


ANESTHETIC MANAGEMENT OF PATIENTS UNDERGOING PITUITARY SURGERY

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SUMMARY – Pituitary tumors account for more than 10% of all intracranial tumors. They often present with symptoms of hormonal hypersecretion, although they may also cause hypopituitarism. Transsphenoidal pituitary surgery has become a commonly performed neurosurgical procedure, which has certain challenges for the anesthesiologist due to many distinct comorbidities associated with various adenomas. This article provides a review of perioperative concerns regarding transsphenoidal pituitary surgery, encountered in a number of these patients. Thorough understanding of preoperative assessment, intraoperative management and potential complications is fundamental for successful perioperative patient care and avoidance of morbidity and mortality.

Key words: *Pituitary neoplasms – surgery; Anesthesia; Preoperative care; Postoperative care*

Introduction

Adenomas are usually histologically benign pituitary neoplasms, which are the result of monoclonal expansion of one cell that underwent somatic mutation. The usual opinion is that pituitary tumors are relatively rare and that they account for 10% of all intracranial tumors; actually, however, they are much more common^{1,2}. In 1981, Burrov *et al.* reported on pituitary adenomas found in 26.7% of non-selected autopsy materials³. Transsphenoidal approach to pituitary tumors is a surgical method over 100 years old, which gained its popularity after Hardy and Guiot had reconfirmed and standardized it as a contemporary microsurgical minimally invasive method⁴⁻⁶.

There is a constantly growing trend in the number of newly discovered pituitary tumors because of an enlarged number of educated endocrinologists, better availability of radioimmunoassay methods, and especially neuroimaging diagnostic methods⁷. The use

of high-resolution neuroimaging methods, especially magnetic resonance imaging (MRI), has led to discovery of incidental pituitary tumors of 3 mm in diameter and bigger in about 20% of “normal” pituitary glands⁸.

Our experience in the management of patients undergoing pituitary surgery is considerable. In 2008, 1316 operations were performed at University Department of Neurosurgery, Sestre milosrdnice University Hospital. There were 271 (20.6%) intracranial tumors, 94 (34.7%) of these pituitary tumors⁹.

The anesthesiologist must have due knowledge of anatomy, physiology, pathophysiology and endocrine function of the pituitary gland, and proper insight into the modern approach in pituitary surgery to be able to appropriately manage these complex patients. Thorough understanding of preoperative assessment, intraoperative management and potential complications is fundamental to successful perioperative patient care and avoidance of morbidity and mortality.

Proper patient preparation for pituitary surgery requires teamwork, including an anesthesiologist, an endocrinologist and a neurosurgeon¹⁰. All patients require meticulous preoperative evaluation and

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Received March 1, 2010, accepted June 15, 2011

screening with special care to patients presenting with Cushing's disease and acromegaly.

The symptoms and clinical signs caused by pituitary tumors can be divided into two groups: those caused by autonomic hyperproduction of growth hormone (GH), prolactin (PRL), adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) or luteinizing hormone (LH); and those caused by compression of the surrounding structures and gland tissue by the tumor itself.

Rarely, pituitary gland tumors present as apoplexy (bleeding inside the tumor) with hypopituitarism, sudden headache, signs of meningism, visual disorders, ophthalmoplegia, or signs of intracranial expansion. These situations are indications for immediate surgical treatment.

Strategies for optimal intraoperative anesthetic management should be carefully planned. Postoperative period necessitates careful monitoring of fluid balance and serum sodium because of an early diagnosis of diabetes insipidus and the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Preoperative Patient Evaluation

Besides routine laboratory tests (complete blood count, electrolytes, coagulation tests, liver function tests, urinalysis), preoperative assessment of patients with pituitary tumors should include levels of pituitary hormones and hormones of connected glands (women with secondary amenorrhea should always have pregnancy test done), cranial MRI, ophthalmic examination and evaluation for the signs of increased intracranial pressure (ICP)¹¹. Detecting the abnormalities in thyroid function tests and abnormal function of adrenal glands is especially important. Levels of these affected hormones must be normalized before elective surgery. A routine, prophylactic administration of hydrocortisone to all patients with pituitary tumors is now avoided and it is given only to patients with low corticoid levels as substitution therapy¹¹. Patients with acromegaly and Cushing's disease often have other comorbidities and should be examined thoroughly.

