REVIEW

Anesthesia for transsphenoidal pituitary surgery

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Purpose of review
Pituitary tumors are commonly encountered in clinical practice. Patients with functioning adenomas frequently present with symptoms of hormone excess, whereas those with nonfunctioning adenomas often present later and have symptoms resulting from mass effect of the tumor. This article examines recent advancements in the preoperative assessment and anesthetic management of patients undergoing transsphenoidal pituitary surgery.

Recent findings
Endoscopic guidance has improved tumor visualization while minimizing the risk of nasal and dental complications and septal perforation. Computer-assisted navigation and intraoperative MRI has further improved surgical outcomes. Airway management may be particularly challenging in patients with acromegaly or Cushing's disease. Both intravenous and volatile agents can be used for anesthetic maintenance. Although pituitary surgery can be intensely stimulating and associated with intraoperative hypertension, most patients require little postoperative analgesia. Postoperative diabetes insipidus is common after pituitary surgery and is typically self-limited. Some patients will require treatment with desmopressin and it is important to avoid 'overshoot' iatrogenic syndrome of inappropriate antidiuretic hormone SIADH and hyponatremia in these patients.

Conclusion
Anesthetic management for pituitary surgery requires thorough preanesthetic assessment of hormonal function and intraoperative management to facilitate surgical exposure while providing hemodynamic stability and allowing for rapid emergence.

Keywords
acromegaly, Cushing's disease, diabetes insipidus, pituitary surgery, transsphenoidal surgery

INTRODUCTION

Pituitary tumors are common in clinical practice, with radiologic and autopsy studies estimating that as many as one in seven people have a pituitary tumor; however, only one in 1000 are clinically symptomatic [1▪]. Treatment goals in the management of patients with pituitary tumors include suppression of hormone hypersecretion, reduction of tumor mass, preservation of normal pituitary function, prevention of long-term effects from excess hormone secretion, and prevention of tumor recurrence. Although medical therapy may suppress hyperfunctioning tumors, surgical resection has become the mainstay therapy with transsphenoidal pituitary surgery being the most common approach used today. Transsphenoidal pituitary surgery presents unique challenges for the neuroanesthesiologist in the preoperative, intraoperative, and postoperative management of patients undergoing tumor resection. Advances and challenges in the anesthetic management of these patients are presented here.

PREOPERATIVE ASSESSMENT

Pituitary adenomas can be classified by size at the time of diagnosis as either microadenomas (<10 mm) or macroadenomas (>10 mm), and as either functioning or nonfunctioning, depending on whether they are hormone-secreting. Patients with functioning adenomas frequently present with symptoms of hormone excess, whereas those with nonfunctioning adenomas often present later and have symptoms resulting from mass effect of the tumor, such as headache, visual loss due to compression of the optic chiasm, or hypopituitarism due to compression of the anterior pituitary. Patients may also be asymptomatic and report for surgery

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Curr Opin Anesthesiol 2013, 26:549–554

DOI:10.1097/01.aco.0000432521.01339.ab

KEY POINTS

- Preanesthetic assessment for transsphenoidal pituitary surgery includes radiologic studies and evaluation of hormone function.
- Intravenous and volatile agents have been used successfully intraoperatively to provide hemodynamic stability and rapid emergence.
- Advances in computer-assisted navigation and intraoperative MRI have improved surgical outcomes.

after the tumor found incidentally during intracranial imaging. Rarely, pituitary tumors cause elevated intracranial pressure because of their size or obstruction of the third ventricle, which may cause headache, nausea, vomiting, and papilledema.

Preoperative management for transsphenoidal pituitary surgery begins with a thorough preanesthetic assessment, including laboratory and radiologic evaluation. Laboratory work-up includes a complete blood cell count to evaluate for anemia, metabolic panel to evaluate for electrolyte abnormalities (hyponatremia in diabetes insipidus, hypercalcemia in patients with multiple endocrine neoplasia, type I, and hyperglycemia in patients with Cushing's disease), as well as a thorough endocrine evaluation. At a minimum, an endocrine assessment includes measurement of serum levels of prolactin, thyroid-stimulating hormone, free thyroxine, luteinizing hormone, follicle-stimulating hormone, testosterone (in men), adrenocorticotropic hormone, cortisol, and insulin-like growth factor-1, a surrogate marker for growth hormone in acromegaly [2,3]. Preoperative MRI or, less frequently, computed tomography aids in diagnosis and differentiation of pituitary adenomas from other disorders, such as other tumors, autoimmune conditions, or vascular lesions, and for surgical planning [1▪].

