Original Article

Avoiding Complications in Endoscopic Trans-Sphenoidal Surgery for Pituitary Adenoma: A Beginner's Perspective

Abstract

Introduction: We aimed to analyze the difficulties and complications experienced while as a beginner in endoscopic transnasal transsphenoidal approach for pituitary adenomas. **Materials and Methods:** We retrospectively analyzed 83 cases done from June 2016 to August 2019. Navigation-guided endoscopic transnasal transsphenoidal approach was used in all the cases. **Results:** Gross total tumor removal was achieved in 55 (66.26%) patients. We found that gross total resection rate was inversely proportional to Knosp grading, and the extent of resection was found to have a statistically significant correlation with grade of tumor ($P < 0.05$). Surgery-related complications were present in 33 of our patients. Nasal complications occurred in six patients: three epistaxis (3.6%) and two hyposmia (2.4%) and one case of septal hematoma (1.2%). Postoperative cerebrospinal fluid leak occurred in six (7.2%) cases, two (2.4%) cases had sinusitis, while two (2.4%) cases had meningitis. There was a very rare case of subarachnoid hemorrhage and one case had sellar hematoma. Endocrinologic complications occurred in 15 (18.07%) patients: anterior pituitary deficiency in five (6.02%) patients, transient diabetes insipidus (DI) in nine (10.84%) patients, and permanent DI in one (1.2%) patient. There was no vascular injury or mortality noted in our study. **Conclusion:** Endoscopic approach is an effective modality for pituitary surgery; with patience, learning lessons from your own mistakes and by adopting right technique, learning curve can be flattened significantly.

Keywords: *Adenoma, complications, endoscopic, pituitary*

**Pawan Goyal,
Aditya Gupta,
Sanjeev Srivastava,
Shilpi Modi[1]**

Departments of Neurosurgery and [1]Pathology, Artemis Hospital, Gurgaon, Haryana, India

Introduction

Surgery for pituitary adenomas has evolved tremendously over a period of time. The transsphenoidal sublabial approach for pituitary tumor surgery was introduced by Cushing[1] in early 20th century. But unfortunately went into disrepute due to poor source of illumination and other technical limitations.

In the 1960s, it saw a revival with the use of microscope introduced by Hardy. An endoscope was adopted for the first time in 1963 by Guiot in the course of traditional transsphenoidal approach to overview the contents of sella turcica.[2]

The wide panoramic view, better tissue illumination, ability to look around the corners, no need of refocusing, and a high image resolution are some of the attributes which make it a better modality as compared to microscope.[3-5]

The benefits of endoscope are tangible, however, there are certain disadvantages such as two-dimensional view, limited zoom and focus capability, and the need for two surgeons.[6]

More importantly, shifting from microscope to endoscope needs a different set of skills. In this series, we present our experience during the first 83 cases and the lessons learned during this journey.

Materials and Methods

Aim

We aimed at doing safe and gross total excision of tumor without causing hypopituitarism.

This is a retrospective analysis of 83 cases of pituitary adenoma operated in the Neurosurgery Department of Artemis Hospital from June 2016 to August 2019.

Navigation-guided transnasal transsphenoidal endoscopic approach was used in all the cases. Analysis for epidemiologic variables,

Address for correspondence:
Dr. Pawan Goyal,
H. No. 104, Tower-2,
Malibu Town, Sector
47, Gurgaon - 122 018,
Haryana, India.
E-mail: drpawangoyal79@gmail.com

hormonal assessment (growth hormone [GH], insulin-like growth factor-1 [IGF-1], prolactin [PRL], cortisol, luteinizing hormone/follicle-stimulating hormone, adrenocorticotropic hormone [ACTH], and T3T4TSH), visual acuity, and perimetry assessment was done.

All the patients underwent preoperative magnetic resonance imaging (MRI) for the assessment of size, parasellar and suprasellar extensions, and neuronavigation. It was labeled as microadenoma (<10 mm), macroadenoma (>10 mm), and giant adenoma (>40 mm).

Assessment regarding the extent of resection was done by a radiologist independently. It was labeled as gross total resection if there was no residual tumor in postoperative MRI, subtotal resection if <20% residual, and partial resection if >20% residual in postoperative MRI.[7]

For functioning adenomas, hormonal assessment was done on follow-up (4–6 weeks) and remission was said to be achieved if normal hormonal levels were achieved along with gross total tumor removal. In secreting adenomas, the criteria of cure are considered to be a fasting random GH level of 2.5 ng/ml, a GH nadir of 1 ng/ml after an oral glucose tolerance test, and an IGF-1 level that is normal for the patient's age in GH-secreting tumors; a PRL level of 25 ng/ml or less in women and 15 ng/ml in men and an ACTH level of 10–90 pg/ml; and a blood serum cortisol level of 50–250 ng/ml in the morning and <50 ng/ml in the evening.[7]

As a routine, all tumors were submitted for histopathological and immunohistochemical analysis.

Surgical complications were evaluated, and postoperative follow-up with laboratory and imaging studies were performed. The follow-up period ranged from 1 to 6 months. We assessed the factors or possible mistakes which lead to each complication and ways to avoid them.

We divided the surgery-related complications into two major groups: (1) those associated with the surgical approach: (i) nasal stage, (ii) sphenoidal stage, and (iii) sellar and suprasellar stage and (2) those associated with the endocrine function of the pituitary gland: (i) anterior insufficiency of the gland and (ii) posterior insufficiency of the gland.

