ORIGINAL ARTICLE

Light at the End of the Tunnel: The Learning Curve Associated with Endoscopic Transsphenoidal Skull Base Surgery

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ABSTRACT

Endoscopic transsphenoidal resection of skull base lesions has been introduced widely as an alternative to microscopic transmucosal approaches. We report the introduction of this technique to our unit, including the learning curve recognized for this procedure, comparing techniques in a concurrent case-control fashion. All patients operated on for sellar, suprasellar, or clival lesions were considered for endoscopic surgery, with 51 patients undergoing endoscopic surgery and 46 having microscopic surgery with the operating method determined by the availability of the ear, nose, and throat surgeon involved with the procedures. Endoscopic surgery compared favorably with microscopic surgery with respect to endocrine control, length of stay, diabetes insipidus, and cerebrospinal fluid leakage. A learning curve was found with a significant fall in complication rates between the first third and most recent third of the cohort. Endoscopic skull base surgery has superior results to microscopic approaches once the initial learning curve is overcome, but this can be done quickly and safely.

KEYWORDS: Endoscopy, transsphenoidal surgery, skull base tumor, learning curve

The history of the use of the endoscope in neurosurgery, and skull base surgery in particular, is fascinating, encompassing many great names and pioneers of this field.[1] The first application of the rigid endoscope by Lespinasse and Dandy as a tool for choroid plexus coagulation occurred in the early years of the 20th century. In pituitary surgery, the endoscope was initially used as an adjunct to the microscope.[2] The development of fiber optics in the 1970s enabled the application of endoscopic techniques to a wider variety of procedures, with otorhinolaryngologists in particular popularizing its use in functional sinus surgery. The development of these techniques allowed their application to pure endoscopic skull base surgery by such pioneers as Jankowski and colleagues[3] and Jho and Carrau.[4] The technique as developed by them and others is now being adopted by many units as an alternative to the traditional methods of transseptal or translabial microscopic transsphenoidal pituitary surgery. The microscopic methods, utilized since their development by Cushing and others, have

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been shown to produce excellent results in terms of tumor clearance, visual outcome, and endocrinologic normalization in experienced hands.

Clearly any new technique introduced must at least equal the results of the methods it replaces and should offer defined advantages. Authors have commented on the differences between endoscopic and microscopic technique[5–7] and the learning curve for the procedure.[8–10] In particular, the endoscope, although giving a wide, well-illuminated, and magnified exposure, does only provide a two-dimensional view, as opposed to the stereoscopic view offered by a microscope. Also, access may be somewhat narrower in the absence of a nasal speculum, with some likening the technique to "operating with chopsticks."[5] The excellent view afforded by the endoscope also allows advancement of the scope into the pituitary fossa itself to visualize (with an angled scope if necessary) all corners of the fossa and an ability to extend resection into parasellar and clival regions.

Our unit began performing pure endoscopic skull base surgery in 2006, and in this study we examine the learning curve associated with this procedure and compare our results with a concurrent cohort of skull base lesions operated on in the same unit by traditional microscopic techniques. We examine outcome measures including cerebrospinal fluid (CSF) leak rate, diabetes insipidus, and control of hormonally active tumors, and although not randomized, we do present a control group operated on by the same surgical team over the same time course.

PATIENTS AND METHODS

All patients operated on via the transsphenoidal route for skull base mass lesions in our unit between June 2006 (when the described technique was introduced to Nottingham) and December 2008 were included in this study. In total, 51 patients underwent endoscopic transsphenoidal surgery and 46 had transseptal microscopic transsphenoidal surgery. The major determinant for selection of surgical method was the availability on a given day of the ear, nose, and throat (ENT) surgeon (A.S.) who coperformed the endoscopic procedures. All cases were performed in the same operating theaters with the same theater staff and neurosurgeons (either I.R. or G.D.). All patients had preoperative magnetic resonance imaging scans demonstrating operable mass lesions. All patients underwent endocrinologic and opthalmologic assessment.