Several tumor types produce unique effects that merit particular attention in the preoperative period. Patients with acromegaly are at increased risk for cardiovascular disease including hypertension, accelerated coronary artery disease, cardiomyopathy, congestive heart failure, and arrhythmias due to the effects of excess growth hormone secretion [4▪,5]. Airway management may be challenging due to hypertrophy of the soft tissues of the mouth, nose, tongue, soft palate, epiglottis and aryepiglottic folds, and prognathism due to bony proliferation of the mandible and may present difficulty for airway management and intubation [6]. Up to 70% of acromegalic patients may have sleep apnea, which places them at increased risk for perioperative airway compromise [7,8].

Cushing's disease, due to excess production of adrenocorticotropic hormone, is associated with increased risk of cardiovascular disease, hypertension, and ischemic heart disease, which is a major cause of perioperative mortality [6,9,10]. Hypertension should be medically managed and patients should be assessed for cardiac risk factors preoperatively. Diabetes mellitus is also common in patient's with Cushing's disease, and blood glucose should be controlled pre and intraoperatively. Immunosuppression, fragile skin, and easy bruising may lead to poor wound healing, hemorrhage, and difficult intravenous cannulation. Airway management may be challenging because of truncal obesity or gastroesophageal reflux. In addition, Cushing's disease is associated with myopathy of proximal muscle groups. Although patients are not more susceptible to neuromuscular blockade due to myopathy, this may impair postoperative ventilation.

Nonfunctioning tumors frequently present later with symptoms of mass effect and may cause panhypopituitarism due to compression of the anterior pituitary. Thyroid hormone and glucocorticoid must be replaced preoperatively and patients are susceptible to water intoxication and hypoglycemia. They may also be sensitive to central nervous system depressants, including general anesthetics and may require blood pressure support intraoperatively.

PERIOPERATIVE MANAGEMENT

Several comprehensive reviews of anesthesia for transsphenoidal pituitary surgery have been previously published [2,6,11]. Here, we review the intraoperative anesthetic goals and highlight advances in surgical technique and anesthetic management. Anesthetic goals for transsphenoidal pituitary surgery include optimizing cerebral oxygenation, maintaining hemodynamic stability, providing conditions to facilitate surgical exposure, preventing and managing intraoperative complications, and allowing for rapid smooth emergence.

SURGICAL APPROACH AND OPTIMIZING THE SURGICAL FIELD

The direct endonasal approach is favored over the sublabial transseptal approach by most surgeons because it requires less dissection and removal of bone; however, a sublabial approach may be necessary in children or in adults with very large tumors. Endoscopic guidance has further improved tumor visualization while minimizing the risk of nasal and dental complications and septal perforation [1▪]. One institution compared traditional microsurgery versus endoscopic endonasal resection in a series of 60 consecutive patients and found improved

remission rate in endoscopically resected tumors (78 versus 43%) but increased incidence of cerebrospinal fluid (CSF) leak [12].

A recent meta-analysis compared short-term outcomes of endoscopic versus microscopic pituitary surgery. It reviewed 38 studies and found that endoscopic surgery was associated with a slightly higher risk of vascular complications; however, there was no difference in incidence of CSF leak, meningitis, visual complications, diabetes insipidus, hypopituitarism, or cranial nerve injury. The endoscopic endonasal approach has also been used in the treatment of skull-based tumors, with success in achieving total tumor removal of 75% in one case series of 40 patients [13].

Computer-assisted navigation and guidance has further improved this technique. MRI images with facial makers used to identify key anatomic features are obtained prior to surgery. Intraoperative co registration of the facial markers with the MRI images aids in directing the angle of approach and ensuring thorough resection of the tumor during surgery.

