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Perioperative Management of Patients Undergoing Transsphenoidal Pituitary Surgery

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Background: *The sellar and parasellar region is a confluence of several critical anatomical structures from various physiological systems located in close proximity to one another. Patients with pathology in this critical region of the central nervous system therefore make up a unique subset of neurosurgical patients that require careful preoperative and postoperative attention to numerous management details involving neurological, visual, and neuroendocrine function. A thorough understanding of the underlying anatomical and physiological principles of each of these systems, as well as the medical and surgical nuances involved in each case, is required to provide optimized management for patients with pituitary pathology. In this review, we discuss the major preoperative and postoperative considerations in patients undergoing resection for pituitary lesions in the modern era of transsphenoidal surgery.*

Keywords: Transsphenoidal surgery, pituitary adenoma, endoscopy, sella turcica

Preoperative Assessment of Patients Undergoing Transsphenoidal Surgery

As with all neurosurgical patients, a thorough preoperative assessment is required prior to the consideration for any operative intervention. In patients with sellar-based lesions, a detailed patient history and review of symptoms is performed, including a thorough assessment of headache, visual dysfunction, neurological complaints, or symptoms referable to endocrine dysfunction. Patients with intrasellar lesions often complain of headaches that are bifrontal or retro-orbital in nature, with frequent radiation to the occipital region. A review of visual symptoms includes questions regarding visual acuity and complaints of blurriness, double vision, peripheral field dysfunction, as well as an assessment of visual function as it pertains to activities of daily life, including reading, working, and exercising. A thorough neuro-endocrine history includes an evaluation for symptoms of hypocortisolemia (i.e. fatigue, nausea, vomiting), or cortisol excess associated with Cushing's Syndrome (weight gain, hair and skin changes, hypertension, diabetes, fatigue, abdominal striae, acne, hirsuitism, anxiety, insomnia, etc).[1] Symptoms and signs of dysfunction of the thyroid axis may include changes in weight, heat or cold intolerance, diarrhea or constipation, or cardiac-related symptoms. Symptoms and signs of acromegaly caused by growth hormone excess frequently include perspiration, acral growth, facial structural changes, snoring or obstructive sleep apnea, diabetes, hypertension, skin tags, or colon polyps, to name a few.[2] Symptoms consistent with hyperprolactinemia include oligomenorrhea/ amenorrhea and galactorrhea in women, and diminished libido or sexual dysfunction in men. A family history should always be obtained in order to identify potential congenital endocrine syndromes, such as multiple endocrine neoplasia-1 (MEN-1).[3] Patients with subjective visual complaints or those with macroadenomas extending in a suprasellar direction should undergo preoperative visual assessment by a neuro-ophthalmologist with full visual field testing.

As with any patients that are being evaluated for surgery, a comprehensive medical history

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and assessment of additional comorbidities should be performed. In particular, cardiac and pulmonary dysfunction may require additional attention or medical clearance prior to an elective operation, and occurs commonly in patients with Cushing's Disease and acromegaly. In many patients with hypopituitarism or hormonal excess syndromes, assessment by an anesthesiologist prior to the operation may be beneficial, as there may be specific concerns relating to intubation and drug administration in this population. A review of a patient's bleeding history and coagulation function, as well as a thorough review of all medications, should be performed; Patients should receive clear instructions on how to manage their medications, especially any anti-platelet or anticoagulation agents, prior to an operation.

The physical examination in patients with sellar pathology consists of a full neurological examination with particular attention to visual and cranial nerve function. The standard visual examination should include an assessment of visual acuity, peripheral field testing by confrontation, a fundoscopic examination to rule out papilledema or optic disc pallor, and evaluation of pupillary function and extraocular eye movements. Patients with pituitary pathology should be examined for the signs of Cushing's Disease, which may include hypertension, moon facies, ruddy complexion, acne, hair loss, hirsuitism, abdominal striae, lipodystrophy, and skin bruising, among many others. Frequent signs of acromegaly include enlarged acral features, soft tissue edema, perspiration, jaw underbite, skin tags, and acanthosis nigricans associated with diabetes mellitus. In the rare patient with Nelson's Syndrome, skin hyperpigmentation is often present due to physiological excess of serum ACTH. A nasal examination should be performed prior to any transsphenoidal surgery, especially in planned reoperation cases, in order to assess any anatomical aberrancies that may exist, such as a perforated nasal septum.