Surgical technique

All the cases were operated by the same team of neurosurgeons.

The patient was positioned supine in the reverse Trendelenburg position, with hips and knee flexed and the trunk elevated 20° in the "beach chair position." The head was rotated 15° toward the surgeon and 15° tilted toward the contralateral shoulder for the ease of insertion of endoscope. The head was fixed with Mayfield head holder in all the cases for the purpose of navigation. Depending

on the orientation of tumor, the head was fixed in either extended or flexed position. We used the right uninostril approach mostly, but occasionally, binsotril approach was also used depending on the anatomy of tumor. In general, a rigid, 4 mm, 18 cm, 0° endoscope was used and less frequently 30° endoscope was also used. Initial nasal decongestion was done with cotton patties (that are soaked in five ampules of adrenaline 1:1000 diluted in 30 ml of 1% xylocaine to widen the space between the middle turbinate [MT] and nasal septum and to have a clear view of important anatomical landmarks such as sphenoethmoidal recess, choana, and sphenoid ostium [SO]) [Figure 1]. Investment of 10–15 min at this stage saves a lot of time and energy during the rest of surgery.

The MT was lateralized in most of the cases. Turbinectomy was seldom needed. Nasoseptal flap based on nasoseptal branch of sphenopalatine artery was raised and parked in the choana. This step was done in all cases except microadenomas.

The SO was identified posterior and inferior to the root of the superior turbinate (ST). The posterior nasal septum was pushed to the opposite side to fracture it and opposite SO was seen. A wide anterior sphenoidotomy was performed by gradually enlarging the sphenoid sinus opening on both sides and removing the sphenoid rostrum. The vomer is drilled, and sphenovomerine suture was removed. This creates an additional space below the sellar floor and helps in easy movements of the instruments. The limits of the sphenoidotomy include: cranially, the superior limit of opening is visualization of the planum sphenoidale, the optico-carotid recesses, and the optic protuberance on both sides and caudally, clival indentation. We used navigation in every case to confirm the adequacy of sphenoidal opening. Intrasphenoidal septal variations and anterior wall of sella are also very well evaluated with navigation. Sphenoid sinus mucosa was removed and venous bleeding was controlled with
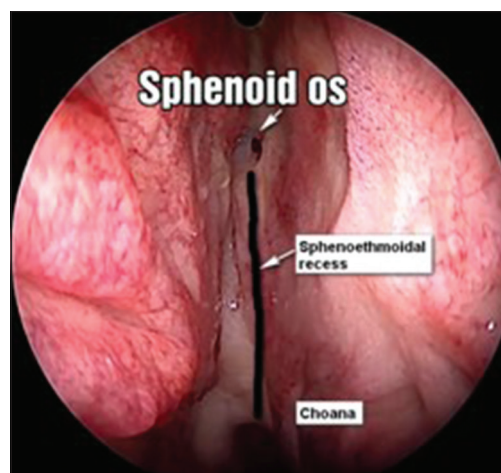

Figure 1: Endoscopic view after decongestion showing sphenoid os, sphenoethmoidal recess, and choana

irrigation. Then, the opening was made in the sellar floor till four blue lines (both the superiorly and inferiorly located inter-cavernous sinuses and the laterally located cavernous sinuses) are seen. The dura was opened in a cruciate fashion. The dura is opened from laterally to medially to prevent inadvertent injury to the sinuses. The tumor was removed by intracapsular approach in piecemeal fashion using curettes and suction. We removed posterior part of the tumor first followed by the lateral part [Figure 2]. Anterior part of the tumor acts as a retractor for arachnoid and is the last part to be removed. Following tumor resection, both 0° and 30° endoscopes were placed into the surgical cavity to explore for any residual tumor. Cerebrospinal fluid (CSF) leak if encountered was repaired with fibrin glue, fat and fascia lata, and vacularized nasoseptal flap. In case of obvious arachnoid breach and CSF leak, we placed lumbar drain and kept it for 3–4 days in the postoperative period.

Results

A total of 83 patients with pituitary adenoma were operated in the Neurosurgery Department at the Artemis Hospital, Gurgaon, during the period between June 2016 and August 2019. There were 43 (51.81%) male and 40 (48.19%) female patients. The age range was 14–70 years, with a mean ± standard deviation (SD) of 42.78 ± 14.09. The follow-up ranged from 1 to 6 months.

Of the 83 pituitary adenomas, 72 were macroadenomas and 7 were giant adenomas. The mean ± SD tumor volume was 8.44 ± 8.29 ml. Anatomic analysis of the tumor was done by Knosp and Hardy–Wilson grading as shown in Tables 1 and 2, respectively.

Gross total tumor removal was achieved in 55 (66.26%) patients, near-total removal in 18 (21.68%) patients, and subtotal removal in 10 (12.04%) patients. We found that gross total resection rate was inversely proportional to Knosp grading, as shown in Table 3. The extent of resection

was found to have a statistically significant correlation with the grade of tumor ($P < 0.05$), if we consider Grade 0–2 as low grade and 3–4 as high grade.

Endocrine remission: Despite achieving gross total resection in 22 functioning adenomas, remission standard was achieved in 14 (63.6%) cases only, as depicted in Table 4.

The purpose of this study is not to evaluate the results and outcomes of the surgery. Hence, we are not going into the details of outcome analysis. Rather, we will be focusing onto the complication analysis and ways to avoid them.

