Review Article

Pheochromocytoma resection: Current concepts in anesthetic management

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Abstract

Pheochromocytoma represents very significant challenges to the anesthetist, especially when undiagnosed. These chromaffin tissue tumors are not uncommon in anesthetic practice and have varied manifestations. The perioperative management of these tumors has improved remarkably over the years, in conjunction with the evolution of surgical techniques (open laparotomy to laparoscopic techniques and now to robotic approaches in the present day). This review attempts to comprehensively address the intraoperative and postoperative issues in the management of these challenging tumors with an emphasis on hemodynamic monitoring and anesthetic technique.

Key words: Anesthetic, pharmacology, pheochromocytoma

Introduction

Pheochromocytomas (PCC) are rare neuroendocrine tumors originating from chromaffin tissue. In the United States, the published incidence is 2-8 diagnoses per million populations, per year.[1] Presently, since the only cure is surgical, these patients represent significant management problems and a high-risk of cardiovascular complications from hypertensive crises. The 2014 Endocrine Society Clinical Practice Guidelines state an overall PCC prevalence of 0.2-0.6% in patients with hypertension. In addition, they suggest that the prevalence of familial and extra adrenal tumors in patients carrying germ-line mutations in PCC susceptibility genes may be as high as 50%.[2]

Perioperative Risk Assessment and Preoperative Planning

Pheochromocytomas represent significant management challenges to the anesthesiologist. From a hemodynamic perspective, few other clinical situations present a more complex and life-threatening situation - particularly when undiagnosed.[3] The latter situation may precipitate a hypertensive crisis, which can be life-threatening, with a published 80% mortality.[4] Preoperative evaluation of these patients is key to successful perioperative management. Roizen *et al.* in 1982[5] proposed a set of criteria (now called the Roizen criteria) to objectively gauge the efficacy of adequate preoperative alpha blockade, and they include:

1. No in-hospital blood pressure >160/90 mmHg for 24 h prior to surgery;
2. No orthostatic hypotension with blood pressure <80/45 mmHg;
3. No ST or T wave changes for 1-week prior to surgery;
4. No more than 5 premature ventricular contractions per minute.

Over the years, these criteria have remained consistently reliable; data does exist in the literature reflecting poorer outcomes when patients have not met these criteria prior to tumor resection. His group also reported that mortality from a pheochromocytoma resection decreased from 13% to 45% before alpha blockade to 0-3% once blockade was instituted.[6] Most centers use some (if not all of these criteria), during the preoperative evaluation process for PCC resection, as indicators of adequate pharmacologic preparation for PCC resection. Alpha blockade has been the mainstay of preoperative preparation for pheochromocytoma patients for over 60 years[7] and has had a long track record of safe use. Multiple approaches to pharmacologic preparation have been proposed, however, to date, there are no randomized trials

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that have compared the efficacy of these varied techniques and there is no universally accepted method of preoperative blood pressure control.[8,9] In most centers, a combination of alpha-adrenergic and beta-adrenergic blockade and calcium channel blockers, in addition, are routinely used. The alpha-adrenergic blockade is typically administered starting 10-14 days preoperatively which, in addition to normalizing blood pressure, also aids in expanding the highly contracted intravascular volume - an often underappreciated issue, especially in the higher risk pheochromocytoma patients (catecholamine cardiomyopathy, myocardial infarction, and patients with refractory hypertension). Successful alpha blockade is reflected by normalizing blood pressure with mild orthostasis. Phenoxybenzamine is the drug most commonly used in the United States for alpha blockade, especially in hypertensive crises at doses ranging from 10 mg twice a day intravenous (IV) as initial dose to a total daily dose of 1 mg/kg, in hospitalized patients. Outpatients typically receive oral equivalent does of 10 mg twice a day for at least 10-14 days preoperatively, doses can be increased every 48 h. Most centers consider the presence of nasal stuffiness in conjunction with postural hypotension to be clinical indicators of adequate alpha blockade.[2] Other more specific short-acting and competitive alpha-1 antagonists include prazosin, terazosin, and doxazosin, which are used in doses of 2-5 mg 2 or 3 times daily for prazosin, 2-5 mg daily for terazosin, and of 2-8 mg daily for doxazosin, which can be increased to 32 mg/day. As is well known, beta blockade should never be used in isolation and only after an adequate length of alpha blockade owing to the catastrophic hypertensive crisis that would ensue with unopposed alpha receptor stimulation.[10,11] The dihydropyridine calcium channel blockers remain useful in the perioperative period as adjuncts largely because they are relatively easier to titrate and less likely to cause orthostatic hypotension.[12] Functioning through the inhibition of catecholamine-mediated calcium influx in vascular smooth muscle, they do not cause reflex tachycardia, lessen the severity of catecholamine-induced vasospasm, and, therefore, are particularly useful in the subset of patients with catecholamine-induced myocarditis/vasospasm. IV nicardipine has been well studied and is most widely used in the perioperative setting.[13-16]