Serum laboratory assessment is imperative in patients that are under consideration for surgical resection of a pituitary lesion. A complete endocrine panel is typically obtained in all patients undergoing work-up for a pituitary lesion, and generally consists of a serum TSH, free T4, ACTH, AM fasting cortisol level, Growth Hormone, IGF-1, prolactin, and gonadal markers. In men, a serum total testosterone (and often sex hormone binding globulin) level can be obtained to assess gonadal function. In women, a detailed menstrual history, in addition to a serum LH, FSH, and estradiol level obtained during the follicular phase, are good screening indicators for hypogonadism. In some cases, dynamic endocrine testing is recommended prior to surgery to obtain a more sensitive assessment of pituitary function or dysfunction. In cases of suspected Cushing's Disease, specialized testing such as a 24-hour urinary free cortisol test, dexamethasone suppression test, or inferior petrosal sinus sampling, may be required to establish a definitive diagnosis prior to recommending surgery.[4] A urine or serum pregnancy test should always be checked in women of reproductive age. As with all patients that undergo evaluation for surgery, a serum CBC, electrolytes, and coagulation lab values are routinely obtained prior to surgery.

Optimization of preoperative medical management in patients with pituitary disease, either for hormonal excess or insufficiency, is an important undertaking prior to any consideration for surgery. Ideally, patients with hypopituitarism should be adequately replaced with stable regimens of the appropriate hormonal substitute(s), especially pertaining to the thyroid and cortisol axes, prior to any operation.[5] Strict management of diabetes insipidus (DI), if present, should be undertaken using vasopressin replacement agents, such as DDAVP. Replacement of the growth hormone and gonadal axes are typically not urgent and can be deferred until after the operation. Many patients with prolactinomas can be managed successfully with dopamine agonist agents alone. In the small subset of patients with prolactinomas that do require surgery (i.e. for medication-resistant tumors or in patients that do not tolerate dopamine agonists), these medications are often times be discontinued prior to the operation. Patients with acromegaly may warrant medical treatment with a somatostatin analogue (i.e. octreotide), dopamine agonist, GH-receptor antagonist (i.e. pegvisomant), or any combination of the above, prior to surgical treatment.[6] In rare cases, patients with Cushing's

Disease will be given ketoconazole or alternative steroid biosynthesis inhibitors in an attempt to normalize serum cortisol levels as a temporizing measure.[7] These drugs are typically discontinued prior to surgery in order to assess for remission in the immediate postoperative state, however, an individualized decision should be made for each patient.

A thorough review of a patient's imaging studies is an imperative part of preoperative planning for transsphenoidal surgery. Standard preoperative imaging of the sellar and parasellar region typically includes coronal and sagittal MR sequences obtained with and without gadolinium-enhancement. Particular attention should be paid to the anatomy of the parasellar sinuses, including the degree of pneumatization of the sphenoid sinus and the anatomy of any horizontal or vertical septations that may be present.[8] The morphology and curvature of the sellar floor is routinely assessed. In cases of a non-pneumatized sphenoid sinus, preparation for drilling should be anticipated. The course of the clival and cavernous internal carotid arteries are identified, and the width between the internal carotid arteries at the sellar level measured. Lesions of the sellar and parasellar region are routinely assessed for their size, degree of extension and invasion into surrounding regions, and anatomic proximity and association to surrounding structures including the internal carotid arteries, pituitary gland and stalk, and optic apparatus. The degree of suprasellar and cavernous sinus extension should be assessed, and may be utilized to predict the anticipated extent of resection and guide the adjunctive operative measures that may be necessary to facilitate the procedure. For instance, patients harboring masses with significant suprasellar extension may benefit from the intraoperative placement of a lumbar drain, which can be utilized during tumor resection to facilitate delivery of the tumor via insuflation of air into the drain. Cystic lesions of the sellar region require careful preoperative consideration, as they may include a wide differential diagnosis of pathology, including cystic adenomas, Rathke Cleft Cysts, craniopharyngiomas, infectious or inflammatory lesions, and intrasellar aneurysms. In some cases, a CT scan of the head may be beneficial to rule out the presence of intra-tumoral calcification, which often lends support to the diagnosis of an adamantinomatous craniopharyngioma. CT or MR angiography may be an important step to rule out an intrasellar aneurysm prior to any consideration for surgery.