Endoscopic technique was based on Kassam and Snyderman (Pittsburgh). Patients were under general orotracheal anesthesia, throat pack in situ, and a single dose of intravenous ceftriaxone was administered at induction unless contraindicated. Patients were positioned supine on the operating table with their neck slightly extended and in-line alignment maintained, but no pin fixation was used. Cocaine-soaked patties were placed into both nostrils around the middle turbinate to vasoconstrict and aid intraoperative visualization. Both nostrils were prepared using cotton buds soaked in chlorhexidine gluconate. A Storz sinus endoscopy stack (Karl Storz Endoscope, Tuttlingen, Germany) was used, with video output to two monitors, one positioned at the patient's head and one adjacent to the patient's hip facing back toward the patient's head. This allows both operating surgeons (standing either side of the chest) good visualization and minimizes crowding. A 4-mm sinus endoscope with Endoscrub (endo-scrub Xomed, Jacksonville, FL) was used for all procedures, usually with a 0' lens, and sometimes utilizing a 30' lens for better visualization during tumor resection. Approaches were made via both nostrils, with no use of a nasal speculum required. Middle turbinates were identified and used as landmarks for the sphenoid ostia. Middle turbinectomy was seldom required, and no fluoroscopy was used. The sphenoid ostia were enlarged using Kerrison's upcut punches and a debrider, leading to a wide anterior sphenoidotomy and removal of any sphenoid septae present. Our technique includes a vascularized mucosal septal flap based on the septal branch of the sphenopalatine artery. This modification was introduced after approximately one-third of the cases discussed in this series, and we feel it may be important in reducing the rate of postoperative CSF leakage. The posterior wall structures could then be readily identified including the carotico-optic recesses, carotid arteries, optic nerves, planum sphenoidale, sella, and clivus.

The sellar floor could then be opened using high-speed drill and upcut punches. For extended approaches, bony removal was continued laterally to expose carotid artery/cavernous sinus or inferiorly through the clivus to access chordomas. No intraoperative Doppler ultrasound was used in this series. Neuronavigation (Stealthstation, Medtronic Navigation, Louisville, CO, USA) was used only for cases involving an extended approach (e.g., clivus chordomas). The pituitary capsule was incised to access pituitary lesions, and the tumor was removed using ring curettes and suction. The inferior portion of tumors was resected initially to delay diaphragm descent. The pituitary fossa was entered and inspected with the endoscope to ensure completeness of tumor removal. The vascularized mucosal flap was placed over the posterior sphenoid defect and held in place with surgicell (Ethicon Inc. Kirkron, Scotland, UK) and retained bone chips. Nasal packing was used in only two cases. No endoscopic procedures had to be converted to microscopic. Patients were encouraged to mobilize upon return to the ward and underwent hormonal assessment at 48 hours postoperatively, with discontinuation of perioperative hydrocortisone at this stage if results were satisfactory.

The transseptal technique employed involved similar positioning and perioperative preparation using cocaine-soaked patties and elevation of the septal mucosa by injection of saline between it and the cartilage. An incision was made into the mucosa, and a Hills elevator (Bolton Surgical, Sheffield, UK) was used to raise the mucosa as far as the vomer keel, with the assistance of a nasal speculum. Under visualization with the operating microscope, the keel was removed and the sphenoid sinus entered. The posterior wall of the sinus was then removed, and resection of the pituitary lesion was accomplished using ring curettes. Packs were inserted into both nostrils and left in situ for 24 to 48 hours postoperatively.

Outcome assessment was performed by case note analysis and retrieval of information from the electronic pathology results and theater management systems. Length of operation was the time from knife to septum or insertion of endoscope until removal of drapes, obtained from electronic time points completed contemporaneously by theater staff. Histology and immunohistochemistry for all cases was assessed by a senior neuropathologist. Diabetes insipidus was defined as biochemical disturbance of fluid balance (elevated serum sodium/osmolarity with inappropriately high urine output) requiring administration of DDAVP (Desmopressin). This was either temporary (patient not on DDAVP at time of discharge) or long term (patient discharged home on DDAVP). CSF leak was defined as visible leak of CSF intraoperatively or leak of β-transferrin-positive fluid from the nostrils postoperatively. Temporary CSF leak was defined as either being stopped intraoperatively or settling with conservative management on the ward. Significant CSF leak was defined as requiring return to theater for repair. Hormonally active tumors were defined as treated successfully if the appropriate endocrine test (prolactin/cortisol levels/insulin-like growth factor or oral glucose tolerance) was normalized in a test more than 3 months postoperatively with the patient off medication. All patients were followed up for at least 3 months.