Several groups have investigated the efficacy of low-field intraoperative MRI in assessing the extent of surgical resection and minimizing the risk of tumor remnants. In one small series of 18 patients, intraoperative MRI showed residual tumor in as many as 50% of patients [14]. A larger series of 229 patients, intraoperative MRI revealed remnant tumor in four of the 184 who underwent planned total tumor resection (false-negative rate of 2.2%) and led to further tumor resection in a total of 47 patients (20.5%) [15▪].

AIRWAY MANAGEMENT

As discussed previously, airway management may be particularly challenging in patients with acromegaly or Cushing's disease. Schmitt *et al.* [16] showed in a prospective study of 128 acromegalic patients that 20% of patients assessed as a Mallampati class 1 or 2 preoperatively were found to be difficult to intubate. Nemergut and Zuo [17] conducted a retrospective review of 121 acromegalic patients and found 9.1% of patients initially approached with direct laryngoscopy were difficult to intubate, necessitating a secondary technique. Similar to the findings of Schmitt *et al.* [16], Nemergut and Zuo [17] also discovered that about 50% of 'difficult-to-intubate patients' had been initially assessed as Mallampati class 1 or 2. These data suggest that acromegaly is associated with a high incidence of unanticipated difficult intubation, despite a reassuring preoperative airway examination. Thus, the prudent practitioner is advised to have a low threshold for the use of 'awake' techniques and should always have secondary techniques readily available. There are no data available to specifically recommend one secondary technique (i.e., video laryngoscopy) over another. An oral airway may be helpful if bag-mask ventilation is difficult.

INDUCTION AND MAINTENANCE OF ANESTHESIA

There is a broad range of acceptable anesthetics for pituitary surgery and various agents can be used for the induction and maintenance of anesthesia. Short-acting agents are favored to facilitate rapid recovery and permit neurologic examination after surgery. Remifentanil (0.25–2 μg/kg/min) in combination with propofol or a volatile agent can be used as it provides hemodynamic stability and allows for a more rapid recovery compared with volatile agents alone [18–20]. In a prospective, randomized, single-blinded study, Cafiero *et al.* [20] compared a propofol target controlled infusion system and remifentanil to sevoflurane and remifentanil for maintenance of anesthesia. No statistically significant differences between the two groups with regard to the hemodynamic changes were observed. Recovery times were considerably shorter after remifentanil–sevoflurane in comparison with remifentanil–propofol target controlled infusion system group [20].

Both intravenous and volatile agents can be used for anesthetic maintenance. In a study of 90 patients undergoing transsphenoidal pituitary surgery, patients were randomized to received propofol, isoflurane, or sevoflurane maintenance with anesthetic level titrated to a bispectral index score between 40 and 60 [21]. Time to emergence and tracheal extubation were comparable in the propofol and sevoflurane groups. Postoperative cognitive function, as measured by modified Aldrete score, at 5 and 10 min was better in the patients receiving propofol.

Chowdhury *et al.* [22] investigated 26 patients undergoing pituitary surgery and compared the effects of propofol versus sevoflurane on thermoregulation in patients undergoing pituitary surgery The aim was to determine which agent better preserved thermoregulation, as both general anesthesia and pituitary tumors are known to impair thermoregulation and predispose patients to hypothermia. The authors found no difference in the time for the temperature to fall 1°C or in the time to return to baseline in either group, suggesting equivalence.

PREPARATION OF THE SURGICAL FIELD

Following induction of anesthesia, local anesthetic containing epinephrine is injected into the nasal mucosa to prepare the nares for endoscopic surgery.

Epinephrine may cause hypertension in patients with Cushing's disease or acromegaly, which maybe require treatment with β-blockers, or vasodilators such as sodium nitroprusside or nitroglycerin [23,24].

Several techniques may be employed to improve surgical conditions. Controlled hypercapnia can temporarily increase intracranial pressure and enhance exposure of the tumor by pushing it inferiorly into the sella [25]. A target $PaCO_2$ of 40–45 mmHg is generally used. For large tumors, a lumbar intrathecal catheter (or 'lumbar drain') may be placed. The injection of isotonic saline or drainage of CSF can move the pituitary up and down in the surgical field, facilitating surgical exposure. For patients with large tumors and suprasellar extension, air may be injected in to the subarachnoid space, which 'bubbles' up and pushes a large tumor down. This also creates a pneumocephalogram that can outline the tumor during intraoperative fluoroscopy. Finally, the lumbar intrathecal catheter may be left in place following surgery if a CSF leak is present.

