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Complications of endoscopic surgery of the pituitary adenomas: analysis of 570 patients and review of the literature

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Abstract Endoscopic transsphenoidal surgery is emerging as a minimally invasive and maximally effective procedure for pituitary adenomas. In this report we analyzed the complications in 624 procedures of endonasal transsphenoidal endoscopic surgery in the treatment of 570 patients with pituitary adenomas. The leading author (MB) operated pituitary adenomas via pure endoscopic endonasal transsphenoidal surgery between January 2006 and August 2011 at the Hacettepe University, Department of Neurosurgery in Ankara. Complications were assessed in 624 surgical procedures under five groups; rhinological, CSF leaks, infection, vascular and endocrinologic complications. We observed a total of 76 complications (12.1%). Rhinological complications occurred in 8 patients (1.3%): 4 epistaxis (0.6%) and 4 hyposmia (0.6%). Postoperative CSF leaks occurred in 8 patients (1.3%), and infectious complications occurred in 8 patients: 3 cases of sphenoidal sinusitis (0.4%), 5 cases of meningitis (0.8%). Only 1 case of internal carotid aneurysm rupture during the opening of sellar floor (0.16%) was observed. Endocrinologic complications occurred in 51 (8.1%) patients: Anterior pituitary deficiency in 12 (1.9%), transient diabetes insipidus (DI) in 29 (4.6%), permanent DI in 3 (0.4%) and inappropriate antidiuretic hormone secretion syndrome occurred in 7 (1.1%). There was no mortality directly related to the surgical procedure. The complication rates observed in our study suggests that the endoscopic pituitary surgery is at least as safe as microscopic transphenoidal surgery. These rates were obtained with due experience and well-coordinated teamwork. To further improve these rates, new technological developments will be helpful.

Keywords Pituitary · Adenoma · Endonasal endoscopic surgery · Complication

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Introduction

Surgical approaches to the sellar region presented a challenge to the surgeon for many years. With the introduction of the endoscope, sellar and parasellar surgery have achieved a new dimension. The endoscope-guided transsphenoidal surgery was standardized in actual clinical practice by Carrau and Jho [1] and Cappabianca et al. [2]. In following years, endoscopic surgery was accepted widely and today is being used in many centers. Many publications on endonasal endoscopic surgery have advocated the less invasive nature of this technique, some others point to a better endocrinologic outcome for functioning adenomas [3–7]. Although it offers enhanced illumination and visualization of the lesions, the complications may occur at every step of the procedure. The aim of this study is to report the results of a series of patients undergoing been pure endoscopic endonasal pituitary surgery, to discuss the pathophysiology of complications and to evaluate the efficacy and safety of this procedure.

Clinical materials and methods

The present retrospective study evaluated 570 consecutive pituitary adenomas patients who underwent 624 pure endoscopic endonasal transsphenoidal surgery, which were performed by the leading author (MB) at Hacettepe University Neurosurgery Department in between January 2006 and August 2011. Any other sellar or parasellar lesions were excluded. All patients underwent neurological, ophthalmological and endocrinological detailed examination prior to surgery and in the follow-up period and were discussed complications with special reference to the relevant literature.

Hormonal and radiological assessment

Endocrine screening was done prior to surgery and on the first, 7th day of the surgery and first, 3rd and 6th month, and every subsequent year after the surgery. On the designated days, multiple measurements of plasma growth hormone (GH), insulin-like growth factor-I (IGF-I), GH level after oral glucose tolerance test (OGTT), prolactin, adrenocorticotrophic hormone (ACTH), cortisol, 24-h urinary free cortisol (when Cushing's disease was suspected), thyroid-stimulating hormone (TSH), free thyroxine, luteinizing hormone (LH) and follicle stimulating hormone (FSH), testosterone, and estradiol levels were studied.

To assess the size and the invasion of the adenoma, all patients underwent magnetic resonance imaging (MRI), with and without administration of intravenous contrast agent prior to surgery. Tumor size was grouped in three categories: microadenoma (<10 mm), macroadenomas (>10 mm) and giant adenoma (>40 mm). Conventional paranasal computerized tomography scans were used in all patients for surgical planning. Sphenoid sinus and septal anatomy were evaluated in detail.

Surgical technique

All patients are consulted to the ear nose and throat (ENT) department for the evaluation of nasal cavity and related infections, for determination of the operational side which is more comfortable and suitable for endoscopic approach. Preoperative preparation of the nasal mucosa consists of pledgets soaked in lidocaine HCl 20 mg/ml and epinephrine HCl 0.0125 mg/ml mixt solution which are placed on medial side of the turbinates through both nostrils for the mucosal decongestion and to decrease mucosal bleeding during nasal phase of surgery. Briefly, after intubation, the oropharynx is packed with gauze to prevent bloody material runoff into the esophagus and trachea. Head is slightly turned toward the surgeon and is elevated about 20 degree for both to reduce intracavernous pressure and to align the paraseptal corridor for optimum ease for endoscope entry. Usually the right nostril is preferred for the operation but in some cases left nostril is utilized due to septal deviation.

In most of the cases, a 4 mm rigid telescope with 0° tip connected to a xenon light source is used as the optic instrument. In some conditions, 30° and 45° telescopes were also used (Karl Storz). A digital Image 1 (Karl Storz) camera is connected to a LCD display (Sony 2140 MD) and a digital recording device (Sony DVO 1000MD). All operations are recorded on digital media for documentation. Some of the operating instruments are the same for microscopic surgery, but most of them are first author's own design which are optimized and designed for endoscopic pituitary surgery. For the first 100 approaches, endonasal nasosphenoidal stage was done by ENT surgeon.