Patients and families should be extensively counseled regarding the goals of the planned surgery, and whether a gross total resection is feasible or anticipated. The potential complications of any intervention should be explained prior to obtaining informed consent. For the majority of transsphenoidal operations, surgical complications include bleeding, infection, cerebrospinal fluid (CSF) leakage, hypopituitarism, visual loss, and carotid artery injury, among others. Any planned sources of potential tissue harvesting for grafting and CSF leak repair, such as abdominal fat graft, should also be explained to the patient. For some extended transsphenoidal approaches, fascia lata can be harvested from the thigh in order to provide an excellent barrier for skull base reconstruction following tumor resection. The possibility of a requirement for transfusion of blood or blood products, although uncommon for patients undergoing transsphenoidal surgery, should be discussed with the patients as well.

Prior to any operation, the surgical plan should be reviewed with the anesthesiology team. This should include a discussion regarding patient positioning, administration of any required medications (i.e. antibiotics or hormone replacement), and the requirement for invasive monitoring or goal physiological parameters. At our institution, patients that demonstrate laboratory evidence of preoperative hypocortisolemia (serum fasting AM cortisol of < 10 mcg/dL) are given an early intraoperative stress dose of intravenous glucocorticoid (i.e. solu-cortef 100 mg). If intraoperative neuronavigation is planned, these images sequences should be prepared and registered prior to the operation. Alternatively, intraoperative fluoroscopy or plain film imaging can be used to assess the intraoperative trajectory to the sella turcica, if necessary. All surgical equipment, including the operative microscope, drill, transsphenoidal instrumentation, and endoscopy equipment,

should be checked prior to the operation.

Post-operative management of Transsphenoidal Patients

Following transsphenoidal surgery, patients are at risk for developing a variety of neuroendocrine or other postoperative complications, which can potentially be minimized or prevented by maintaining a high degree of awareness for such issues on the part of the neurosurgical team and nursing staff. Serial clinical monitoring of a patient's neurological and visual status is imperative following transsphenoidal surgery, as patients may develop untoward complications such as postoperative hematomas, epistaxis, ischemic events, hydrocephalus, CSF leaks, or meningitis. Maintaining a constant state of vigilance for these uncommon, but serious, events in all patients is absolutely critical. If a CSF leak is suspected in the postoperative period, a noncontrast CT scan of the head is a useful study that may demonstrate the presence of intracranial air in the event of a CSF leak. Although the majority of patients do not require insertion of nasal packing at the time of surgery, some patients (especially those with or intraoperative CSF leaks requiring sellar floor reconstruction, Cushing's Disease, and acromegaly) may benefit from their insertion. If used, nasal packing can typically be removed on postoperative day one. Postoperative epistaxis infrequently develops following transsphenoidal surgery, and can typically be treated successfully with routine nasal packing for 2-3 days. In rare refractory cases of epistaxis, reoperation or endovascular embolization of an arterial bleeder may be required.[9]

Aberrancies of fluid homeostasis and serum electrolytes occur quite commonly following transsphenoidal surgery. An understanding of the underlying physiology, coupled with monitoring of a patient's volume status, as well as serum and urine laboratory studies, may make a significant difference in a patient's postoperative course. Although a foley catheter is not inserted at the time of surgery in the majority of patients at our institution, strict measurement of a patient's intake, output, and daily weight should be carried out in order to provide a continuous assessment of volume status. In the first several days following surgery, frequent serum sodium levels are obtained to assess for diabetes insipidus (DI) or early hyponatremia. Excessive urine output, defined as that greater than 250 cc/hour for 2-3 hours, may be further evaluated by obtaining a serum sodium level and urine specific gravity to rule out DI, and guide the decision to treat with DDAVP. DI is usually a transient phenomenon following transsphenoidal surgery, and although patients may be able to maintain neutral fluid balance by drinking to satiety, in cases of clear-cut DI it is often beneficial to administer DDAVP prior to bedtime to allow patients to sleep comfortably, rather than require them to continuously drink water in order to replace the fluid loss caused by excessive urine output.[10] Following the initial trend towards DI in the first few days after a pituitary operation, there is a tendency to develop SIADH and delayed hyponatremia approximately one week following the operation.[11] At our institution, the majority of patients are discharged home on postoperative day 2 or 3, and the potential complication of symptomatic delayed hyponatremia can be evaluated and potentially prevented by obtaining outpatient serum labs on postoperative day 7.[12] A serum sodium and cortisol level (if the patient is not taking glucocorticoid supplementation) is typically drawn at that time to rule out any delayed hyponatremia or hypocortisolemia. Patients with mild hyponatremia that are asymptomatic can often be managed conservatively at home with fluid restriction and follow-up laboratory studies. Patients with moderate or severe hyponatremia, or those developing symptoms referable to hyponatremia, should be admitted for fluid restriction, frequent sodium monitoring, and potential administration of hypertonic saline to be used only in rare cases of refractory hyponatremia.