INTRAOPERATIVE MONITORS

Routine monitors are used during induction and maintenance of anesthesia, including electrocardiogram, pulse oximetry, temperature, and noninvasive blood pressure monitoring. Patients with acromegaly or Cushing's disease who present with cardiac disease may require invasive monitoring. If invasive monitoring is indicated, it is important to remember that acromegalic patients with carpal tunnel syndrome may suffer from ulnar artery compression. These patients are 'radial dominant' and thus radial artery catheterization for invasive arterial monitoring may have higher associated risks [2].

Surgery is typically performed with a patient in the semiseated position, such that the head and torso are elevated above level of the heart. This helps to minimize bleeding, optimize drainage but may place the patient at increased risk for venous air embolism (VAE). A multiorifice catheter may be placed at the junction of the superior vena cava and the right atrium to allow for aspiration of air if a VAE is detected intraoperatively; however, most centers do not routinely do this. The incidence of a VAE is less than 10% if the head-up angle is less than 40° – and almost all of these are asymptomatic [2]. Thus, a simple strategy to reduce the incidence of clinically significant VAE is to keep the head-up angle less than 40°.

POSTOPERATIVE PAIN

Although pituitary surgery can be intensely stimulating and associated with intraoperative hypertension, most patients require little postoperative analgesia. A retrospective study of nearly 900 patients found that the median postoperative opioid requirements was less than 4 mg of morphine [26]. The pituitary has the highest concentration of endogenous opioids in the central nervous system and it is possible that its manipulation during surgery releases these endogenous opioids, diminishing the need for postoperative opioid analgesia. Increased need for postoperative opioid analgesics was associated with the later diagnosis of diabetes insipidus and decreased consumption was associated with the intraoperative use of a lumbar intrathecal catheter [26].

As a neurologic assessment, including visual field testing, is absolutely critical in the early postoperative period, it is important to not overtreat intraoperative hypertension with opioids, which may delay emergence from anesthesia. The perioperative use of acetaminophen (or paracetamol) is opioid-sparing and should not impair postoperative neurologic assessment. The use of bilateral infraorbital nerve blocks has been shown to reduce postoperative pain in patients undergoing nasal surgery and be useful in this setting [27]. Ketorolac has been successfully used for this indication [26]; however, it carries a theoretically increased risk of bleeding, even though this has been demonstrated [28].

DISORDERS OF WATER BALANCE

Although postoperative diabetes insipidus is common after pituitary surgery, it is important to eliminate other causes of polyuria such as overzealous intraoperative fluid administration or osmotic diuresis (secondary to mannitol administration or hyperglycemia). Nevertheless, in patients with a pituitary adenoma, the incidence of transient diabetes insipidus is as high as 16.6% [29]. Antidiuretic hormone is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, packaged, and transported down the hypothalamoneurohypophyseal tract to the posterior pituitary. In the posterior pituitary, it undergoes final maturation and is stored for future release. Diabetes insipidus can result from damage anywhere along this pathway.

Treatment of diabetes insipidus requires replacing fluid losses, initially with isotonic fluids for resuscitation, and later with hypotonic fluids if increased urine output continues. If diabetes insipidus is diagnosed, most patients will be able to maintain intravascular volume if allowed to drink freely. If patients are unable to match urine losses with oral intake, treatment with desmopressin (DDAVP) should be considered. If DDAVP is utilized,

it is important to follow serum sodium and osmolality to avoid 'overshoot' hyponatremia. Serum sodium and osmolality should be monitored closely. Doses are adjusted, titrating to urine output and osmolality (target urine osmolality 150–155 mEq/l within 24 h of initiating treatment). Mild diabetes insipidus (some residual antidiuretic hormone effects are present) can occasionally be treated with carbamazepine (200–600 mg/day), chlorpropamide (100–500 mg/day), or clofibrate (500 mg four times daily).