Cardiovascular Evaluation

All patients needing surgical removal of these tumors need a thorough cardiovascular evaluation. A 12-lead electrocardiogram will reveal the presence and/or extent of left ventricular strain, hypertrophy, bundle branch blocks, and ischemia. Preoperative echocardiography is essential to assess global systolic and valve function as well as to outline the severity of diastolic dysfunction that should include strain rate assessment (which essentially is an index of myocardial deformation that correlates with severity of diastolic dysfunction). Patients with longstanding tumors may develop severe dilated cardiomyopathy with varying degrees of heart failure, raising the overall perioperative risk. More routine findings in preoperative echocardiograms include moderate to severe left ventricular hypertrophy in conjunction with varying degrees of diastolic dysfunction that correlate with the severity, duration, and degree of blood pressure control. Catecholamine cardiomyopathy has been well described (catecholamine-induced cardiomyopathy)[17] as a form of myocardial stunning from the toxic effects of catecholamines on the myocardium. When severe, it can be associated with both cardiogenic (from severe systolic and diastolic dysfunction) and noncardiogenic pulmonary edema. The latter is modulated by the synergistic effects of cell-secreted factors on pulmonary vascular endothelium.[18] Another important indication for preoperative echocardiography in these patients is to rule out primary cardiac PCC in select patients. These may also be incidental findings on preoperative trans-thoracic echocardiograms. Cardiac magnetic resonance and/or computed tomography may be indicated to better delineate these masses. These are rare but have been well described in younger patients, as well as in association with multiple paraganglioma syndromes. These tumors are usually benign but tend to be locally invasive. Surgical dissection is usually impossible-given their infiltrative nature.[19]

Surgical Approach

Complexity of anesthetic management is largely dictated by surgical approach. Across most centers, the laparoscopic approach is preferred for most pheochromocytoma resections supported by data over the years that attests to the well-documented advantages of laparoscopic approaches in general — less postoperative pain, earlier mobilization and recovery, reduced incidence of postoperative pulmonary and thromboembolic complications, shorter hospital stays and overall cost effectiveness.[20-23]

Most experienced centers perform minimally-invasive adrenalectomy via laparoscopic and retroperitoneoscopic approaches as the gold standard for a pheochromocytoma resection, particularly for adrenal masses <6 cm diameter and weight <100 g.[2]

Open procedures are typically reserved for larger masses and extra-adrenal tumors with limited access. Factors such as surgeon expertise, convenience, and preference are usually taken into consideration, although laparoscopic approaches

should be the primary surgical technique. In addition, transperitoneal versus retroperitoneal techniques are a factor to be considered.[24,25] For patients with bilateral adrenal PCC as well as those with multiple endocrine neoplasia-2 and Von-Hippel-Lindau syndromes with unilateral masses, bilateral cortical-sparing adrenalectomy has been proposed because of the high incidence of synchronous and metachronous disease in these familial syndromes.[26] Given the high-risk nature of these patients, all complex pheochromocytoma resections should ideally be performed in centers that routinely perform the pheochromocytoma surgery.

Anesthetic Goals

As mentioned earlier, pheochromocytoma resection is widely considered to be among the most challenging in anesthetic practice, with the primary goal being the delivery of an anesthetic which provides stable hemodynamics in the face of catecholamine surges (especially at laryngoscopy, peritoneal insufflation, surgical stimulation, and tumor handling) followed by the opposite scenario following tumor ligation. Careful planning and meticulous technique are essential, in addition to close communication with the surgical team. The key issues are summarized below:

Preinduction

Relief from anxiety prior to anesthetic induction is a key component, as apprehension can predispose to catecholamine surges. Ideally, a long-acting benzodiazepine such as lorazepam or diazepam administered the night before the operation (as tolerated) in addition to a judicious dose of IV midazolam prior to transfer to the operating suite creates a calm patient less prone to hypertensive crises at induction. Invasive arterial monitoring via an intra-arterial catheter is an absolute indication in all pheochromocytoma patients prior to anesthetic induction as continuous beat-to-beat monitoring allows for close hemodynamic monitoring (and rapid pharmacologic intervention as needed) of one of the most critical portions of the anesthetic-direct laryngoscopy and endotracheal intubation.[27] A large-bore peripheral IV catheter is also inserted preinduction routinely. Histamine receptor 2 antagonists (H2 blockers) are also indicated in appropriate patients; however, antiemetics like metoclopramide can provoke a hypertensive crisis and are best avoided. Although short-acting alpha 1 antagonists can be administered on the morning of the procedure, longer-acting agents such as phenoxybenzamine and doxazosin are traditionally withheld 12-24 h prior to the operation.[28] Attention must be paid to the organization of vasoactive infusions to be used intraoperatively. Traditional vasodilator set up includes nitroglycerin, sodium nitroprusside, nicardipine, diltiazem as indicated, esmolol infusion for heart rate control, magnesium sulfate, and vasoconstrictors such as norepinephrine and vasopressin. In patients with the catecholamine cardiomyopathy, inotropes to be added include epinephrine and dobutamine, with milrinone available in the setting of right ventricular dysfunction. For rapid volume expansion, colloids, plasma expanders, and blood products are arranged as indicated. All infusions are connected to tubing that leads to a manifold for central venous administration. In terms of invasive monitoring, central venous cannulation is absolutely indicated for fluid management as well as delivery of vasoactive agents. In addition, pulmonary artery catheters as well as intraoperative transesophageal echocardiography (TEE) probes are placed in appropriate patients. Consideration should be given to the use of rapid transfusion systems for patients with large masses as well as tumors with caval or aortic involvement.

Anesthetic induction

As outlined above, anesthetic induction is one of the most critical portions of the procedure, with every effort being made to limit the hemodynamic stresses of direct laryngoscopy. Agents commonly used include propofol and etomidate. Ketamine is usually avoided due to its sympathomimetic effects, as are ephedrine and meperidine. Of importance, airway instrumentation should only be attempted after obtaining adequate anesthetic depth to avoid tachycardia and hypertension. Propofol has been documented to be safe in these patients; etomidate has the advantage of conferring cardiovascular stability, especially in volume-depleted patients.[29,30] All agents that cause histamine release should be avoided. The choice of neuromuscular blocker prior to laryngoscopy is critically important in the pheochromocytoma resection. The depolarizing agent, succinylcholine, has the potential for causing catecholamine surges from the muscle fasciculations that it produces which can mechanically compress the tumor, in addition to stimulation of the autonomic ganglia, both of which can be detrimental.[31] Pancuronium, a nondepolarizing agent, has a vagolytic effect that can trigger a pressor response in these patients.[32] Of all the agents used for neuromuscular blockade prior to endotracheal intubation, vecuronium is the most widely used and preferred. It has no autonomic effects, does not cause histamine release, and is the most commonly used paralytic for a pheochromocytoma resection at Mayo Clinic.[33] Attenuation of the pressor response to laryngoscopy is a crucial aspect of anesthetic induction and adjuncts commonly used include fentanyl in small doses, IV lidocaine, esmolol 0.5 mg/kg bolus, and infusion as indicated, as well as infusions of nitroglycerin, nicardipine, or sodium nitroprusside as needed. Inhaled agents are the mainstay of the anesthetic for a pheochromocytoma resection. In the past few years, enflurane and isoflurane have been extensively used[34,35] without complications. Halothane (which is not

currently in use in the United States) is contraindicated in pheochromocytoma patients as it is arrhythmogenic, sensitizing the myocardium to circulating catecholamines.[35] Desflurane, which is favored in ambulatory anesthesia for its low blood-gas partition coefficient (and resultant rapid emergence) does cause significant sympathetic stimulation and is considered by many to be avoided.[36] Sevoflurane is widely used for pheochromocytoma excision. Given its relatively favorable hemodynamic profile, it is less irritable to the airways than desflurane and lacks arrhythmogenic potential. Nitrous oxide is benign in these patients. Opiate use in the pheochromocytoma resection can vary based on the approach (open vs. laparoscopic), patient opiate tolerance, and hemodynamic issues encountered. Long-acting opiates such as morphine and hydromorphone are routinely used, although some institutions have reported the use of remifentanil successfully.[37]