Nasosphenoidal stage

Under induced hypotension, the endoscope is inserted into the nasal cavity and the middle turbinate is lateralized to form a large opening for the instruments. The ostium is observed and widened to enter the sphenoid sinus. At this step we usually see the posterior septal branch of sphenopalatine artery and coagulate it in order to prevent the risk of the late onset epistaxis. In most of the cases we start the operation from the right nostril of the patient, and middle turbinate excision is seldom needed. In extended approaches, following a wide opening of the sphenoid ostia, we perform partial inferior middle turbinectomy at the tumor side (or very rarely total middle turbinectomy) and use the binostril approach.

Second step is large anterior sphenoidotomy and posterior septectomy with Kerrison rongeur and backbite rongeur. The drilling of the base of the sphenoid, especially removal of the sphenovomerine suture is an important step that not only helps to expose the clivus and all sellar floor, but also significantly increases the maneuverability of instruments, augments the efficacy and safety of endoscopic surgery by improving access to the tumor, and helps to control any bleeding in the same manner as with microsurgery. At the end of the nasosphenoidal stage, exposure of the sella from one carotid protuberance to the other and craniocaudally from the planum sphenoidale to clivus is achieved. Intrasphenoidal septal variations and the anterior wall of sella are very well evaluated with both coronal and sagittal paranasal CT scans preoperatively. Intercarotid distance is measured in great care with MRI and CT scans and these measures are rechecked intraoperatively with the aid of designed 10 mm scaled- dissector by the leading author. The remaining part of the procedure, the sellar stage, is performed using a bimanual technique, with the assistant holding and cleaning the telescope.

Sellar stage

The second stage of the endoscopic pituitary surgery is sellar stage. The face and floor of the sella is opened by the high speed drill or small pituitary rongeur depending on the thickness of the bone. Bone is removed from one carotid protuberance to the other. If necessary, the bone over the cavernous sinus can be removed. The dural opening is then made from the medial cavernous sinus walls and from the intercavernous sinus to clivus. First incision should be made parallel to the intercavernous sinus and lateral to medial direction. Starting point of incision should be determined after a careful inspection and additionally checked with the Doppler probe to avoid carotid injury. The reason for opening from lateral to medial and superior to inferior is to promote safer control to prevent any inadvertent maneuver of the dura knife.

Using the mononostril bimanual technique, the tumor removal is performed with the same principles as the microscopic technique. A macroadenoma is usually encountered directly beneath the dura, and decompression can begin immediately. The interior is debulked in standard fashion using curettes and suctions. When a cavity is opened, the endoscope can be introduced into it, allowing direct visualization of the residual tumor.

In cases of significant intraoperative CSF leaks, our repairing strategies are as follows; If diaphragm defect is less than 5 mm or CSF flow rate is low, a piece of free fat covered by Surgicel is placed into the sellar cavity as to fit well and to compress the defect. A piece of gelfoam covered by Surgicel is placed as an overlayer graft. Sphenoid sinus is packed with gelfoam to support the 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 as to fit well and to compress the defect. Then underlayer and overlayer free fascia lata grafts are placed in the sellar floor. In some cases, we place an external lumbar drainage system and keep it for 5 days after surgery. If the defect diameter is more than 15 mm, Foley balloon catheter should be used to support the grafts. We do not use tissue adhesive such as fibrin sealant in order to support the fascia lata grafts. Also intraoperative retractor and postoperative nasal packing are not used in routine cases.

Patients are discharged from the clinic after one to two postoperative days with a scheduled date for the next appointment.

Postoperative control

In 24 h after the surgery, pituitary MRI and endocrinological evaluation were repeated. Hormonal assessment (same as the preoperative hormonal screening) was performed at the first and the seventh postoperative days, first, third and sixth postoperative months and, then, annually. Complications are classified according to the anatomical structures through the operative stages mainly as rhinological, CSF leaks, infection and vascular complications. Endocrinological complications are grouped in another section as anterior and posterior pituitary dysfunctions. In this report we do not discuss anesthetic complications or pulmonary thromboembolism.

Results

In this report we did not give any information about clinical cure rates, and extend of the removal of the tumor. Our aim is to discuss the complications of the endoscopic transsphenoidal surgery that occurred in 624 operations of 570 patients (Table 1). The distrubutions of the patients and relation to complications are given in Tables 1 and 2. The analysis of the complications are as follows.

Table 1 Distribution of the adenomas according to hormonal activity and the size

Type of lesion	Number of patients	Type of adenoma according to size
Pituitary adenomas	570	437 macro
		133 micro
Nonfunctioning	153	139 macro (2 giant adenoma)
		14 micro
GH secreting	203	153 macro (1 giant adenoma)
		50 micro
PRL secreting	122	106 macro (6 giant adenoma)
		16 micro
ACTH secreting	85	57 macro
		28 micro
TSH secreting	7	7 macro
No. of reoperation	54	41 macro
		13 micro