Even though pituitary surgery is typically performed in an uninfected field, a swab of nasopharynx is obtained to confirm the absence of pathogens.

Prolactinoma

Prolactinomas (tumors that produce hyperprolactinemia) are the most common type of secretory (functioning) pituitary tumors. They mostly are microadenomas (less than 10 mm in diameter) that generally affect women. Macroadenomas (more than 10 mm in diameter) are more often found in men and they usually cause visual abnormalities because of optical nerve compression. To diagnose a prolactinoma, MRI must be positive and serum level of prolactin must be more than 20 ng/mL (400 mU/L). Nonfunctioning tumors may also increase the level of prolactin compressing the pituitary stalk ("stalk effect"). This way they reduce the inflow of dopamine (which is a prolactin-inhibiting hormone) from hypothalamus to the pituitary gland. The first method in treating prolactinomas is administering dopamine agonist bromocriptine and the alternative cabergoline. Bromocriptine can cause serious hypotension during anesthesia and other side effects such as nausea, vomiting and congestion of nasal mucosa. In case of resistance to medical therapy with dopamine agonists or its poor tolerance, occurrence of neurologic symptoms or spontaneous cerebrospinal fluid (CSF) leakage, surgical treatment is indicated¹².

Adenoma Secreting GH

Adenomas that secrete GH are often large and result in acromegaly (when present in adults) or gigantism (when present in prepubertal patients causing excessive growth prior to epiphyseal fusion)¹³. Clinical signs of acromegaly are enlarged mandible, hands, feet, growth of soft, connective tissue and signs of peripheral nerve compression^{14,15}. It is also very often accompanied by diabetes mellitus and hypertension, premature coronary disease and cardiomyopathy in some patients. Because of enlarged fingers, pulse oximetry may be difficult to perform. Proximal myopathy and chest deformity can compromise respiratory function, especially in the early postoperative period. Soft tissue of the mouth, tongue, pharynx, epiglottis and vocal cords, and laryngeal cartilage are also affected². Anatomical features that are often present in these patients are macroglossia, macrognathia and prognathism¹⁵. Paresis of the recurrent laryngeal nerve can be seen¹⁶. One fourth of patients with acro-

megaly have an enlarged thyroid gland that compresses the trachea. All of these features make intubation difficult and demanding thorough airway evaluation prior to the induction of anesthesia, and action according to the algorithm for difficult or impossible intubation if needed¹⁷. If in doubt, indirect laryngoscopy is recommended. After adenoma resection, vocal cords regain normal structure and function in about 10 days². Obstructive sleep apnea (OSA) can affect up to 70% of these patients and can lead to a high perioperative risk. OSA is complicated by the risk of perioperative airway compromise, especially in early postoperative period and preoperatively due to benzodiazepines and/or narcotics given as premedication. In these patients, caution is warranted when administering narcotics and benzodiazepines, which should always be done in the presence of qualified personnel. Also, patients with chronic untreated OSA have an increased risk of developing right heart failure due to pulmonary hypertension¹⁸. One third of acromegalic patients have hypertension¹⁵. Myocardial hypertrophy and fibrosis reduce function of cardiac ventricles, which can persist after the surgery². The risk of death due to cardiovascular and respiratory disease (insufficiency) is increased compared with healthy subjects. Diabetes mellitus or glucose intolerance is often present in acromegalic patients and hypoglycemic episodes may occur after surgery.

Tumors Secreting ACTH

Cushing's disease is characterized by hypersecretion of adrenocorticotrophic hormone (ACTH) by pituitary adenoma and by clinical signs of corticoid excess: glucose intolerance or diabetes mellitus, amenorrhea, hypernatremia, hypokalemia, metabolic alkalosis, hypertension, left ventricle hypertrophy, ECG changes, acne, abdominal striae, hirsutism, bruises, central obesity ("moon face" and "buffalo torso"), osteoporosis, proximal myopathy, muscle wasting and weakness, sleep apnea, kidney stones, gastroesophageal reflux and mental status changes.