Complications due to the surgical approach

Surgery-related complications were present in 33 of our patients and have been summarized in Table 5. CSF leak and endocrine dysfunction were the major contributor in the list, and most of them were managed satisfactorily. There was no major vessel injury or mortality noted in our study.

Table 1: Knosp grading of cases

Knosp grade	NF	GH secreting	PRL secreting	Corticotrophin secreting	Total, *n* (%)
0	1	5	3	1	10 (12.04)
1	16	7	2	1	26 (31.32)
2	16	2	3	0	21 (25.30)
3	10	2	5	0	17 (20.48)
4	7	1	1	0	9 (10.84)

NF – Nonfunctional; GH – Growth hormone; PRL – Prolactin

Table 2: Hardy-Wilson grading of cases

Grade	*n* (%)	Grade	*n* (%)
0	14 (16.86)	I	7 (8.43)
A	32 (38.55)	II	63 (75.90)
B	32 (38.55)	III	8 (9.63)
C	5 (6.02)	IV	5 (6.02)
D	0		
E	0		

Table 3: Gross total resection rate(GTR) vs Knosp grading

Knosp grade	NF	GH secreting	PRL secreting	Corticotrophin secreting	Total, *n* (%)
0	1	5	2	1	9 (90)
1	15	6	2	0	23 (88.4)
2	11	2	2	0	15 (71.42)
3	6	1	1	0	8 (47.05)
4	0	0	0	0	0 (0)

NF – Nonfunctional; GH – Growth hormone; PRL – Prolactin

Table 4: Analysis of remission rate in functional adenomas

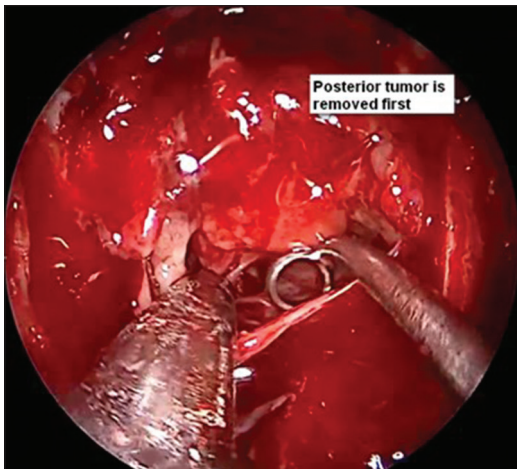| Tumor type	Gross total removal	Remission rate (%)
GH secreting	14	8 (57.1)
PRL secreting	7	5 (71.4)
Corticotrophin secreting	1	1 (100)
Total	22	14 (63.6)

GH – Growth hormone; PRL – Prolactin

Figure 2: Endoscopic view showing removal of the posterior part of the tumor first

Nasal complications

In the 1st postoperative week, one patient (1.29%) developed septal hematoma. Three (3.8%) patients had epistaxis, two were managed conservatively, while one suffered delayed major bleeding from mucosal branches of the sphenopalatine artery. In this particular patient, nasal packing failed twice. Fearing some major vessel injury, diagnostic angiography was done which came out to be negative. Finally, nasal reexploration was done under anesthesia, and bleeding from the mucosal branches of sphenopalatine artery was found which was controlled with cauterization and repacking. Another complication seen was hyposmia in two (2.4%) of our patients.

Sphenoid sinus complications

Two patients (2.4%) developed postoperative sinusitis within the first 2 months and the symptoms were postoperative headaches, dizziness, and fever. MRI demonstrated the presence of sphenoid sinusitis, which was cured conservatively with antibiotics.

Sellar and suprasellar complications

Cerebrospinal fluid leak

The most common complication in this region was CSF leakage. There was arachnoid breach noted in 23 patients in the intraoperative period. Repair was done with fat, fascia, and fibrin glue, and lumbar drain was inserted in them for 3–4 days. However, four patients still needed surgical reexploration for repair. Two patients did not have any arachnoid breach, but developed CSF leak in the postoperative period. One patient was managed with lumbar drain, while another patient had leak from the cribriform plate, which was discovered on reexploration and repaired successfully.

Hence, overall, six (7.22%) patients had CSF leak and five (6.02%) needed reexploration.

Two (2.4%) patients developed meningitis which was managed with antibiotics.

Subarachnoid hemorrhage

One (1.2%) patient was operated for macroadenoma. Surgery went uneventful except for arachnoid breach which was repaired with fat, fascia, and glue. There was no major bleeding during surgery, but the patient was restless and irritable after extubation. Immediate computed tomography (CT) scan was done which showed pneumocephalus and bleed in the prepontine and interpeduncular cistern [Figure 3]. It was followed by MRI brain which showed small infarct in the midbrain.

Sellar hematoma

One case of pituitary adenoma with apoplexy was operated uneventfully. However, on the 1st postoperative day, the patient started complaining of severe headache and blurring of vision. On CT scan, there was a large sellar hematoma with suprasellar extension. The patient was taken up for surgery immediately, and he had rapid recovery without any complication [Figure 4].

Parasellar complications: No parasellar complications were noted in our study.