Table 2 General features and course of complications

Category of complication	Type of complication	Patient age, sex	Lesion type	Onset of complication	Treatment
Rhinologic	Epistaxis	59, M	Macroad, GH	8th h	Coagulation
		49, F	Macroad, PRL	2 days	Coagulation
		42, M	Macroad, NF	10 days	Coagulation
		42, F	Macroad, mixt type	15 days	Nasal tamponade
	Hyposmia	49, F	Macroad, PRL	1 month	Medical
		58, M	Macroad, NF	1 month	
		35, F	Macroad, PRL	1 month	
		61, F	Giant macroad NF	1 month	
CSF complications	Postoperative CSF leak	56, M	Macroad PRL,	2nd day	ELD + surg
		34, F	Macroad, GH, apoplexia	2nd day	ELD + surg
		29, F	Macroad, GH	5th day	ELD + surg
		38, F	Macroad, NF	5th day	ELD + Surg (Fasia + foley catheter)
		28, M	Macroad, GH	5th day	ELD + surg
		15, F	Macroad, ACTH	7th day	
		64, F	Microad, GH	5th day	ELD + surg
		29, F	Microad, GH	5th day	ELD + surg
Infectious	Sphenoid sinusitis	17, F	Macroad, ACTH	1st year	Medical
		50, F	Macroad, GH	6th month	
		42, F	Microad, ACTH	6th month	
	Meningitis	56, M	Macroad PRL, rhinorea	1st week	
		34, F	Macroad, GH, rhinorea	1st week	
		54, M	Macroad NF,	1st week	
		41, M	Macroad, PRL (peroper CSF leak)	2nd week	
		57, M	Macroad ACTH	2nd week	
Vascular	Aneurysm rupture	41, F	Macroad ACTH Cushing,	Intraoperative	Endovascular
Endocrinological	Anterior pituitary dysfunction	22, M	Microad, ACTH	7th day cortisol and thyroid deficiency, 6th month control only thyroid	Medical
	Multiaxis	37, F	Macroad, NF	7th day cortisol and thyroid deficiency, 6th month control only thyroid	
		50, F	Macroad, GH	7th day cortisol and thyroid deficiency, 6th month control only thyroid	
		46, M	Microad, GH	1st day cortisol deficiency, thyroid and ADH deficiency, still present	

Table 2 continued

Category of complication	Type of complication	Patient age, sex	Lesion type	Onset of complication	Treatment
		49, M	Microad, PRL	7th day control cortisol and thyroid deficiency	
	Anterior pituitary dysfunction	42, F	Microad, ACTH	1st day, cortisol deficiency, 6th month normal	
	One axis	22, F	Macroad, PRL	1st day cortisol and still present	
		46, M	Microad, ACTH	7th day cort def., still present	
		63, F	Macroad, ACTH	1st day cort, still present	
		31, F	Macroad, NF	7th day control, cortisol def.	
		18, F	Macroad, ACTH	7th day control, thyroid def.	
		80, F	Macroad, NF	7th day cort def., still present	
	Diabetes insipidus	29 transient	21 macroad	After 2 days, resolved in a week	Medical
			8 microad		
		3 permanent	3 macroad	1st week	
	SIADH	7 patients	6 macroad, 1 microad	1st week	Medical

NF non-functional, *ACTH* adrenocorticotrophic hormone, *GH* growth hormone, *PRL* prolactin, *macroad* macroadenoma, *microad* miroadenoma, *M* male, *RCC* Rathke's cleft cyst, *ELD* External Lumber Drainage

Rhinologic complications

Four (0.6%) patients had postoperative epistaxis. Two of them suffered from epistaxis 8 h after the surgery who required coagulation by ENT colleagues. The other two patients experienced late onset bleeding on the 10th and 15th days of surgery. The former patient had surgery and for the latter patient posterior nasal nasal packing was needed to control bleeding. There were four patients with transient hyposmia in two prolactinoma and two nonfunctioning adenoma cases. Three patients had recovered from hyposmia after 3 months. One patient with giant nonfunctioning adenoma recovered after 6 months. First diagnosis and recovery of the hyposmia were checked with the smell of tobacco. None of the patients developed anosmia.

CSF leakage

In our series during the surgery intraoperative low-flow CSF leak was present in 44 patients. In these patients, CSF leak control and sellar floor reconstruction has been done with a piece of free fat covered by Surgicel® (Ethicon, Somerville, NJ), which is placed into the sellar cavity as to fit well and to compress the defect. This fat graft is supported by an underlayer of fascia lata graft than a piece of gelfoam covered by surgicel is placed as an overlayer to support this fascial graft. Among these patients, external lumbar drainage was placed in 6 patients who had large diaphragm defect. In four patients whose defect is much larger, so balloon catheter was placed at the end of the surgery.

Among the described patients above, eight patients (1.3%) had postoperative CSF leakage in the postoperative 2nd, 5th and 7th days, were reoperated for sellar reconstruction on the same days. In these eight patients, more strict sellar reconstruction was done when compared to our routine intrasellar packing for intraoperative CSF leak and external lumber catheter was installed. A double layer of fascia lata graft was placed in both intradural and epidural space and they are supported by fat tissue wrapped with Surgicel. Lumbar drainage was placed and kept for 5–7 days after the operation. CSF drainage scheme was 100 cc/q8 h (every 8 h) for the first 2 days, 75 cc/q8 h/day for the 3rd–4th days and 50 cc/q8 h/day for the 5th–6th days. On the 6th or 7th day, drainage was stopped to check recurrence of the CSF leakage before withdrawing the catheter. The patients performed well after the reoperation, none of them needed any more operation.