Invasive Monitoring in Pheochromocytoma Resection

Aside from standard American Society of Anesthesiologists monitors, intra-arterial monitoring is the gold standard in the pheochromocytoma resection for beat-to-beat blood pressure monitoring. Central venous catheterization and monitoring is essential in these patients and has been the standard of care for over 50 years.[38] It allows for monitoring of right atrial pressure and the delivery of vasoactive agents as mentioned earlier. Swan-Ganz catheterization may be indicated in patients with poor left ventricular function from a catecholamine cardiomyopathy, pulmonary hypertension, or significant myocardial disease. Measurement of cardiac output, mixed venous oxygen saturation, as well as pulmonary capillary wedge pressure, may be particularly useful in these higher-risk patients.[39] The utility of pulmonary artery catheters in these patients may be greater postoperatively following tumor resection for more accurate fluid management in the intensive care unit, particularly in the unstable patient.[40] Intraoperative TEE has the added advantage of real-time monitoring of intravascular volume status, as well as the earlier detection of myocardial wall motion abnormalities aiding the diagnosis of intraoperative myocardial ischemia. PCC resection can involve significant hemodynamic fluctuations as will be discussed below.

Intraoperative Hypertension and Hypotension

Hypertension during resection may arise from general sources specific to all operations (positioning, skin incision, intubation) and is usually transient and responds to quick therapy, in these situations, the catecholamine release is from excessive stores in nerve endings.[41] On the other hand, tumor manipulation usually generates a far more dramatic pressor response that is directly related to significant increases in plasma levels of norepinephrine and epinephrine.[42] These situations may be associated with severe hemodynamic instability including significant reductions in cardiac output, and associated left ventricular systolic and diastolic dysfunction. Wall motion abnormalities may be noted with intraoperative TEE in the setting of myocardial ischemia. Acute hemodynamic crises during resection are not uncommon and must be immediately treated. The typical hemodynamic crisis in tumor resection may be epinephrine or norepinephrine mediated (depending upon which catecholamine is predominantly secreted by the tumor) and manifests either as severe bradycardia accompanied by hypertension or with severe tachycardia and tachyarrhythmias. Immediate responses should include deepening the depth of anesthesia and rapidly administering direct arterial vasodilators, sodium nitroprusside being the key drug in conjunction with nitroglycerin, to reduce preload. Both drugs have a rapid onset of action and are easily titratable. In resistant cases, nicardipine and/or fenoldopam have been used with success.[43] The latter being a dopamine (DA-1) agonist causes peripheral vasodilation in conjunction with increasing renal blood flow. In addition, an infusion of an ultrashort-acting beta blocker as an adjunct to control heart rate is extremely effective.[44] Magnesium sulfate has been increasingly used for hemodynamic control in the pheochromocytoma resection. It is a potent vasodilator inhibiting catecholamine release by directly inhibiting their receptors and is a strong calcium antagonist.[45] It is used in the operating room (OR) as an IV bolus in the dose of 1-3 g. Multiple data points exist in the pheochromocytoma literature attesting to its benefit in hemodynamic situations like the pheochromocytoma with severe, resistant hypertension.[46,47] Being an established antiarrhythmic, it has been used successfully to treat ventricular arrhythmias in pheochromocytoma patients[48] as well as pediatric patients with these tumors. In addition, pheochromocytoma can be rarely associated with Takotsubo cardiomyopathy,[49] another condition known to be associated with elevated catecholamine levels. Some have suggested a possible role for magnesium as an important therapeutic agent in these patients.[50] Communication with the surgeon is critically important before tumor manipulation is begun to reduce the likelihood of major hemodynamic events. Hyperglycemia is common as a result of catecholamine excess, and insulin infusion therapy, as indicated, should be routine management in these patients.

Sudden hypotension may occur following ligation of the tumor. This, in conjunction with a contracted plasma volume, surgical