Endocrine complications

Anterior pituitary insufficiency

Out of the 83 patients, 5 (6.02%) developed postoperative partial insufficiency of the pituitary gland. Three (3.6%) had multiaxis (cortisol and thyroid deficiency) and two (2.4%) had thyroid deficiency only. Assuming postoperative hypopituitarism after removal of large tumors, all patients were treated empirically with steroids and thyroid replacement drugs until the first endocrinological examination at our center. As a protocol, we did endocrinological evaluation at 6 weeks. Depending

Table 5: Surgical complications in this series	
Complications	*n* (%)
Nasal	6
Septal hematoma	1 (1.2)
Epistaxis	3 (3.6)
Hyposmia	2 (2.4)
Sphenoid sinus	2
Sinusitis	2 (2.4)
Sellar and suprasellar	10
Postoperative CSF leak	6 (7.2)
Meningitis	2 (2.4)
SAH	1 (1.2)
Sellar hematoma	1 (1.2)
Endocrine	15
Anterior pituitary insufficiency	5 (6.02)
Posterior pituitary insufficiency	10 (12.04)
Temporary	9 (10.84)
Permanent	1 (1.2)

CSF – Cerebrospinal fluid; SAH – Subarachnoid hemorrhage

Figure 3: Postoperative computed tomography showing subarachnoid hemorrhage in the interpeduncular cistern
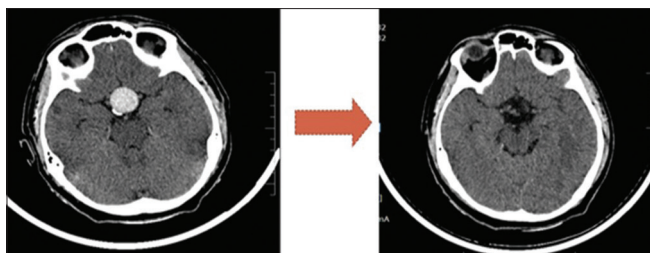
Figure 4: Pre- and post-operative computed tomography images of sellar hematoma

on the results, regulation with hormonal replacements followed.

Posterior pituitary insufficiency

Ten (12.04%) patients developed diabetes insipidus (DI) during the postoperative course. In nine (10.8%) patients, DI was transient and ceased within the 1st postoperative week, whereas in one (1.2%) patient, it persisted and labeled as permanent requiring vasopressin therapy for 3 months.

Discussion

Patients with tumors of pituitary gland are commonly encountered, representing approximately 10% of diagnosed brain neoplasms.[8]

Jankowski *et al.* were the first to use endonasal endoscopy for removal of pituitary adenoma.[9]

Currently, endoscopic surgery is the most widely used technique for pituitary adenoma due to its advantages such as rapidity, good tolerance, effectiveness, and low complication rate.[10]

However, neurosurgeons are not very familiar with nasal anatomy as well as transnasal endoscopic approaches. This leads to a plethora of difficulties and complications, especially in the early part of learning curve.

Hence, one should keep assessing his/her outcomes to take advantages of this approach and avoid complications.

For a beginner, smooth transition from microscopic to endoscopic approach can be facilitated by a proper case selection. Patients with a nonfunctioning adenoma confined to sella in a well-pneumatized sphenoid sinus are the best cases.[6]

Preoperative planning with meticulous study of MRI and CT of the patient is of paramount importance. Sphenoid sinus anatomy is specific for each individual like as is the case with finger prints. One can be lost easily without a proper preoperative planning.[11]

Navigation is useful especially in complex sphenoid anatomy, redo cases, or in extended transsphenoidal procedures.[6] Just like blindfolds prevent a horse from going astray, navigation also helps to keep surgeon on correct path or direction during surgery.[12]

We experienced that there was a significant decrease in the complication rate after first fifty cases. The incidence rate of few complications was relatively higher in our experience, which is expected as sample size was smaller as compared to some other similar studies. Table 6 shows a comparative analysis of complications in our study with some other studies on complications.

Nasal complications

The most common problem a beginner faces during this stage is poor exposure and continuous oozing from the nasal mucosa in an underprepared nasal corridor. This oozing can make the surgery difficult and frustrating at times. Hence, adequate time for nasal decongestion should be given, which saves a lot of time and makes life easier during the rest of the steps of surgery.

Nasal vascular complications are described in 0.7%–7% of cases.[13,14,19-31] We had an incidence of bleeding in three (3.61%) of our cases.

It can be avoided if nasal mucosa is treated respectfully. Hemostasis should be ensured at the end of surgery and no foreign bodies or free bone chips should be left behind.

Sphenopalatine artery arises near superior meatus or between superior and middle meatus. Hence, caution should be exercised while doing mucosal dissection in this region, especially while raising nasoseptal flap.[11]

Delayed bleeding can occur from these vessels after surgery when blood pressure returns to normal levels. Hence, adequate hemostasis should be ensured to prevent any such issue.

Hyposmia is another complication seen in this procedure. We met with hyposmia in two (2.4%) of our cases. Charalampaki *et al.* experienced hyposmia in 2.2%,[15] while Berker *et al.* had it in 0.6% of cases.[11] It occurs due to excessive coagulation on the lateral nasal wall near ST and upper half of the MT as olfactory nerve fibers traverse in this region. This problem can also arise if nasoseptal flap extends superiorly up to the upper half of MT.

Sphenoid sinus complications

A lot many complications can happen in sphenoid sinus due to its complex anatomy and relation to many vital structures such as optic nerves, internal carotid arteries, and maxillary division of trigeminal nerves.