In one patient with nonfunctional macroadenoma, a balloon catheter was placed and kept for 5 days following reconstructive surgery. All patients who had postoperative

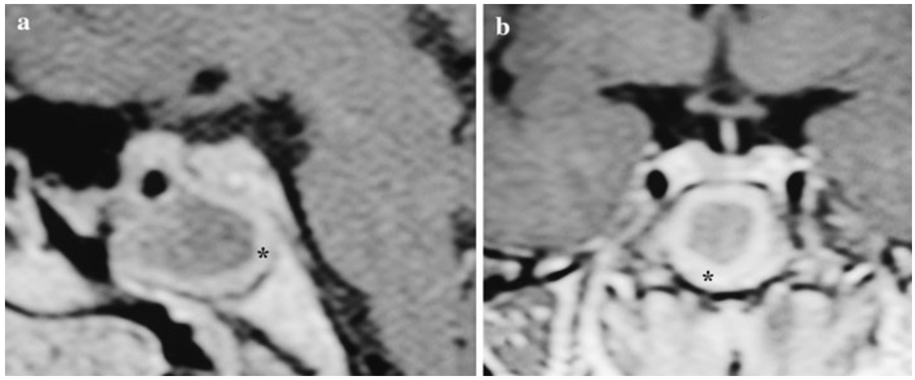

Fig. 1 A 42-year-old female patient with ACTH secreting microadenoma, suffered from headache and fever at 3rd month visit. Her control MRI revealed sphenoid sinusitis which is seen as an enhancement of the sphenoidal wall (**a** sagittal view, **b** coronal view; *asterisk*: sphenoid wall enhancement)

CSF leak, had intraoperative leakage during the first surgery. We did not use any substitute tissue adhesive.

When we perform the extended endonasal endoscopic approaches for intrasellar and/or cavernous expansile adenomas, we use double layer fascial (underlayer and overlayer) graft and lumbar drainage routinely.

Infectious complications

Three patients (0.48%) developed post-operative sinusitis. Two of these cases were macroadenomas and one of them was microadenoma secreting ACTH. The symptoms occurred at 6 months to 1 year after surgery as post-operative headache and fever. A 17-year-old female patient with Cushing syndrome bearing pituitary macroadenoma developed sphenoid sinusitis a year after the operation. She suffered from nasal discharge, frontal fullness and headache. MRI demonstrated the presence of sphenoid sinusitis (Fig. 1a–b), which was cured conservatively with antibiotics within 2 months.

Five patients suffered from meningitis. In all these patients, intraoperative CSF leak has occurred during the endoscopic surgery and routine sellar reconstruction described above has been performed. Two of these patients developed meningitis after a second surgery for postoperative CSF leak. One of these patients (56-year-old, male) with PRL-secreting macroadenoma has experienced postoperative CSF leak 2 days after the surgery. The patient was reoperated for CSF leak, and external lumbar drainage was placed on the same day and kept for 5 days after the surgery. He developed headache, neck stiffness and fever on the 5th day of the reconstruction operation. The other patient was a 34-year-old female with GH secreting macroadenoma. She was reoperated for postoperative CSF leak on the second day of surgery with lumbar drainage. She also suffered from headache and fever on the 5th day of the surgery and diagnosed as meningitis. Another patient with nonfunctional macroadenoma suffered from the same symptoms a week after the endoscopic pituitary adenoma surgery. The remaining two patients had neck stiffness and headache with fever 2 weeks after the pituitary surgery. One of these patients with PRL-secreting macroadenoma had intraoperative CSF leak and was treated with balloon catheter. This catheter was kept for 7 days. All of these five patients were treated with appropriate parenteral antibiotics according to the CSF culture results; they recovered completely within 3 weeks.

Vascular complications

There was only one patient with internal carotid artery aneurysm rupture which has been previously reported in literature [8]. A 41-year-old female patient with ACTH-secreting macroadenoma underwent microscopic transsphenoidal surgery without any complications. Six years later, the patient attended to the clinic with Cushingoid appearance. MRI revealed invasive macroadenoma encircling right carotid artery. A secondary endoscopic transsphenoidal surgery was performed. During the bony removal of the sellar floor, massive arterial hemorrhage has occurred. Patient was referred to endovascular unit under general anesthesia and cerebral angiography revealed a cavernous ICA aneurysm. It was treated by endovascular stent-graft placement, and the injury left no neurological deficit in the follow-up period.

Endocrine complications

Twelve patients experienced anterior pituitary dysfunction and five of them had multiaxis deficiency. A 46-year-old male patient with GH-secreting microadenoma suffered from panhypopituitarism a day after the surgery. The other four patients two of them with microadenoma secreting ACTH, PRL and one non-functional, one GH secreting macroadenomas revealed thyroid and cortisol deficiency 7 days after the surgery. At the 6th month visit, serum cortisol levels have been normalized and they required only thyroid replacement therapy. Remaining seven patients experienced one axis anterior pituitary dysfunction on the first and 7th days after the surgery respectively. Serum cortisol levels were normal on the 6th month visit in two patients, but the other patient required steroid replacement.

Thirty two patients presented with diabetes insipidus after surgery. The course was temporary in twenty nine patients with spontaneous resolution in 48 h, whereas in three patients it persisted and required vasopressin therapy.

Syndrome of inappropriate ADH (SIADH) was present in seven patients, and one of these patients required prolonged treatment (water restriction) for 2 months. Four patient was treated water restriction, the other three was treated with water restriction plus sodium replacement. In case of prolonged SIADH more than a week, meningitis takes into a consideration.

Discussion

The introduction of endoscope to neurosurgical operations has become one of the most remarkable advances for the treatment of midline supra and infratentorial lesions [9]. In last decades, endoscopic approach to sellar lesions has become the most widely used and accepted procedure particularly for pituitary adenomas [1, 10]. There are many advantages of the use of endoscope in pituitary surgery such as close-up view of the anatomy, wider surgical site visualization and variable working angle and less complications within the nose, avoiding the use of packing.

In this report, we present the surgical complications of 570 pituitary adenomas cases that had undergone only endoscopic surgery. To our knowledge, this series has the largest number of cases in literature as being pure pituitary adenomas. Majority of our cases are macroadenomas, predominantly GH secreting adenomas (Table 1).

We have also excluded Rathke's cleft cysts and craniopharengiomas. The complication rate in our series in 624 operations is 12.1%, and our mortality rate is 0%. Previously published endoscopic series reports complication rates ranging from 10 to 26.3% and surgery-related mortality rate has been reported as zero to 0.68% (Table 3) [10–25].