Therapy with metyrapone or ketoconazole can reduce the effects of excess cortisol, which has a high perioperative morbidity and mortality. Activation of renin-angiotensin-aldosterone system and enlarged blood volume cause hypertension in 80% of cases of Cushing's disease². Heart ultrasound in these patients

shows left ventricle hypertrophy and asymmetric septal hypertrophy¹⁹. ECG changes that occur are inversion of T waves and high voltage QRS complexes. All of these changes are normalized after the surgery. Sleep apnea is also often present.

Glucose intolerance is found in 60% and diabetes mellitus in one third of patients, and is caused by lower rate of insulin secretion and higher resistance of insulin receptors^{2,14}.

Patients with Cushing's disease tend to have hypokalemic metabolic alkalosis resulting from mineralocorticoid activity. These abnormalities should be corrected preoperatively with supplemental potassium and spironolactone¹³. Advanced osteoporosis can cause fractures due to inappropriate patient positioning on the operating table. Obesity and gastroesophageal reflux are often found in these patients, so routine pretreatment with H₂ antagonists and occasionally with metoclopramide is advised. A high serum concentration of glucocorticoids causes immunosuppression, which makes these patients susceptible to infection.

Because of the adipose tissue excess on the arms, an appropriate size cuff must be prepared for accurate blood pressure measurements. Adipose tissue, fragile skin and blood vessels due to hypercortisolism can make intravenous access technically difficult.

Tumors That Secrete TSH, FSH and LH

Tumors that secrete TSH are very rare (2.8% of all pituitary tumors) but aggressive and are always treated surgically. They cause hyperthyroidism with elevated serum levels of TSH.

Adenomas that secrete FSH and LH cause premature puberty or menstrual bleeding in menopause and hypogonadism in men. They account for 15% to as much as 40% of all pituitary adenomas and it is thought that 80% of clinically nonfunctional pituitary tumors are gonadotropine-derived²⁰.

Nonfunctioning Tumors

Nonfunctioning tumors compress gland tissue and cause hypofunction. They can also cause apoplexy (bleeding within the pituitary gland) or Sheehan's syndrome (postpartum infarction of the pituitary gland). Therapy is surgery or radiotherapy. They make

20%-25% of all pituitary tumors. First symptoms are often visual disturbances, headache and diabetes insipidus; large tumors can cause signs of increased ICP and panhypopituitarism. Cortisol deficit and hyponatremia must be corrected before the surgery.

Surgical Approach

Transsphenoidal approach *via* endoscopic or microsurgical method is used in over 95% of pituitary tumors and has significantly lower rates of morbidity and mortality⁵. Surgical approach *via* bifrontal craniotomy is more demanding and often results in long term hormone substitution. Since convulsions can occur after such an approach, anticonvulsants are given as premedication in our hospital.

Anesthetic Management

The main goal of anesthetic management is to maintain hemodynamic stability, preserve adequate cerebral oxygenation and perfusion, secure appropriate positioning of the patient, facilitate surgical exposure, provide rapid awakening after the surgery, and assess neurologic functions^{21,22}.

Supplementation of glucocorticoids in patients with hypopituitarism is started on the evening before the operation with 100 mg of hydrocortisone i.v., second dose is given just before or at the beginning of the operation, and the third dose is given on the evening after the operation (between 4.00 and 6.00 p.m.). This is a rather traditional approach that is still often used and is thought to markedly overtreat patients. Recommendations for perioperative management of glucocorticoid therapy include performance of 0800 hour cortisol test and short ACTH 1-24 (Synacthen) test to prove ACTH deficiency. If test results are abnormal, the patient should be commenced on standard maintenance doses of glucocorticoid (15-30 mg hydrocortisone daily while waiting for surgery. These patients should be given supraphysiological glucocorticoid cover for 48 hours perioperatively using hydrocortisone 50 mg i.v. every 8 hours on day 0, 25 mg i.v. every 8 hours on day 1, and 25 mg i.v. at 0800 hours on day 2¹⁸. If ACTH 1-24 test is normal, no perioperative glucocorticoid cover is needed. However, if selective adenectomy is not possible and surgery is extensive, glucocorticoids are instituted. All patients with

Cushing's disease require perioperative glucocorticoid cover.