In a series of more than 800 patients, Nemergut *et al.* [29] found that 12.4% of patients required treatment with DDAVP at some point during their hospitalization. Persistent diabetes insipidus requiring long-term treatment with DDAVP was noted in only 2% of all patients, suggesting most diabetes insipidus is transient and self-limited. An observable intraoperative cerebrospinal fluid leak was strongly associated with an increased incidence of both transient (33.3%) and persistent (4.4%) diabetes insipidus. Patients with a microadenoma were more likely to suffer transient diabetes insipidus than those harboring a macroadenoma (21.6 compared with 14.3%) but were not more likely to experience persistent diabetes insipidus [29].

BONY DEFECT

It is important to remember that after any transsphenoidal procedure, patients have a persistent bony defect. There are several reported cases of intracranial nasogastric tube placement up to 14 days after transsphenoidal surgery [30,31]. It is unknown for how long the bony defect persists; however, nasal intubation and placement of a nasogastric tube is contraindicated for at least 14 days and should always be carefully considered.

CONCLUSION

Anesthesia for transsphenoidal pituitary surgery requires thorough preoperative assessment of hormone function and can provide optimal surgical conditions, while maintaining cerebral oxygenation and hemodynamic stability. Recent studies have shown that a variety of anesthetic approaches may be used. Advances in computer-assisted navigation and intraoperative MRI improve surgical outcome.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 635–636).

1. McCutcheon IE. Pituitary adenomas: surgery and radiotherapy in the age of
■ molecular diagnostics and pathology. Curr Probl Cancer 2013; 37:6–37.

Review of surgical management of pituitary adenomas.

2. Nemergut EC, Dumont AS, Barry UT, Laws ER. Perioperative management of patients undergoing transsphenoidal pituitary surgery. Anesth Analg 2005; 101:1170–1181.
3. Vance ML. Perioperative management of patients undergoing pituitary surgery. Endocrinol Metab Clin North Am 2003; 32:355–365.
4. Mosca S, Paolillo S, Colao A, *et al.* Cardiovascular involvement in patients
■ affected by acromegaly: an appraisal. Int J Cardiol 2012.

Examines cardiac comorbidities in patients with acromegaly.

5. Berg C, Petersenn S, Lahner H, *et al.* Cardiovascular risk factors in patients with uncontrolled and long-term acromegaly: comparison with matched data from the general population and the effect of disease control. J Clin Endocrinol Metab 2010; 95:3648–3656.
6. Smith M, Hirsch NP. Pituitary disease and anaesthesia. Br J Anaesth 2000; 85:3–14.
7. Fatti LM, Scacchi M, Pincelli AI, *et al.* Prevalence and pathogenesis of sleep apnea and lung disease in acromegaly. Pituitary 2001; 4:259–262.
8. Piper JG, Dirks BA, Traynelis VC, VanGilder JC. Perioperative management and surgical outcome of the acromegalic patient with sleep apnea. Neurosurgery 1995; 36:70–74.
9. Razis PA. Anesthesia for surgery of pituitary tumors. Int Anesthesiol Clin 1997; 35:23–34.
10. Hurley DM, Ho KK. MJA practice essentials – endocrinology. 9: Pituitary disease in adults. Med J Aust 2004; 180:419–425.
11. Lim M, Williams D, Maartens N. Anaesthesia for pituitary surgery. J Clin Neurosci 2006; 13:413–418.
12. D'Haens J, Van Rompaey K, Stadnik T, *et al.* Fully endoscopic transsphenoidal surgery for functioning pituitary adenomas: a retrospective comparison with traditional transsphenoidal microsurgery in the same institution. Surg Neurol 2009; 72:336–340.
13. Ensenat J, de Notaris M, Sanchez M, *et al.* Endoscopic endonasal surgery for skull base tumours: technique and preliminary results in a consecutive case series report. Rhinology 2013; 51:37–46.
14. Tabakow P, Czyz M, Jarmundowicz W, Lechowicz-Glogowska E. Surgical treatment of pituitary adenomas using low-field intraoperative magnetic resonance imaging. Adv Clin Exp Med 2012; 21:495–503.
15. Kim EH, Oh MC, Kim SH. Application of low-field intraoperative magnetic
■ resonance imaging in transsphenoidal surgery for pituitary adenomas: technical points to improve the visibility of the tumor resection margin. Acta Neurochir (Wien) 2013; 155:485–493.