Our series seem to have lower complication rates than other series cited above. This possibly depends on many factors; the most important ones are the following: First, the steep learning curves in endoscopic surgery: we have worked in close contact with ear nose and throat surgeons (ENT) in all steps of the surgery especially in the nasosphenoidal stage. Every case must be handled together with close collaboration before, during and after endoscopic surgery with ENT colleagues especially within 100 cases. After that time this collaboration must continue for

Table 3 Complication rates from major endoscopic pituitary series in literature

	Rhinologic complications		CSF leak (%)	Infectious complications		Vascular injury	Endocrine complications			CNS complications		Death
	Epistaxis (%)	Hyposmia		Sinusitis	Meningitis		Anterior pituitary deficiency	DI (%)	SIADH	Intracerebral hematoma	Ophthalmopathy	
Jho [5]			6	1.2%	1.2%		11%	3				
Cappabianca et al. [10]	1.3		2	2%	0.6%	0.6%	3.42%	13.6		0.68%	0.68%	0.68%
Divitiis et al. [12]	1.7		2.1	2.1%	0.4%	0.4%	14.5%	3.1		1.2%	0.4%	0.4%
Kabil et al. [17]	1		2		None		3%	1				None
Frank et al. [11]	0.7		1.2	None	0.4%	None	3.1%	1.4	7.6%	0.4%	None	None
Rudnick et al. [14]	0.4		0.9		0.4%		3.6%					
Dehdashti et al. [4]	1		3		1%		3%	1		0.5%	None	None
Charalampaki et al. [31]	1.4	2.2%	3.7	1.4%		0.7%	4.4%	5.9				0.7%
Gondim et al. [32]	1.9	None	2.6	1.6%	0.6%	1%	11.6%	6.3	None	0.6%	0.3%	1%
Zada et al. [37]	3	None	1	None	None	None	None	3	2%	None	None	None
Zhou et al. [13]	1.6		0.5		0.8%			3.7			0.6%	None
Present study	0.6	0.6%	1.2	0.4%	0.7%	0.16%	1.92%	4.6	1.1%	None	None	None

preoperative investigation and discussion of cases with ENT. Especially extended, revision or complicated cases must be operated together. This will help to reduce the rate of complications.

The second important factor is the preoperative planning with paranasal CT and pituitary MRI. The sphenoid sinus anatomy has lots of variations; one can be lost easily without a proper preoperative planning [26]. Sphenoid sinus anatomy is specific for each individual like as is the case with finger print. One should thoroughly review the relationship between intrasphenoidal septa and carotid protuberance. By this way, adequate sellar opening will be achieved and the risk of harm to carotid protuberance and optic protuberance will be prevented. Accordingly, we review the bony structures in the sphenoid sinus in detail with paranasal CT especially in coronal and sagittal sections before the operation. The sphenoid septum is localized to label the midline and concomitant various septi are also marked on the CT. Next, the sellar floor is analyzed whether it is eroded or thinned. In some cases, paranasal CT scans do not indicate the exact bony structure of the sellar floor [27]. In all planes of pituitary MRI and paranasal sinuses CT we measure the intercarotid distance, sellar floor width, anterior sellar wall height, sellar depth, and tumor depth, height and suprasellar extensions. These data are recorded carefully and rechecked intraoperatively to open the sella securely. During the endoscopic nasosphenoidal stage we don't need to use fluoroscopy to determine the sellar localization.

The third but not the least important factor is to take precautions to overcome the disadvantage of the two dimensional view of the endoscope which is the most important limitation of the endoscope. Surgeon must look at the flat TV screen to see the surgical field in which the inferior depth perception is missing [5, 10]. To overcome this difficulty we use the preoperative measurement data in paranasal CT and pituitary MRI as described above. To sense these measurement data in stages of surgery, especially sellar floor opening, anterior sellar wall height etc.; we have modified and redesigned some special instruments and reform them to become scaled 'three dimensional' under the endoscopic field: a dissector with standard width of 10 mm marked in mm on it to see on the endoscope screen, 10 mm marked tumor-aspirators which have the opening on the tip and dorsum of the instrument. These markings are very useful to understand the depth of tumor and helps to overcome the disadvantages of two dimensional view.

We have discussed the complication rates of endoscopic surgery in pituitary adenomas presented in literature. We have collected the series of pituitary adenoma cases, not the endoscopic surgery of other sellar or parasellar surgeries, and compared our complication rates with a subgroup of experienced neurosurgeons that had performed more than 100 endoscopic pituitary surgeries (Table 3).

Advantages of the endoscopic surgery

Currently, endoscopic surgery is the most widely used technique for pituitary adenomas due to its advantages such as: rapidity, good tolerance, effectiveness and low complication rate [28]. The average time of the surgical procedure is 40 min (30–50 min), which is compatible with the literature. Another advantage of this technique is the comfort of the patient in postoperative period. Postoperative pain is generally absent or minimal; therefore, analgesic therapy is not routinely provided. We generally do not use nasal packing after the surgery, only two patients required nasal packing; one patient with postoperative epistaxis and one patient after resurgery of rhinorhea. In the standard procedure, the time of postoperative recovery is very short and it is possible to discharge the patient on the day or the day after surgery if the endocrinological complications absent.