We encountered sinusitis in two (2.4%) of our cases treated with antibiotics. In the literature, the rate of such complication varies between 0.5% and 5.7%.[7,13,15-17,19,26,32]

To prevent this complication, artificial material should be avoided for packing[15,17] and ostium should be kept wide open with respect to osteomeatal complex.[7]

Table 6: Comparison of complications amongst major endoscopic pituitary series in literature

Complications	Cappabianca *et al.*[7]	Berker *et al.*[11]	de Divitiis *et al.*[13]	Zhou *et al.*[14]	Charalampaki *et al.*[15]	Jho[16]	Gondim *et al.*[17]	Dehdashti *et al.*[18]	Present study
Epistaxis	1.3	0.6	1.7	1.6	1.4		1.9	1	3.6
Hyposmia	-	0.6	-	-	2.2		None	-	2.4
CSF leak	2	1.2	2.1	0.5	3.7	6	2.6	3	7.2
Sinusitis	2	0.4	2.1	-	1.4	1.2	1.6	-	2.4
Meningitis	0.6	0.7	0.4	0.8	-	1.2	0.6	1	2.4
Anterior pituitary deficiency	3.42	1.92	14.5	-	4.4	11	11.6	3	6.02
DI	13.6	4.6	3.1	3.7	5.9	3	6.3	1	12.04
Vascular injury	0.6	0.16	0.4	-	0.7	-	1	-	None
Death	0.68	None	0.4	None	0.7	-	1	None	None

DI – Diabetes insipidus; CSF – Cerebrospinal fluid

Sellar and suprasellar complications

Cerebrospinal fluid leak

Pituitary adenomas are tumors of extraarachnoidal origin, so usually grow outside the confines of CSF. As the tumor lies in close relationship to the diaphragma sellae and subarachnoid space, there is always a risk of iatrogenic arachnoid breach. Hence, CSF leak is a very common complication of this surgery.

We had a total of six (7.2%) cases with postoperative CSF leak. Five (6.02%) cases needed reexploration. CSF leaks have been reported varying from 0.5% to 10.3%.[14,33]

There are multiple reasons which can lead to CSF leak. If one tries to remove tumor *en mass* without mobilizing it first, it can lead to arachnoid tear and CSF leak.[6] Tumor should be approached in a step-wise manner. The posterior part should be removed first followed by the lateral. The anterior part acts as a retractor for arachnoid and should be removed at last. In large tumors, an empty space is created which leads to traction on the arachnoid, and it can get torn when patient exhales or coughs in the postoperative period and causes leak.[3]

Injury to cribriform plate can also lead to leak. This occurs if we are operating too far superiorly. Sometimes, it may be associated with outfracturing of MT.[34]

It is imperative to identify the tear in the diaphragm and/or arachnoid membrane during the surgery and should be dealt with immediately. In cases of intraoperative CSF leak with diaphragm defect <5 mm or low CSF flow rate, a piece of free fat covered by Surgicel® is placed into the sellar cavity as to close the defect. A piece of Gelfoam® covered by Surgicel is placed as an overlayer graft. If diaphragm defect is large (5–10 mm) and/or flow rate of CSF is high, a piece of free fat covered by Surgicel is placed into the sellar cavity to seal the defect. Then, underlayer and overlayer-free fascia lata grafts are placed over the fat. If the defect diameter is more than 15 mm, Foley balloon catheter should be used to support the grafts.[11] Nasoseptal flap and Fibrin sealant can be used additionally in large defects. It is better to put an external lumbar drainage system for 3–5 days in large defect repairs.

Two (2.4%) of our cases of leak met with meningitis and were treated successfully with antibiotics. The reported rate of meningitis in literature varies from 0.4% to 2.19%.[7,13,16,18,19,25,35] CSF leak avoidance is the most important factor to prevent this complication.

We had a case of subarachnoid hemorrhage (SAH) followed by brainstem infarct in early part of our learning curve. No reoperation was needed, and the patient survived except that he did have Holmes' tremor in the long-term follow-up. This is a relatively rare complication and very few cases have been reported so far. An extensive search of the literature yielded only four such case reports.[36-39]

There are multiple reasons which can lead to this complication. Blood may seep through the arachnoid defect leading to SAH and vasospasm. Blind tumor dissection can lead to arachnoid tear and perforator injury. An indirect injury to an artery caused by traction due to descent of the capsule during tumor debulking may lead to SAH.[37,40]

To prevent this, the arachnoid membrane should be protected. Once breach occurs, instant repair and hemostasis should be achieved. Never try to pull the tumor. First mobilize and then try to remove the tumor.[6] In very large tumors, additional transcranial approach might be used.

We had sellar hematoma with suprasellar extension in one of our cases which needed reexploration. This is a relatively rare event, reported to occur in 0.13% of patients.[41]

Large tumors of size >3 cm with suprasellar extension are known risk factors for sellar hematoma formation.[42]

Parasellar complications

Injury to internal carotid artery is one of the dreaded complications which can occur during aggressive dissection of macroadenomas extending into cavernous sinuses. The overall incidence is 0%–0.68%.[17] We did not meet with any such complication in our series. Probably, the use of

navigation was of great help as we used it in every case regardless of the size of lesion. It is especially of great help in redo cases and cases with complex sphenoid sinus anatomy. Use of intraoperative Doppler is also strongly recommended especially in redo cases which present with changes of usual anatomy.[17]

Endocrine complications

Transient pituitary dysfunction is very common in both anterior and posterior lobes due to surgical trauma with reported incidence rate of 2.5%–20%.[10,18] Permanent DI has been reported in the range of 1.32%–3.42%.[7,43,44] It occurs due to the damage of magnocellular neurons in the posterior lobe either due to traction or due to direct injury. Permanent DI can occur if injury occurs at a higher level in stalk near to the hypothalamus, or when there is loss of 85% or more of hypothalamic magnocellular neurons.[45]

Permanent DI is actually regarded as a real surgical complication as temporary form might be secondary to simple manipulation of pituitary gland. We had an incidence of temporary DI of 10.84%, while the incidence of permanent DI was 1.2%.