Intravenous antibiotic prophylaxis in our hospital includes cefuroxime 1.5 g or amoxicillin clavulanate 1.2 g given prior to induction of anesthesia and for the next 24 h. This single-agent antibiotic covers gram-positive organisms most frequently found on pharyngeal mucosa. In 2010, the Croatian national guidelines for antimicrobial prophylaxis in surgery were published and their recommendation for antimicrobial prophylaxis in pituitary surgery is cefazolin 1 g i.v. plus clindamycin 600 mg i.v. preoperatively and 8 hours after the surgery²³.

Careful investigation of the airways before the surgery, especially in patients with acromegaly, is required because of the reasons explained above. Four degrees of difficult airways have been defined in acromegalic patients: first degree represents no difficulty, second degree represents hypertrophy of nasal and pharyngeal mucosa with normal vocal cords and glottis, third degree includes stenosis of the glottis and/or vocal cord paresis and, finally, fourth degree includes pharyngeal mucosal hypertrophy, abnormalities of the glottis and soft tissue around it¹⁸. In patients categorized as having third and fourth degree of difficult airways, flexible fiberoptic intubation is recommended.

After intubation, a pharyngeal pack must be placed to limit the risk of aspiration and filling of the stomach with blood and debris, which can lessen the likelihood of nausea and vomiting postoperatively.

Topical application of local anesthetics and vasopressor solutions to the mucosal surface of the nose is employed during surgical preparation. Most preferred are lidocaine-epinephrine mixtures. The routine use of relatively large quantities of these mixtures can result in significant systemic effects like arterial hypertension and cardiac dysrhythmias. Fortunately, these effects are transient and should be treated with short acting agents. Excessive use of vasoconstrictors may cause systemic vasoconstriction, which can produce significant increase in afterload. Cases of myocardial ischemia have also been reported.

Some surgeons place an intrathecal catheter in order to manipulate CSF pressure and facilitate tumor resection. This is usually done in patients with large tumors with suprasellar extension. The catheter is usually placed at the L3-L4 interspace. This allows

for 5-10 mL boluses of saline or air to increase CSF pressure and produce prolapse of large tumors into the intrasellar operative field. If air is used, nitrous oxide must be discontinued to avoid an increase in ICP and development of expanding pneumocephalus.

For transsphenoidal surgical approach, the patient is positioned in a semi-recumbent position with the head elevated above the heart to facilitate venous drainage. The neck is extended and the head is turned slightly to the side to facilitate surgical access to nasal cavity. Endotracheal tube (ETT) and breathing tubes should be carefully fixed to prevent dislodgement of ETT because it is inaccessible during the operation.

All patients should have graded compression stockings during the surgery to prevent venous pooling in lower extremities, venous thrombosis and pulmonary embolism.

Anesthetic Technique

Anesthetic technique and the choice of anesthetic agents are similar to other intracranial surgeries. Also, anesthetic selection depends on the patient's comorbidities, neurologic disease, allergies and anesthetic history. Maintenance of anesthesia using ether, total intravenous anesthesia or balanced anesthesia with inhalation agent, muscle relaxant and opioid depends on the anesthesiologist's individual preference²⁴. In the presence of signs of raised ICP, nitrous oxide is avoided¹⁸. Although volatile anesthetics desflurane, sevoflurane and isoflurane raise ICP by increasing cerebral blood flow (isoflurane least of all), their effect is time-dependent and with continued administration blood flow returns to normal. Also, simultaneous hyperventilation and administration of these volatile agents prevent increases in ICP¹³. Some authors advocate maintaining anesthesia with intravenous agents in the situation of raised ICP¹⁸. The proximity of cranial nerves II-VI to the pituitary makes early postoperative assessment of their integrity very important. To facilitate rapid emergence from anesthesia, a rapidly metabolizing agent such as propofol and remifentanyl (remifentanyl is not yet available in Croatia), or inhalation agents with low blood solubility such as sevoflurane or desflurane should be used. If remifentanyl is used, a longer-acting opioid should be used to provide analgesia at the end of the surgery (when remifentanyl is discontinued) to prevent complicated emergence

because of pain. Neuromuscular blockade needs to be maintained during the procedure to prevent any patient's movements, which could lead to serious injury. Since the head is elevated above the level of the heart, there is a possibility of air embolism if a lesion of cavernous sinus occurs. In this case, it is important to discontinue nitrous oxide. There is a minimal blood loss during transsphenoidal surgery; however, it could be catastrophic if carotid artery is injured. Therefore, all patients should have large-bore intravenous access for rapid volume resuscitation.