Nasal complications

Nasal or rhinological complications are discussed in two groups in the present report: nasal vascular complications and hyposmia-anosmia. Nasal vascular complications due to bleeding of posterior septal branch of sphenopalatine artery are described in 0.7–7% of cases treated [11–14, 17–25, 29, 30]. In our series, we had 4 cases of nasal bleeding (0.6%); three of them were reoperated, and in one case with late onset bleeding, nasal tamponade was adequate for the treatment. All these four cases except for one are macroadenomas and late onset epistaxis was seen. This is most probably due to extended approach for resection of large adenomas. Taking into account that the sphenopalatine artery usually arises near the superior meatus or between the superior and middle meatus, it is important to be cautious while performing mucosal dissection in this region. Therefore, we recommend multiple coagulation of the artery during the operation and to always recheck the anatomical origin of the artery at the end of the surgery even though there is no bleeding at the site (Fig. 2). It is a known fact that during early postoperative hours and days, when the blood pressure increases to the normal levels, rebleeding can occur from previously coagulated and/or noncoagulated vessels. If delayed bleeding occurs, management options include nasal packing and/or cauterization [10, 14, 29].

Hyposmia is another nasal complication and was seen in 4 patients in our series. Charalampaki et al. [31] had presented 16 patients with hyposmia and 3 with anosmia out of 200 pituitary adenoma operated via endoscope. Gondim

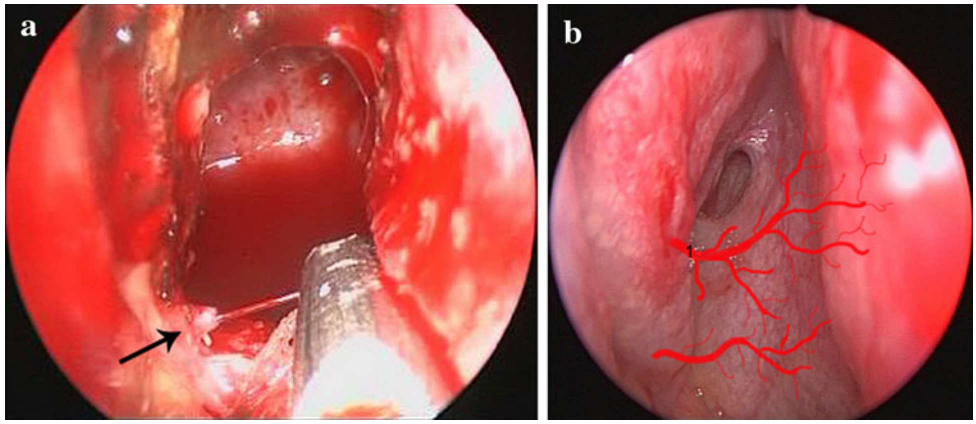

Fig. 2 **a** Endoscopic visualization and **b** anatomical scheme of the posterior septal branch (1) of the sphenopalatine artery, arrow head is pointing out the same bleeding artery (1)

et al. [32] did not observe any hyposmia or anosmia in 301 patients. Although hyposmia is hard to be recognized by the patient, it is an unpleasant complication. To overcome this complication, surgeon should avoid excessive coagulation of the lateral nasal wall especially superior turbinate and ½ superior part of the middle turbinate which included the olfactory nerve fibers (Fig. 4).

It should be emphasized that this complication rate is still lower than the microscopic transsphenoidal technique [33–35]. There are two major factors in less nasal complications: firstly, the active and close collaboration with an ENT surgeon. Secondly endoscopic technique 'skips' the nasal phase including septal incision and starts in the sphenoethmoidal recess [11, 36]; therefore the total time of the surgery is decreased and nasal mucosa is kept vital.

It is known that the origin of the posterior septal branch of sphenopalatine artery is present on the posterior tip of the middle turbinate (Fig. 3, # 5–6) and branches of the olfactory nerve innervate the whole superior turbinate and superior half of the middle turbinate (Fig. 4).

Middle turbinectomy performed in the nasal stage of endoscopic surgery may cause damage to posterior septal branch of the sphenopalatine artery and epistaxis may occur. Since nasal turbinates are well vascularized structures, during middle turbinectomy bipolar coagulation is needed and this may damage the branches of olfactory nerve that innervates especially the superior half of the middle turbinate causing hyposmia. Therefore, different from other endoscopic surgical techniques, we only lateralize the middle turbinate and do not perform middle turbinectomy except from extended approaches. In extended surgeries, mostly we only excise the inferior half of the middle turbinate to protect the olfactory nerve branches.

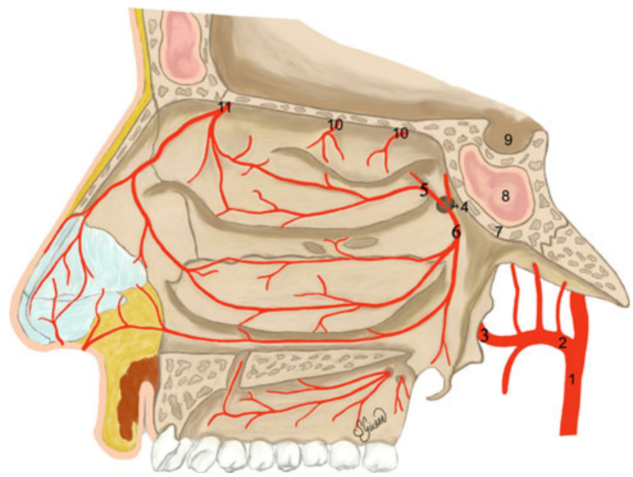

Fig. 3 Anatomical scheme of nasal cavity, origin of the posterior septal branch of sphenopalatine artery, lateral wall. 1: external carotid artery; 2: maxillar artery; 3: sphenopalatine artery; 4: sphenopalatine foramen; 5–6: posterior lateral nasal branches of sphenopalatine artery; 7: body of sphenoid bone; 8: sphenoidal sinüs; 9: hypophyseal fossa; 10: lateral nasal branches of posterior ethmoidal artery; 11: anterior lateral branch of anterior ethmoidal artery