Statistical analysis of the results was performed using data-appropriate tests, including chi-square test of proportions (Pearson), Fisher exact test for analyses where expected frequency for any cell was less than 5, Student t test (two-tailed), Mann-Whitney U test, and analysis of variance. All tests were performed using the analytical package from the Vassarstats Web site. A p value of less than 0.05 was adopted as the threshold for significance.

RESULTS

During the period from June 2006 until December 2008, 51 patients underwent totally endoscopic skull base surgery via the binostril technique, and 46 patients underwent surgery via the described transseptal microscopic technique (Table 1). In total, 46 patients were women and 51 were men, with no significant difference between endoscopic and microscopic groups (chi-square $p = 0.740$). The groups were also well matched in terms of age, with mean age 48.6 years in the endoscopic group and 53.8 years in the microscopic group (t test $p = 0.127$). The groups were overall equivalent for numbers of operations on previously operated tumors, although there was an excess of these operations in the first third of the endoscopic cohort (9 of 17 procedures redo, compared with 1 of 17 in final third; chi-square overall $p = 0.144$, first third $p = 0.004$). Histology was equivalent overall (Fisher exact 0.169), but with all chordomas and an excess of craniopharyngiomas in the endoscopic group (Table 1).

Table 1 Demographic Details of Cohort

	Endoscopic Surgery ($n = 51$)	Microscopic Surgery ($n = 46$)	p Value
% female	49.0	45.7	0.740
Mean age (y)	48.6	53.8	0.127
Recurrent lesions (%)	27.5	15.2	0.144
Pituitary adenoma (n)	40	42	
Craniopharyngioma (n)	5	1	
Chordoma (n)	3	0	
Others (n)	3	3	

Overall rates of diabetes insipidus (Table 2) were not significantly different between the two cohorts (Fisher exact $p = 0.249$). Four patients undergoing endoscopy were discharged home on DDAVP compared with one patient operated on microscopically, but most of these settled after several months. Equally, overall rates of CSF leak were not significantly different with microscopic or endoscopic surgery (Fisher exact $p = 0.129$). Five endoscopic patients had to be reoperated on for CSF leak compared with three microscopic patients. Length of hospital stay was not significantly different between groups with a median of 5 days in

Table 2 Results of Two Surgical Groups

	Endoscopic Surgery	Microscopic Surgery	p Value
Diabetes insipidus overall (n)	13	6	0.123
Diabetes insipidus long term (n)	4	1	0.365
CSF leak overall (n)	13	5	0.0703
CSF leak requiring surgical repair (n)	5	3	0.717
Length of hospital stay (d)	5	5	0.818

CSF, cerebrospinal fluid.

each group (Mann-Whitney $p = 0.818$). Most of the hospital stay for endoscopic patients was concerned with endocrine and fluid balance assessment, with patients usually mobile, comfortable, and pack free on day 1 postoperatively. Patients who suffered a CSF leak had significantly longer hospital stays (on average an extra 5 days, Mann Whitney $p = 0.0225$). Diabetes insipidus also significantly increased hospital stay (mean of 7 extra days, Mann Whitney $p = 0.00025$). Perhaps surprisingly, redo surgery was not significantly associated overall with increased rate of CSF leak (Fisher exact $p = 0.314$) or increased hospital stay (Mann-Whitney $p = 0.655$). We also examined operative length with an overall mean of 88 minutes for microscopic surgery and 114 minutes for endoscopic surgery (t test $p = 0.0031$), but with a trend to parity of operative length as experience improved with the endoscopic technique.

No patient in the endoscopic group had any visual deterioration postoperatively, significant postoperative epistaxis, or reported nasal complications. One patient in the endoscopic cohort (an extended approach) suffered a carotid bleed intraoperatively, leading to packing of the area and abandonment of surgery. Successful endoscopic surgery was performed 3 months later. One patient operated on endoscopically died 7 months postoperatively from medical complications of post-CSF leak meningitis. One endoscopic patient suffered meningitis, was treated medically, and made a complete recovery, and one endoscopic patient suffered a transient sixth nerve palsy following resection of a tumor extending into cavernous sinus. Two patients in the microscopic group had postoperative pituitary fossa hematomas requiring evacuation surgically, but with good long-term outcomes.

Eleven (four corticotropin, six growth hormone, and one PL [Prolactin]) hormonally active tumors were operated on endoscopically, and 17 (eight corticotropin, eight growth hormone, and one PL) microscopically (Table 3). One endoscopic corticotropin tumor recurred biochemically (treated with stereotactic radiotherapy), and five microscopically operated tumors recurred (three reoperated), but there was no significant difference statistically (Fisher exact $p = 0.191$). The patients with chordomas all went for radiotherapy or proton beam therapy postoperatively.