MRI should be assessed beforehand to have an idea regarding the location of pituitary gland. Overly aggressive stalk manipulation should be avoided.[46]

Anterior pituitary dysfunction is also a common complication associated with this surgery. The risk is especially high in large tumors that distort, diminish, and lift the gland superiorly toward diaphragma sellae.[46] The risk of postoperative hypopituitarism varies from 5% to 25% for pituitary adenomas.[31,47] We had an incidence of 6.02% in our series. Hypothalamus–pituitary–adrenal axis is the most susceptible, affecting postoperative cortisol and ACTH response. One should always try to identify normal gland by its distinguished orange color and tendency to resist curettage and suction. Too much use of bipolar cautery in sellar cavity and aggressive manipulation should be avoided to prevent the damage of normal pituitary gland.[11]

On a completely opposite spectrum is the failure of hormonal remission despite imaging total removal in functioning adenomas. After primary surgery for Cushing's disease, the initial remission rate is between 25% and 100%.[48] Up to approximately 50% of acromegaly patients show persistence of the disease after pituitary surgery.[49] We also had remission rate ranging from 57.1% to 100% across different tumor categories, as shown in Table 4. Infiltration of medial walls of cavernous sinus and remnants of tumor capsule left behind are hypothesized to be the reasons behind this.[50] Hence, higher remission rates are observed in less invasive tumors and more experienced hands.

In endoscopic skull base surgery, learning curve can at times be a steep learning curve as mentioned by Bhatt.[12]

He has interestingly discussed the genesis of this learning curve. There is no doubt that as one advances along the learning curve, the surgical procedure may proceed more efficiently, consuming lesser time and with better outcomes.

Learning curve may appear steep because of two reasons. First, if surgeon is not experienced and starts his/her career with *de novo* training and performs endoscopic skull base surgeries. Secondly, it can appear steep to a well-trained and experienced surgeon who is transitioning from microscopic to endoscopic approach. As mentioned by Bhatt, experienced surgeons may at times find difficulty changing surgical technique and unlearning what they have been doing for several years or may be decades. However, still, there is a large body of evidence which suggest that experienced surgeons are good in transforming their approach without any worsening of clinical outcomes.[12]

All the cases in this series have been performed by a team of two experienced neurosurgeons. The senior author (AG) has a vast experience of 20 years in the field of neurosurgery including working as a faculty at a premier institute (AIIMS) in India. He was regularly doing pituitary surgery through microscopic approach and he then shifted gradually to endoscopic approach. The second surgeon (PG) had keen interest in neuroendoscopy right from the beginning. He gained experience and refined his skills by attending cadaveric workshops, live operative workshops, and assisting senior neurosurgeons over a period of 5–6 years before finally starting doing it independently.

We divided our first 82 cases (total 83 cases in study) into two groups of 41 each to have an assessment of our learning curve, as shown in Table 7. We found that our gross total excision rate increased (63.4% vs. 70.7%), but more importantly, it increased in invasive tumors (55.88% vs. 71.05%) though the difference was not statistically significant ($P = 0.18$). Endocrine remission rate also improved to some extent (58.33% vs. 70%) in functional tumors with gross total excision. With improvement in skills, severe complications leading to reexploration or prolonged hospital stay or permanent morbidity (CSF leak, SAH, sellar hematoma, epistaxis needing reexploration, meningitis, and permanent DI) were brought down from eight in the first half to four in the second half.

Apart from the things of statistical significance, there are other things which cannot be stratified but are of great importance such as ease of handling of instruments in narrow space, cleaner operative field, and swift movements, which become better with more experience.

Though it has been mentioned that learning curve hits a plateau in terms of outcomes, it can continue for several years depending on the complexity of the end points considered such as higher rates of gross total

Table 7: Analysis of learning curve	First half	Second half	*P*
Number of cases	41	41	
Gross total removal (%)	26 (63.4)	29 (70.7)	0.48
Invasive tumor*	34	38	
Gross total removal in invasive tumor (%)	19 (55.88)	27 (71.05)	0.18
Severe complications**	8	4	0.21
Gross total removal in functional adenomas	12	10	
Endocrine remission in functional adenomas with gross total removal (%)	7 (58.33)	7 (70)	0.89

*Invasive tumor (above Knosp grade 0); **Severe complications (which lead to reexploration or prolonged hospital stay or permanent morbidity)

resections (from 67% in the first half to 75% in the second half), better hormonal remission rates (from 83% in the first half to 89% in the second half), and lesser complications (6.4% in the first half to 6.2% in the second half) as experienced by Younus *et al*.[51]