CSF leakage

The second step in endoscopic transsphenoidal approach is the anterior sphenoidotomy. Then sphenoid sinus is visualized in great extent with different angle endoscopes. Sellar floor is excised with Kerrison rongeur or drilled to get access to the dura and the adenoma. The most frequent complication at this stage of the procedure is the intraoperative CSF leak. Indeed, intraoperative CSF leak has become a frustrating outcome of this type of surgery because of the close relationship of the pituitary to the diaphragm sella and subarachnoid space. Intraoperative CSF leakage can occur during or after the tumor removal. This can occur during the exploration of cavernous sinus and diaphragmatic recesses and usually stops spontaneously. CSF leakage frequency and persistence increase in patients who had previous surgery, or in patients with suprasellar extension of the macroadenoma and during extended endoscopic approaches. It is crucial to identify

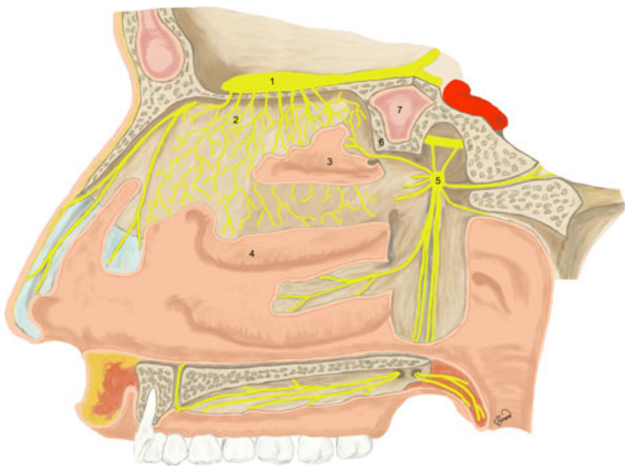

Fig. 4 Anatomical scheme of nasal cavity, innervation area of olfactory nerve, superior and middle turbinate. 1: olfactory bulb; 2: olfactory nerves; 3: superior nasal turbinate; 4: middle nasal turbinate; 5: pterygopalatine ganglion and branches; 6: body of sphenoid bone; 7: sphenoidal sinüs

the tear in the diaphragm and/or arachnoid membrane during the surgery and seal it immediately.

If the tumor expands the diaphragm or invades it, intraoperative CSF leakage can occur during the surgery. There is no radiologic sign or technique yet to show the prior diaphragm violation by the tumor. On coronal T2 W high resolution pituitary MR images, presence of high intensity just beneath the sellar diaphragm or subtle disruption of diaphragm continuity might alert the neurosurgeon preoperatively about a probable invasion.

In our series, 44 patients presented with some degree of intraoperative CSF leak during surgery. Macroadenomas are more commonly accompanied with CSF leak and we have observed that this occurs as dripping from the epidural space. Such leaks happen because usually, in macroadenomas, the surgeon works close to the diaphargma sella and the subarachnoid space. In six (0.9%) patients with macroadenomas, although reconstruction of sellar floor (as described above) was attempted, a postoperative CSF leak was observed and it was treated by surgery. Intra and extradural fascia was placed with fat graft support as explained above. Unfortunately, two patients suffered from meningitis a week after the reoperation. Previously published rates of postoperative CSF leaks after endoscopic approaches range between 0.5 and 6.0% [10–13, 16–25, 37], and these data are compatible with our study, postoperative CSF leaks occurred in our 8 patients (1.3%). Besides, our complication rate is one of the best scores presented in literature, despite the fact that the number of macroadenoma cases is higher. In our series, all of the eight patients submitted to resection of macroadenomas presented postoperative CSF leaks, which is similar with the literature. CSF leak risk is higher in macroadenomas than microadenomas [11, 33].

Two important precautions should be taken to reduce the risk of postoperative CSF leak during surgery. One is to keep the diaphragm intact. In endocrine active tumors, our aim is the encapsular removal of the adenoma and therefore a defect in diaphragm may occur. Also in macroadenomas with a diaphragm, arachnoid of suprasellar cistern may be injured. In these cases, a strict reconstruction with double layer fascia graft as previously described is performed. As a second precaution, we always perform Valsalva manoeuvre at the end of the sellar reconstruction to check if there is any CSF leak during surgery. If there is not any CSF leak at end of the reconstruction in the primary surgery, external lumbar catheter will not be necessary. Another important issue is that CSF leak should be treated intraoperatively as soon as it is detected. These are two important and vital steps that we perform in cases of intraoperative CSF leak to prevent postoperative CSF leaks.

Use of tissue adhesive is still debatable in CSF leaks repair. We prefer not to use tissue adhesives in our cases as we believe that it will not present any advantage in the closure of the leaks. We are able to see this data from our series as we have 5 cases in the first 300, 3 cases in the last 300 of our patients. So we believe that precise and diligent closure technique is the most important parameter in handling such cases. The cost, preparation time, foreign body reactions are among the drawbacks that outweigh the advantages of using fibrin sealant or any other tissue adhesives.

Infectious complications

Sphenoid sinus plays an important role as being a corridor in between nostril and sella, therefore the anatomy has to be analyzed carefully. Mucoceles, fracture of the sphenoidal bone, injury of the optic nerves, and postoperative infection of the sinus are reported complications in literature related to the sphenoidal sinus [10, 14, 33, 34]. We have seen only one mucoselle case, and three patients with sinusitis which were effectively treated with antibiotics. In the literature, the rate of such complication varies between 0.5 and 5.7% [5, 7, 10–12, 22, 31, 32]. To reduce the rate of this complication, the use of artificial material for postoperative packing of the sinus must be advocated [31, 32].

