able to significantly advance their skills, yet few residents will graduate with >250 autonomous experiences conducting the critical portion of a particular procedure, save for the most routine operations in the highest volume programs. One possible solution is the development of formal operative coaching models, which have demonstrated some success in general surgery.^{69,70} Another solution would be formal cooperation with senior partners during the first years of practice or a stratification of referrals by anticipated difficulty level during the initial 50–100 operations in a given domain.^{43,68} In any such case, the present board examination system could potentially be mobilized as a reasonable waypoint for ensuring that any formal early career safety could be reasonably discontinued in tandem with formal board certification. Ultimately, these possibilities are speculative, but further research focused on these critical questions in surgical education will be required to resolve the demands of tendering equally safe care with present and future patients.

Our study is subject to a number of significant limitations, including those associated with any retrospective, systematic review, such as the prominent risk of confounding or selection biases. More specifically, in a study focused on complications or

other adverse events such as ours, the susceptibility to reporting bias is particularly elevated. As with several of our predecessors, we attempted to strike a balanced approach to exclusion criteria, in the interest of maximizing study inclusion (and therefore the sample population), without subjecting the data to marked risk of bias. One such example was our decision to restrict included studies to those published during the endoscopic era: whereas capturing a larger sampling frame in terms of MS series would have markedly increased the number of cohorts and patients included, this was considered an inadequate tradeoff for the associated confounding due to time-based differences in patient management, which would have included advances in instrumentation, microscopy, and imaging that may have improved the microsurgical ICA injury rate during the contemporary moment compared with earlier hypothetical sampling frames that would have been included in only 1 of the 2 comparator groups.

Our minimum criterion for expert-level surgical experience of 250 cases, although informed by our own practice and our familiarity with the broad literature on the subject, is fundamentally arbitrary, as a formal threshold analysis could not be reliably derived from the literature. From a methodologic perspective, this aspect of our study design opens the results to at least 2 noteworthy exposures to possible systematic error. First, although case volume is an easy-to-measure and ostensibly objective metric, using it as a surrogate marker for experience is potentially confounded by several other factors. These include aspects of the individual surgeons, such as their training pathways (e.g., residency, skull base fellowship, endoscopic-focused fellowship) and the eras in which they trained (e.g., before duty hours restrictions, after development of endoscopic technology) as well as features of their practice environments, where access to senior neurosurgeons or otorhinolaryngologists, the presence of a residency or fellowship training program, and overall skull base case volume may have influenced their outcomes. Second, whereas our study gives us a representative comparison between 2 groups of expert surgeons who preferentially use technically distinct approaches to transsphenoidal pituitary adenoma resection, it does not explicitly answer the question of how much greater the relative risk of ICA injury is among less experienced surgeons, and it does not identify an inflexion point along the experience-risk curve beyond which one more closely resembles an expert than a novice. In designing the current study, we seriously considered incorporating a comparison between the included publications and the publications identified by our systematic review but excluded for surgeon volumes <250 cases.

Although such an analysis is conceptually appealing, we also considered the very high susceptibility to reporting bias associated with short, early career series. Furthermore, as the estimated event rates for ICA injury would still be quite low among samples of less experienced surgeons, and given that the reported series do not constitute a comprehensive sample of cases from the early careers of all skull base surgeons, it would be very challenging to adjust for the possibility that certain series did not include ICA injuries simply due to random chance. Correspondingly, our ultimate determination was that such an analysis would carry too much risk of bias, and it was not performed within the spectrum of the current study. Despite these shortcomings, our article marks an essential step forward in our understanding of this core question in contemporary neurosurgery and highlights the importance of redirecting attention away from the MS versus EEA debate and toward a creative and forward-thinking solution for the critical training shortfall we anticipate encountering within a generation of surgeons.

CONCLUSIONS

We report the first systematic review comparing MS and EEA for TSR of pituitary adenoma in a population of highly experienced neurosurgeons reporting an experience of at least 250 cases, with a specific focus on the incidence of ICA injury. In contrast to the few preceding meta-analyses that have attempted to answer this question using a more global sample of studies, we found that among these advanced surgeons and teams, cerebrovascular injury during TSR for pituitary adenoma was exceedingly rare, not significantly associated with either MS or EEA, and inversely correlated with surgeon experience. Correspondingly, we recommend consolidating care in centers of excellence and with dedicated pituitary teams wherever possible, which we anticipate will simultaneously increase both patient safety and trainee exposure to a high volume of complex cases. In parallel, significant academic attention within the neurosurgical community should be directed toward the goals of improving early exposure to high-fidelity simulation and developing models that more reliably and realistically approximate intraoperative experience. Our findings are both encouraging and intimidating, but above all, they highlight transsphenoidal pituitary adenoma surgery as a critical niche for adopting a more evolved perspective on neurosurgical treatment and a more advanced approach to education and training at the resident and junior faculty levels alike.

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