Conclusion

This series represents the learning curve for a beginner, and it was experienced that difficulties and complications start decreasing significantly after initial 40–50 cases. One has to be patient and bear with initial longer surgical duration, absence of depth perception unlike a microscope, the clutter of instruments in narrow field with less maneuverability, and difficulty in achieving hemostasis. Though the best strategy to deal with complications is to avoid them, proper learning of tips and tricks can reduce them significantly.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Cushing H. The Weir Mitchell Lecture. Surgical experience with pituitary disorders. JAMA 1914;63:1515-25.
2. Guiot G, Rougerie J, Fourestier M, Fournier A, Comoy C, Vulmiere J. Une nouvelle technique endoscopique: Explorations endoscopiques intracra ˆniennes. Presse Med 1963;72:1225-31.
3. Jho HD. Endoscopic pituitary surgery. Pituitary 1999;2:139-54.
4. Jho HD, Alfieri A. Endoscopic transsphenoidal pituitary surgery: Various surgical techniques and recommended steps for procedural transition. Br J Neurosurg 2000;14:432-40.
5. Jho HD, Alfieri A. Endoscopic endonasal pituitary surgery: Evolution of surgical technique and equipment in 150 operations. Minim Invasive Neurosurg 2001;44:1-2.
6. Sharma BS, Sawarkar DP, Suri A. Endoscopic pituitary surgery: Techniques, tips and tricks, nuances, and complication avoidance. Neurol India 2016;64:724-36.
7. Cappabianca P, Cavallo LM, Colao A, de Divitiis E. Surgical complications associated with the endoscopic endonasal transsphenoidal approach for pituitary adenomas. J Neurosurg 2002;97:293-8.
8. Dumont AS, Nemergut EC 2nd, Jane JA Jr, Laws ER Jr. Postoperative care following pituitary surgery. J Intensive Care Med 2005;20:127-40.
9. Jankowski R, Auque J, Simon C, Marchal JC, Hepner H, Wayoff M. Endoscopic pituitary tumor surgery. Laryngoscope 1992;102:198-202.
10. Tabaee A, Anand VK, Barron Y, Hiltzik DH, Brown SM, Kacker A, *et al*. Endoscopic pituitary surgery: A systematic review and meta-analysis. J Neurosurg 1992;111:545-54.
11. Berker M, Hazer DB, Yücel T, Gürlek A, Cila A, Aldur M, *et al*. Complications of endoscopic surgery of the pituitary adenomas: Analysis of 570 patients and review of the literature. Pituitary 2012;15:288-300.
12. Bhat DI. Endoscopic transsphenoidal surgery: A revolutionary evolution. Neurol India 2019;67:1024-6.
13. de Divitiis E, Cappabianca P, Cavallo M. Endoscopic endonasal transsphenoidal approach to the sellar region. In: De Divitiis E, Cappabianca P, editors. Endoscopic Endonasal Transsphenoidal Surgery. Vienna: Springer; 2003. p. 91-130.
14. Zhou T, Wei SB, Meng XH, Xu BN. Pure endoscopic endonasal transsphenoidal approach for 375 pituitary adenomas. Zhonghua Wai Ke Za Zhi 2010;48:1443-6.
15. Charalampaki P, Ayyad A, Kockro RA, Perneczky A. Surgical complications after endoscopic transsphenoidal pituitary surgery. J Clin Neurosci 2009;16:786-9.
16. Jho HD. Endoscopic transsphenoidal surgery. J Neurooncol 2001;54:187-95.
17. Gondim JA, Almeida JP, Albuquerque LA, Schops M, Gomes E, Ferraz T, *et al*. Endoscopic endonasal approach for pituitary adenoma: Surgical complications in 301 patients. Pituitary 2011;14:174-83.
18. Dehdashti AR, Ganna A, Karabatsou K, Gentili F. Pure endoscopic endonasal approach for pituitary adenomas: Early surgical results in 200 patients and comparison with previous microsurgical series. Neurosurgery 2008;62:1006-15.
19. Frank G, Pasquini E, Farneti G, Mazzatenta D, Sciarretta V, Grasso V, *et al*. The endoscopic versus the traditional approach in pituitary surgery. Neuroendocrinology 2006;83:240-8.
20. Rudnik A, Kos-Kudła B, Larysz D, Zawadzki T, Bazowski P. Endoscopic transsphenoidal treatment of hormonally active pituitary adenomas. Neuro Endocrinol Lett 2007;28:438-44.
21. Kabil MS, Eby JB, Shahinian HK. Fully endoscopic endonasal vs. transseptal transsphenoidal pituitary surgery. Minim Invasive Neurosurg 2005;48:348-54.
22. Casler JD, Doolittle AM, Mair EA. Endoscopic surgery of the anterior skull base. Laryngoscope 2005;115:16-24.
23. White DR, Sonnenburg RE, Ewend MG, Senior BA. Safety of minimally invasive pituitary surgery (MIPS) compared with a traditional approach. Laryngoscope 2004;114:1945-8.
24. Shen CC, Wang YC, Hua WS, Chang CS, Sun MH. Endoscopic endonasal transsphenoidal surgery for pituitary tumors. Zhonghua Yi Xue Za Zhi (Taipei) 2000;63:301-10.

25. Santos Rde P, Zymberg ST, Abucham Filho JZ, Gregório LC, Weckx LL. Endoscopic transnasal approach to sellar tumors. Braz J Otorhinolaryngol 2007;73:463-75.

26. Senior BA, Ebert CS, Bednarski KK, Bassim MK, Younes M, Sigounas D, *et al*. Minimally invasive pituitary surgery. Laryngoscope 2008;118:1842-55.

27. Higgins TS, Courtemanche C, Karakla D, Strasnick B, Singh RV, Koen JL, *et al*. Analysis of transnasal endoscopic versus transseptal microscopic approach for excision of pituitary tumors. Am J Rhinol 2008;22:649-52.