Patients with preoperative evidence of hypopituitarism should be maintained on sufficient stress doses of hormonal replacement during the initial perioperative period, and then kept on physiological maintenance doses of replacement agents until it is appropriate to assess their pituitary function in a controlled manner. Patients with evidence of hormonal excess typically undergo appropriate lab testing

during the first few days following surgery to assess for evidence of early endocrinological remission. At our institution, patients with Cushing's Disease do not receive steroids at any time during the operation, unless necessary, and are assessed in the postoperative period by obtaining a serum cortisol level every 6 hours until a nadir level is reached.[13,14] If the postoperative cortisol level drops below 5 mcg/dL, especially in conjunction with the development of symptoms of hypocortisolemia, immediate glucocorticoid therapy is administered intravenously and then transitioned to physiological oral maintenance doses until the function of the normal gland can be reassessed in a delayed and controlled setting. On the other hand, patients that are thought to have normal cortisol function prior to surgery are not given intraoperative glucocorticoid doses, and are assessed postoperatively with an AM fasting cortisol obtained on postoperative days 1 and 2. If there is evidence of new hypocortisolemia (cortisol < 10 mcg/dL) on these laboratory studies, glucocorticoid replacement is initiated until they are reassessed by an endocrinologist in a delayed fashion. Although some centers use a cortisol level of 15 mcg/dL as a threshold for predicting postoperative hypopituitarism, at our institution patients with postoperative levels of < 10 mcg/dL receive steroid replacement.[15] In patients with acromegaly, a postoperative day 1 serum GH level may serve as a predictor of early remission, although the gold standard test is a delayed IGF-1 level obtained 6 weeks following surgery.[16] Patients with acromegaly undergoing successful tumor resection may demonstrate brisk fluid diuresis of previously third-spaced fluid that mimics diabetes insipidus (DI) in the early postoperative period, requiring differentiation from DI by obtaining a serum sodium level and urine specific gravity level.[17] Finally, in the small proportion of patients with prolactinomas that require surgical resection, a postoperative day one or two morning prolactin level may be checked, which typically normalizes in cases of remission.

Following discharge, patients are usually seen in the clinic for routine follow-up one week after surgery, then again at the 6-week postoperative time point for routine endocrine and postoperative evaluation, in order to account for equilibration of the hypothalamic-pituitary-adrenal axis as well as the longer half life of thyroid hormone. Postoperative MR imaging is obtained 3 months following the operation, in order to allow sufficient resolution of postoperative changes prior to any meaningful assessment regarding the extent of tumor resection. Routine imaging studies may then be obtained annually, or more often as indicated. Patients with sellar pathology may have delayed tumor recurrences occurring up to several years after successful remission, therefore mandating continued endocrinological and imaging surveillance, even beyond a decade following initial remission.

Conclusions

Patients with pathology of the sellar and parasellar region comprise a unique subset of neurosurgical patients that are ideally managed via a multidisciplinary specialty approach, consisting of neurosurgeons, endocrinologists, pathologists, and ophthalmologists. Providing optimized care for patients with pituitary disease requires a thorough understanding of the neurological, visual, and endocrine facets corresponding to various pathological entities encountered in the sellar region. Developing excellence in the management of patients, both before and after transsphenoidal surgery, is contingent upon attention to the details of each case on numerous levels, and maintaining a sense of awareness and clinical judgment for what is an expected versus atypical treatment course for patients with varying sellar lesion types.

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