Table 3 Control of Hormonally Active Tumors

	Endoscopic Surgery	Microscopic Surgery	*p* Value
Endocrinologically active tumors (*n*)	11	17	
Corticotropin secreting (*n*)	4	8	
Growth hormone secreting (*n*)	6	8	
PL (Prolactin) secreting (*n*)	1	1	
Biochemical control achieved (*n*)	10	11	0.191

To evaluate the learning curve associated with adoption of the new endoscopic technique, we divided the 51 endoscopic patients into three cohorts of 17 cases each: early, middle, and late cases (Table 4). The numbers of complications of all kinds fell during the course of the cohort. The rate of CSF leak (all types) fell significantly from 7 of the first 17 patients to 1 of the last 17 undergoing endoscopy (Fisher exact $p = 0.0391$). Although (compared with microscopic technique) endoscopy was significantly more likely to cause a leak in the early cases (Fisher exact $p = 0.0116$), this trend disappeared in the middle and late cases (Fisher exact $p = 0.117$ and 0.673, respectively). Length of stay also fell significantly between the first and final thirds from a median of 7 days to a median of 5 days (Mann-Whitney $p = 0.0357$). Diabetes insipidus rate fell from 6/17 to 1/17 in the final third, not quite statistically significant (Fisher exact $p = 0.0855$). Mean length of surgery improved significantly between early and late cases and also between middle and late cases (t test $p = 0.0023$ and 0.0043, respectively). Although endoscopy was significantly slower than microscopy initially and in the middle third of cases (t test $p < 0.001$), this difference had disappeared in the late cases (t test $p = 0.705$).

DISCUSSION

The technique of pure endoscopic transsphenoidal resection of skull base tumors is rapidly being adopted by many units as a replacement for traditional transseptal or

Table 4 Learning Curve for Endoscopic Cohort

	Early Cases ($n = 17$)	Middle Cases ($n = 17$)	Late Cases ($n = 17$)	*p* Value (Early vs Late Cases)
Diabetes insipidus (*n*)	6	6	1	0.0855
CSF leak (*n*)	7	5	1	0.0391
Length of stay (d)	7	6	4	0.0357
Mean length of operation (min)	133.9	117.7	90.5	0.00226

CSF, cerebrospinal fluid.

sublabial techniques. The new technique seems to offer obvious advantages of a wide-ranging, well-illuminated and magnified view, with the ability to overcome by the use of angled scopes the line-of-sight limitation of the operating microscope. However, the established microscopic techniques have been shown to have excellent results in terms of both postoperative complications and tumor control,[11] and clearly any new technique should be superior to that which it supplants. The key question is whether the perceived visual advantages of endoscopy for the operating surgeon translate into benefit for the patient (i.e., reduced complications and better tumor clearance). Many series have been reported of the results of the new technique,[12–14] some in comparison with a control group,[15–19] but only two randomized trials comparing the two modalities have been published. One trial was very limited,[20] having just 10 patients in each arm and with a very high microscopic complication rate. The other trial focused on prolactinomas,[6] with 22 patients in each arm and finding significant reductions in complications, operating time, and length of hospital stay. Most series do consistently report short-term results that are equivalent to those of published series of microscope results. Longer-term follow-up for endoscopic resection is clearly needed to establish oncological success in the longer term, and this may be the most important factor in determining acceptability of the new technique.

Our current report is not randomized in a scientific way, but includes an element of pseudo-randomization based on the availability of ENT surgical assistance. The two groups were well matched statistically and were treated over the same time period by the same surgical team. It is somewhat unusual in the literature for endoscopic results to be reported with a concurrently acquired control group; most present results of either the endoscopic technique alone or in comparison with a historical control group.[15,19] It may be that this is because surgeons are unwilling to dilute their experience with the new technique and that the learning curve can be climbed more quickly with complete crossover to endoscopy. O'Malley et al[8] reported a rate of complications (28% CSF leak rate) similar to our rate in their series of 25 microscopic and 25 endoscopic cases, collected consecutively. They found an excess (nonsignificant) of CSF leaks in the endoscopic arm, which we also found after a similar number of cases; the excess disappeared in our series as experience increased further. Casler et al[17] also reported a 27% CSF leak rate in their initial experience of the technique compared with 20% in their concurrent microscopic cases ($n = 15$ each arm). Neal et al[16] reviewed 50 cases performed sublabially ($n = 15$), transseptally ($n = 21$), or endoscopically ($n = 14$), finding 28% CSF leakage in the endoscopic group compared with 47 to 53% in the other groups, with a significant reduction in hospital stay for endoscopy. Our current study, with 51 endoscopic and 46 microscopic cases, presents the largest case-control series accumulated concurrently reported in the literature.