28. Minet WW, Sommer DD, Yousuf K, Midia M, Farrokhyar F, Reddy K. Retrospective comparison of an endoscopic assisted versus a purely endoscopic approach to sellar tumour resection. J Otolaryngol Head Neck Surg 2008;37:759-67.

29. D'Haens J, Van Rompaey K, Stadnik T, Haentjens P, Poppe K, Velkeniers B. Fully endoscopic transsphenoidal surgery for functioning pituitary adenomas: A retrospective comparison with traditional transsphenoidal microsurgery in the same institution. Surg Neurol 2009;72:336-40.

30. Pádua FG, Voegels RL. Severe posterior epistaxis-endoscopic surgical anatomy. Laryngoscope 2008;118:156-61.

31. Ciric I, Ragin A, Baumgartner C, Pierce D. Complications of transsphenoidal surgery: Results of a national survey, review of the literature, and personal experience. Neurosurgery 1997;40:225-36.

32. O'Malley BW Jr, Grady MS, Gabel BC, Cohen MA, Heuer GG, Pisapia J, *et al*. Comparison of endoscopic and microscopic removal of pituitary adenomas: Single-surgeon experience and the learning curve. Neurosurg Focus 2008;25:E10.

33. Thawani JP, Ramayya AG, Pisapia JM, Abdullah KG, Lee JY, Grady MS. Operative strategies to minimize complications following resection of pituitary macroadenomas. J Neurol Surg B Skull Base 2017;78:184-90.

34. Laws ER Jr., Kern EB. Complications of trans-sphenoidal surgery. Clin Neurosurg 1976;23:401-16.

35. Persky MS, Brunner E, Cooper PR, Cohen NL. Perioperative complications of trans sheptosphenoidal excision for pituitary adenomas. Skull Base Surg 1996;6:231-5.

36. Goyal N, Basheer N, Suri A, Mahapatra AK. Subarachnoid hemorrhage after transsphenoidal surgery for pituitary adenoma: A case report and review of literature. Neurol India 2012;60:337-8.

37. Matsuno A, Yoshida S, Basugi N, Itoh S, Tanaka J. Severe subarachnoid hemorrhage during transsphenoidal surgery for pituitary adenoma. Surg Neurol 1993;39:276-8.

38. Tsuchida T, Tanaka R, Yokoyama M, Sato H. Rupture of anterior communicating artery aneurysm during transsphenoidal surgery for pituitary adenoma. Surg Neurol 1983;20:67-70.

39. Zhou WG, Yang ZQ. Complications of transsphenoidal surgery for sellar region: Intracranial vessel injury. Chin Med J (Engl) 2009;122:1154-6.

40. Kuroyanagi T, Kobayashi S, Takemae T, Kobayashi S. Subarachnoid hemorrhage, midbrain hemorrhage and thalamic infarction following transsphenoidal removal of a pituitary adenoma. A case report. Neurosurg Rev 1994;17:161-5.

41. Atkinson JL, Nippoldt TB, Koeller KK. Reoperation for sella haematoma after pituitary surgery. Clin Endocrinol (Oxf) 2008;68:413-5.

42. Younus I, Gerges MM, Godil SS, Uribe-Cardenas R, Dobri GA, Ramakrishna R, *et al*. Incidence and risk factors associated with reoperation for sellar hematoma following endoscopic transsphenoidal pituitary surgery. J Neurosurg 2019:1-7. doi:10.3171/2019.6.JNS191169. [Epub ahead of print].

43. Gondim JA, Schops M, de Almeida JP, Albuquerque LA, Gomes E, Ferraz T, *et al*. Endoscopic endonasal transphenoidal surgery: Surgical results of 228 pituitary adenomas treated in a pituitary center. Pituitary 2010;13:68-77.

44. Rotenberg B, Tam S, Ryu WH, Duggal N. Microscopic versus endoscopic pituitary surgery: A systematic review. Laryngoscope 2010;120:1292-7.

45. Schreckinger M, Szerlip N, Mittal S. Diabetes insipidus following resection of pituitary tumors. Clin Neurol Neurosurg 2013;115:121-6.

46. Matthew S, Agam BS, Gabriel Z. Complications associated with transsphenoidal pituitary surgery: Review of the literature. Clinical Neuro 2018;65:69-73.

47. Roelfsema F, Biermasz NR, Pereira AM. Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: A structured review and meta-analysis. Pituitary 2012;15:71-83.

48. Pivonello R, De Leo M, Cozzolino A, Colao A. The treatment of Cushing's disease. Endocr Rev 2015;36:385-486.

49. Del Porto LA, Liubinas SV, Kaye AH. Treatment of persistent and recurrent acromegaly. J Clin Neurosci 2011;18:181-90.

50. Shou X, Shen M, Zhang Q, Zhang Y, He W, Ma Z, *et al*. Endoscopic endonasal pituitary adenomas surgery: The surgical experience of 178 consecutive patients and learning curve of two neurosurgeons. BMC Neurol 2016;16:247.

51. Younus I, Gerges MM, Uribe Cardenas R, Morgenstern PF, Eljalby M, Tabaee A, et al. How long is the tail end of the learning curve? Results from 1000 consecutive endoscopic endonasal skull base cases following the initial 200 cases. J Neurosurg 2020 Feb 7;1-11. doi: 10.3171/2019.12.JNS192600. Online ahead of print.