After removal of the tumor, Valsalva maneuver may be utilized to test for CSF leak. Sella is then packed with autologous fat before it is reconstructed.

Monitoring

Monitoring includes ECG, pulse oximetry, end-tidal CO₂, noninvasive arterial blood pressure, respiratory volumes and pressures. Patients with Cushing's disease and, to a lesser extent, patients with acromegaly may present with significant cardiovascular disease, which together with intraoperative hemodynamic changes represent anesthetic risk. In these patients, invasive arterial blood pressure monitoring is necessary and it enables an early detection of hypo- and hypertension and their immediate treatment. Cardiac drug therapy should be continued until the time of surgery and again as soon as oral intake begins after the surgery. Routine placement of arterial catheters and central intravenous access should be omitted^{2,21}. If tumor location is such that it compromises visual field, visual evoked potential (VEP) monitoring can be used, but extraordinary sensitivity of VEP to anesthetics, high incidence of false-negative and false-positive results have made VEP unnecessary and costly^{18,21}.

Intraoperative Complications

Complications during transsphenoidal approach are rare and are usually due to lesion of the surrounding structures, i.e. carotid artery, cranial nerves II-VI, venous sinuses and optic nerves and chiasm. Transcranial approach carries risks like all other craniotomies. Convulsions can occur and anticonvulsant prophylaxis is a prudent choice. Anosmia is also possible because of the lesion of olfactory nerve.

Emergence

At the end of the surgery, pharyngeal packs are removed and mouth cavity suctioned. Patient is extubated after spontaneous breathing and reflexes have returned. Rapid awakening facilitates immediate neurologic assessment but patient must be hemodynamically stable and respiration sufficient. Straining or coughing should be minimal because it can precipitate hemorrhage, CSF leakage and dislodgement of nasal tamponade.

Acute Postoperative Care

The postoperative care after pituitary surgery requires airway management, analgesia, close neurologic and endocrine assessment, fluid balance control and monitoring for possible complications. Surgical complications include bleeding, CSF leak, visual changes and meningitis. Endocrine disorders that are commonly encountered are hypopituitarism, diabetes insipidus and SIADH.

All patients are at an increased risk of airway obstruction after transsphenoidal approach. Blood and secretions in the pharynx and nasal packs can compromise airway patency. Meticulous suctioning of oropharynx is necessary. Acromegalic patients with OSA have a high risk of respiratory obstruction as any other patient with OSA and should be closely monitored.

Pituitary surgery usually causes moderate pain but nasal packs can cause significant discomfort. Pain management in these patients includes non-steroid anti-inflammatory drugs, paracetamol and opioids if needed.

Continuous neurologic assessment is necessary. Any cranial nerve palsy, visual change or mental status changes should be addressed with imaging or re-exploration.

Endocrine management in the postoperative period should consist of a team approach, which includes an endocrinologist, anesthesiologist and a surgeon. Again traditionally, hydrocortisone given preoperatively to patients with hypopituitarism is continued postoperatively for several days lowering the dose by 25% each day until starting the oral dose of prednisone 20 mg in the morning and 10 mg in the evening. However, postoperative glucocorticoid replace-

ment should be decided based on 0800 hour plasma cortisol levels measured on days 1-3 for patients with normal ACTH 1-24 test results and on days 3-5 for those with abnormal test results. If cortisol level is <100 nmol/L, maintenance therapy with 15-30 mg/day hydrocortisone is needed. For patients with cortisol level of 100-250 nmol/L, 10-20 mg hydrocortisone in a single morning dose should be given and further testing of hypothalamic-pituitary-adrenal (HPA) axis is required. In patients with cortisol level of 250-450 nmol/L, glucocorticoid replacement is needed during times of stress and they require further HPA testing. Patients with cortisol level of 450 nmol/L are not ACTH deficient¹⁸. If plasma cortisol levels after pituitary surgery in patients with Cushing's disease are low, they require physiologic hydrocortisone replacement therapy and a review of HPA axis. The aim is to gradually withdraw hydrocortisone as the ACTH suppression recovers²⁵. Deficiencies in any pituitary hormone must be adequately replaced. Besides glucocorticoids, this most frequently involves thyroid hormone²⁶.