bleeding, and anesthetic-induced vasodilation may cause profound, persistent hypotension. This can, to some extent, be pre-empted by close communication with the surgeon allowing for large-volume fluid bolus administration just prior to tumor ligation. It is not uncommon for the anesthesiologist to administer 2-3 L of fluid (crystalloid and colloid) prior to tumor ligation, in addition to rapidly discontinuing all vasodilators. Data from the British literature[51] would suggest that massive fluid resuscitation is more effective than vasopressor administration in these situations. Patients who are persistently hypotensive may benefit from intraoperative TEE examination to assess ventricular filling. In terms of vasoactive agents, DA-1, norepinephrine, and vasopressin have been used with success; however, in refractory circulatory shock, acute vasopressin therapy has been increasingly used with documented success.[52,53] Because vasopressin does not rely on peripheral adrenergic receptors for its pressor effect, it is particularly effective for refractory hypotension following tumor resection. In addition, once all agents have been in use to little or no effect and fluid therapy has been fully optimized, the use of IV methylene blue may be considered. It has been documented recently for hemodynamic rescue following the pheochromocytoma resection.[54] Methylene blue is an indicator dye that has been used for treatment of malaria, methemoglobinemia, neonatal hypotension, as well as in the surgical setting to detect urinary tract leaks.[55,56] It appears to function through a cyclic guanosine monophosphate inhibition mechanism that plays a key role in vasoplegic syndromes.[57] It has been reported to have been used in refractory vasoplegic patients with hepatic and renal failure, as well as in the cardiac arena.[58] Since experience is mostly anecdotal, it cannot be universally recommended in unstable hypotensive patients; however, in doses ranging from 1 to 2 mg/kg it has been used in conditions dominated by profound and pressor-resistant vasoplegia.[59]

Consideration should also be given to rapid steroid replacement in the hypotensive patient following bilateral adrenalectomies.

Pheochromocytoma in Uncommon Situations

Emergency surgery in patients with documented PCC or residual PCC from previous operations is not to be taken lightly. Unless it is a true surgical emergency, all patients will need at the very least, assessment of serum and urine catecholamines, complete blood counts and electrolytes, as well as cardiac evaluation with transthoracic echocardiogram as indicated. In the event of a true surgical emergency, complete invasive hemodynamic monitoring is indicated with arterial cannulation, central venous or pulmonary artery cannulation, intraoperative TEE, as well as the availability of appropriate vasodilators such as nitroglycerin, sodium nitroprusside, and nicardipine to immediately treat hypertensive crises as they arise.

Pheochromocytomas in pregnancy is rare, estimated to occur in 1 out of 54,000 pregnancies.[60,61] Although rare, when undiagnosed (it can be overlooked given the much higher prevalence of gestational hypertension and preeclampsia), it has a very high maternal and fetal mortality of close to 50%.[62,63]

Laboratory diagnosis is similar to PCC in nonpregnant patients via assessment of fractionated metanephrines (metanephrine and normetanephrine) in blood and urine. In pregnant patients, as per Lenders, PCC can be excluded if the plasma-free metanephrine test is negative.[64] Preoperative alpha blockade is also the standard of care in this patient population, with the caveat that blood pressure should be maintained to perfuse the uteroplacental circulation. In terms of surgical intervention, most centers employ laparoscopic adrenalectomy, with adrenal cortical-sparing surgery in patients with bilateral disease. In pregnancy, the optimal time for PCC resection is the second trimester — before 24 weeks gestation or after delivery.[65,66] In late trimester patients with PCC, Lenders recommends PCC resection simultaneous with C-section or after delivery.

Immediate Postoperative Management

All pheochromocytoma patients need intensive monitoring postresection, usually in the intensive care unit. Patients who exhibit persistent hemodynamic instability may need postoperative ventilation. Electrolyte and endocrine abnormalities must be ruled out in drowsy and unresponsive patients where hypoglycemia and hyponatremia should be considered high on the differential diagnosis. Appropriate blood glucose and electrolyte monitoring is indicated. Careful attention must be paid to fluid management. In the vast majority of patients who undergo laparoscopic tumor resections, postoperative issues are minimal. Persistent hypotension may indicate surgical bleeding, inadequate fluid resuscitation, or residual anesthetic-induced vasodilatation. In patients who are persistently hypertensive postoperatively, fluid overload, return of autonomic reflexes, inadvertent ligation of the renal artery, or presence of residual tumor should be considered in the differential diagnosis.[67]

It is important to keep in mind that hypertension may persist in a significant number of patients (50%) following PCC resection, with a tumor recurrence rate of 14% in primary

adrenal disease and 30% in extra-adrenal disease. This indicates that long-term follow-up should be considered on all patients following PCC resection.[68]

Conclusion

Patients with pheochromocytoma are at significant risk for major adverse cardiac complications in the perioperative period. Successful management requires careful preoperative optimization, meticulous intraoperative planning, and hemodynamic management. All patients need to be monitored vigilantly in the postoperative period given the high-risk of complications as described above.

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