Meningitis is another dangerous complication which prolongs the hospital stay requiring high doses of parenteral antibiotics. In our series, we had seen five cases of meningitis that had intraoperative CSF leak and reconstruction with fat and fascia graft was done during surgery for adenoma excision. Only two of them suffered from postoperative CSF leak and were reoperated for reconstructive surgery. In literature, the rate of meningitis has been presented as 0.4–2% [10–13, 16–25]. We did not observe meningitis in the last 200 cases and there are three reasons for that: First of all, the surgeon becomes more experienced as the number of cases increases. Second reason is that the antibiotic prophylaxis protocol has been changed within time. For the first 300 patients, sulbactam-ampiciline was given in induction period of the anesthesia. However, for the last 200 patients, in addition to sulbactam-ampiciline, first generation cephalosporine was also given in induction. If the patient is reoperated for rhinorhea, the doses are doubled. The third reason is that for the last 200 patients at the end of the surgery, the whole nasal cavity was washed with antiseptic solutions after the closure of the sellar floor. Overall, in patients with preoperative CSF leaks, we always recheck the reconstruction with ENT surgeon. By this way, a major decrease in our complication rates for meningitis and postoperative CSF leakage has been observed.

Endocrine complications

Complications related to glandular injury are markedly transient in the beginning. The temporary form of anterior pituitary dysfunction might be secondary even to simple manipulation of the pituitary gland and/or skull base structures [32]. Temporary DI is thought to be caused by temporary dysfunction of vasopressin-producing neurons as a result of surgical trauma [32]. If a decrease in hormone profile is seen or an increase in serum Na level is detected, patient should be followed closely. This transient hormone level fall frequently recovers, and patient is cured within 6 months time. Therefore, we have only analyzed and compared permanent pituitary dysfunction. Postoperative anterior pituitary dysfunction is reported to occur in less than 1% of the patients submitted to endoscopic pituitary surgery according to the review of Tabaee et al. [28] in a meta-analysis. In the transsphenoidal microscopic surgery published by Ciric et al. [30], this rate is given as 7.2%, which is relatively high when compared to recent studies of endoscopic surgery. There are several reasons for anterior pituitary deficiency present after the surgery which are preventable. One reason is the excessive use of the tumor aspirator in the sellar cavity. Second reason is inappropriate manipulation and resection of the normal pituitary gland neighboring the adenoma tissue. Lastly, bipolar coagulation in sellar cavity after the resection of the adenoma tissue may cause excessive heat damage to pituitary gland. Permanent diabetes insipidus is present in lower rates: 1–5% in endoscopic series [10–13, 17–20] and 0.9–7.6% [23] in microsurgery series. In this series it is in 0.4%, and is lower than endoscopy and microsurgery reports (Table 3). In apoplectic adenoma cases, sudden evacuation of the tumor cavity may cause displacement of the stalk and this may cause early onset hyponatremia. To overcome these endocrine problems, as the last step of the surgery; neutral and 30 degrees endoscope is inserted into the surgical cavity and neuroendocrine structures, normal pituitary gland and stalk are visualized and illuminated in close contact. Bipolar coagulation must be avoided in close proximity of the stalk to prevent it from thermal injury. To restore hemostasis in vicinity of the stalk, the neurosurgeon must prefer Surgicel instead of coagulation.

Vascular complications

One of the scariest complications in endoscopic pituitary surgery is the vascular injury-carotid artery damage. Since the endoscopic view is wider than the microscopic view, surgeon may see and reach to parasellar anatomical structures more easily. This may increase the risk of arterial damage and the result may be life threatening. In our series, the complication rate is 0.16% which is the lowest rate amongst other reports (0.2–1%) [9, 21, 24, 34]. As the endoscopic view is two dimensional and the surgeon's eye is on the TV screen, special technical movements are required to handle an intraoperative ICA injury. In our previous report we have described a maneuver: moving the endoscopic back to the level of the middle turbinate to pack the sella or sphenoid sinus with cottonoids or homeostatic agents [7]. Since any damage to carotid artery has devastating results; in the case of a major and uncontrolled bleeding, the surgeon should pause the surgery and, if possible, conventional angiography should be performed immediately.

Other very rare complications at the parasellar stage of the surgery are reported as coma, intracerebral hemorrhage and cranial nerve palsies which have not been observed in our present series. We did not also observe any mortality in our series, and in major series it has been reported as 0–1% [21].

Conclusion

In this report, the complication rates are comparable with the literature, and favorably the unexpected complications such as death, cranial nerve palsies and intracerebral hemorrhage did not occur. Although the majority of the cases are macroadenomas and GH secreting adenomas, a low complication rate has been observed contrary to the expectation. Overall the low complication rate in this present series depends on several factors: (1) well-learned sphenoidal sinus and sellar anatomy with the help of ENT surgeon especially in the learning curve period, (2) detailed preoperative planning with the paranasal sinus CT and MRI scans with neuroradiological consultation (3) using newly invented instruments to overcome the difficulties brought by two dimensional view of the endoscope (4) the sufficient experience of the neurosurgeon.

The complication rates observed in our study suggests that the endoscopic pituitary surgery is at least as safe as microscopic transphenoidal surgery. However, the decision as to which approach should be chosen must be based on the preference, skill and experience of the individual neurosurgeon.

To achieve better outcome, well-coordinated teamwork between the endocrinologist and other colleagues, such as neuroradiologist, an otorhinolaryngologist, a neuropathologist, a neuroanatomist who specializes in endoscopic surgery, is considered a prerequisite of success in pituitary surgery.

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