A meta-analysis recently published[21] of the literature up to 2006 demonstrated outcomes for pituitary adenoma endoscopic resection comparable to microscopic series, with reported CSF leak rates in these large studies ranging from 0 to 27% and overall diabetes insipidus rates from 0 to 22%. Our current study reports overall CSF leak rate of 12% (postoperative leaks only; 25% overall) and diabetes insipidus rate of 8% long term (25% all diabetes insipidus). However, in the final subcohort of 17 patients, these figures fell to 0% postoperative leaks and 0% long-term diabetes insipidus. It appears that generally the larger series had the lowest complication rates, and this would be in keeping with the existence of a learning curve for endoscopic resection. It would be interesting to read whether the majority of complications encountered in these large cohorts were also during the initial cases. We would anticipate that our results would show an ongoing complication rate in line with our final third of patients, a rate favorably comparable with the large published series and with our own microscopic results.

The concept of a learning curve with novel surgical procedures is recognized in many areas of surgery. It can be broadly defined as the number of cases necessary to perform for outcomes to tend toward the long-term mean rate. The existence of a need to adapt technique and learn new skills has been recognized by the pioneers of endoscopic transsphenoidal surgery, with suggestions made as to means of easing the procedural transition.[22] The use of the endoscope as an adjunct during microscopic resection has been advised as a "halfway house" position to gain familiarity with the two-dimensional view and endoscope handling. We adopted such measures, and both senior neurosurgeons were very familiar with ventricular neuroendoscopy and the microscopic transseptal approach. All procedures were undertaken after visiting a center already practicing endoscopic skull base surgery and in full conjunction with an ENT surgeon experienced in functional endoscopic sinus surgery (FESS) techniques. Despite these measures, it is clear that a learning curve does exist for this procedure; our results improved significantly between the early and late cases in all respects. Not all published series have examined this aspect, but most series that have agree with our findings of a definite improvement of outcome as experience improves.[8,9] Some disagree, finding no incremental improvement of results with time.[10] Overall, and especially in comparison with the final group of 17 patients, we feel endoscopic results at least equal and may well surpass those obtained from the microscopic technique. Certainly there would appear to be a trend toward better hormonal control in secretory tumors. We are moving away from using the microscopic technique and now use an endoscopic approach whenever possible logistically.

From our data, we would consider that the plateau in outcomes occurred in the middle third of our cohort (between 18 and 34 patients). This is keeping with other published studies that have suggested the experience needed to achieve plateauing in the outcome measures may be from 17 to 40 cases. This is similar to the numbers suggested to achieve full competency for other surgical procedures.

This study suffers from the disadvantage of not being formally randomized, like most others in this area, though our cases were accumulated during the same time frame. Our overall follow-up for these patients remains short, and a true measure of the efficacy of tumor control will not be available until our two groups have been followed for several more years. More accurate estimation of the learning curve would only be possible through pooled analysis of many centers' experience in adopting this technique, and this study only represents one unit's experience in the transition to the endoscopic technique. Local factors such as tumor referral pattern, level of experience of FESS/other endoscopic techniques, and anatomy of operated tumors could doubtless significantly influence our estimate of 18 to 34 cases. Within these caveats, we believe that endoscopic transsphenoidal surgery can be introduced safely to new units and can quickly produce outcomes superior to microscopic techniques.

CONCLUSIONS

In recent years, the technique of endoscopic transsphenoidal skull base surgery has been reported in the literature to provide equivalent or improved outcomes, compared with the traditional microscopic transseptal or sublabial methods. A learning curve does exist for this procedure, with results plateauing between 18 and 34 cases. Results after this amount of experience are an improvement on microscopic transseptal resection. Any unit considering transition to endoscopy should take all steps possible to minimize the learning phase and lessen any patient complications.

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