Diabetes insipidus usually occurs in the first 24 hours after the surgery and usually after more than 80% of neurons producing vasopressin have been destroyed or functionally impaired. About 25% of postoperative patients have transitory diabetes insipidus lasting for several days to weeks, and in 0.5% it stays permanent^{2,27}. Symptoms that arise suspicion are polyuria (more than 2 mL/kg/h of urine output), hypotonic urine (specific gravity <1.005) and hypernatremia (>145 mmol/L). Urine output and its specific gravity must be monitored. Therapy is desmopressin acetate 0.1 mcg i.v./i.m. and volume resuscitation (0.45% NaCl i.v. or H₂O orally) with electrolyte monitoring because desmopressin can cause significant hyponatremia.

SIADH is reported in 9%-25% of patients after transsphenoidal surgery and is usually manifested a week after the surgery^{2,28}. It is characterized by inappropriate secretion of ADH regardless of plasma osmolarity, which causes low serum sodium (<135 mmol/L), low serum osmolarity (<280 mOsmol/L) and concentrated urine with euvolemia (or slight hypervolemia) and normal renal function. Since SIADH causes water retention in the body, first therapeutic measure is water restriction (800-1000 mL/day). If

significant hyponatremia (<120 mmol/L) is present, it should be treated with hypertonic saline (1.8% or 3%). Correction of serum sodium for severely symptomatic patients should be done at rates of 1-2 mEq/L/h for 3 to 4 hours and then at a slower rate of 0.5 mEq/L/h (a total of 12 mEq/L over 24 hours) to avoid central pontine myelinolysis as a complication. The rate of sodium correction in asymptomatic patients is 0.5 mEq/L/h (to a total of 10 mEq over 24 hours).

Cerebral salt wasting syndrome (CSWS) is a rare cause of hyponatremia and it should be distinguished from SIADH because restriction of water in this case can be deleterious to patients. This syndrome is found in patients with cerebral lesions when elevated urine output is present, and is characterized by hyponatremia and hypovolemia (opposite to SIADH). Patients with CSWS have evidence of extracellular fluid depletion (negative fluid balance, low central venous pressure, increased urea, tachycardia, etc.) and treatment is replacement of sodium and fluid losses.

Conclusion

Patients with pituitary tumors require a complex approach and coordination between the endocrinologist, the neurosurgeon and the anesthesiologist. Significant preoperative systemic manifestations and systemic diseases secondary to pituitary dysfunction should be controlled prior to surgery. Optimal intraoperative anesthetic management depends on the understanding of the patient's disease and the requirements of pituitary surgery. Rapid emergence from anesthesia is important because early neurologic assessment can reveal most common and most serious surgical complications. All patients require long-term follow-up with an endocrinologist to assess their hormonal status.

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Sažetak

ANESTEZIJA KOD OPERACIJSKOG ZAHVATA NA HIPOFIZI

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Tumori hipofize čine više od 10% svih intrakranijskih tumora. Oni se često manifestiraju simptomima hipersekrecije hormona, ali mogu isto tako izazvati hipopituitarizam. Transsfenoidna kirurgija hipofize postala je čest neurokirurški zahvat koji pred anesteziologa postavlja stanovite izazove zbog mnogih istodobno postojećih bolesti udruženih s raznim adenomima. Ovaj članak daje pregled pitanja koja treba razmotriti prije pristupanja transsfenoidnoj kirurgiji hipofize u većine ovih bolesnika. Potpuno razumijevanje prijeoperacijske procjene, intraoperacijskog zbrinjavanja i mogućih komplikacija bitno je za uspješnu perioperacijsku skrb, kao i za izbjegavanje pobola i smrtnosti.

Ključne riječi: Novotvorine hipofize – kirurgija; Anestezija; Prijeoperacijska skrb; Poslijeoperacijska skrb