Evaluates the efficacy of low-field intraoperative MRI in transsphenoidal pitutary adenoma resection.

16. Schmitt H, Buchfelder M, Radespiel-Troger M, Fahlbusch R. Difficult intubation in acromegalic patients: incidence and predictability. Anesthesiology 2000; 93:110–114.
17. Nemergut EC, Zuo Z. Airway management in pituitary disease: a review of 746 patients. J Neurosurg Anesthesiol 2006; 18:73–77.
18. Gemma M, Tommasino C, Cozzi S, *et al.* Remifentanil provides hemodynamic stability and faster awakening time in transsphenoidal surgery. Anesth Analg 2002; 94:163–168.
19. Gargiulo G, Cafiero T, Frangiosa A, *et al.* Remifentanil for intraoperative analgesia during the endoscopic surgical treatment of pituitary lesions. Minerva Anestesiol 2003; 69:119–123; 124–126.
20. Cafiero T, Cavallo LM, Frangiosa A, *et al.* Clinical comparison of remifentanil–sevoflurane vs. remifentanil–propofol for endoscopic endonasal transphenoidal surgery. Eur J Anaesthesiol 2007; 24:441–446.
21. Ali Z, Prabhakar H, Bithal PK, Dash HH. Bispectral index-guided administration of anesthesia for transsphenoidal resection of pituitary tumors: a comparison of 3 anesthetic techniques. J Neurosurg Anesthesiol 2009; 21:10–15.
22. Chowdhury T, Prabhakar H, Bharati SJ, *et al.* Comparison of propofol versus sevoflurane on thermoregulation in patients undergoing transsphenoidal pituitary surgery: a preliminary study. Saudi J Anaesth 2012; 6:12–15.
23. Keegan MT, Atkinson JL, Kasperbauer JL, Lanier WL. Exaggerated hemodynamic responses to nasal injection and awakening from anesthesia in a Cushingoid patient having transsphenoidal hypophysectomy. J Neurosurg Anesthesiol 2000; 12:225–229.
24. Pasternak JJ, Atkinson JL, Kasperbauer JL, Lanier WL. Hemodynamic responses to epinephrine-containing local anesthetic injection and to emergence from general anesthesia in transsphenoidal hypophysectomy patients. J Neurosurg Anesthesiol 2004; 16:189–195.

25. Korula G, George SP, Rajshekhar V, *et al.* Effect of controlled hypercapnia on cerebrospinal fluid pressure and operating conditions during transsphenoidal operations for pituitary macroadenoma. J Neurosurg Anesthesiol 2001; 13: 255–259.

26. Flynn BC, Nemergut EC. Postoperative nausea and vomiting and pain after transsphenoidal surgery: a review of 877 patients. Anesth Analg 2006; 103:162–167.

27. Mariano ER, Watson D, Loland VJ, *et al.* Bilateral infraorbital nerve blocks decrease postoperative pain but do not reduce time to discharge following outpatient nasal surgery. Can J Anaesth 2009; 56:584–589.

28. Magni G, La Rosa I, Melillo G, *et al.* Intracranial hemorrhage requiring surgery in neurosurgical patients given ketorolac: a case-control study within a cohort (2001–2010). Anesth Analg 2013; 116:443–447.

29. Nemergut EC, Zuo Z, Jane JA, Laws ER. Diabetes insipidus after transsphenoidal surgery: a review of 881 patients. J Neurosurg 2005; 103:448–454.

30. Hande A, Nagpal R. Intracranial malposition of nasogastric tube following transnasal transsphenoidal operation. Br J Neurosurg 1991; 5:205–207.

31. Paul M, Dueck M, Kampe S, *et al.* Intracranial placement of a nasotracheal tube after transnasal trans-sphenoidal surgery. Br J Anaesth 2003; 91:601–604.