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MINIREVIEWS

Update in perioperative anesthetic management of pheochromocytoma

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Abstract

Pheochromocytoma is a tumor that originates from either chromaffincells in adrenal medulla or in other paraganglia tissues of the sympathetic nervous system. The perioperative management is quite challenging especially in view of hemodynamic fluctuations. Pheochromocytoma is challenging in view of the impact of excessive and depleted catecholamines in the perioperative period. It requires a through preoperative evaluation and optimization with meticulous intraoperative management. The postoperative period requires vigilance to prevent any untoward complication. In this review we review these concepts based on recent evidence for an optimal outcome.

Key words: Phaeochromocytoma; Anaesthesia; Surgery; Analgesia; Drugs

Core tip: The paper is a comprehensive review of the most important pathophysiological and diagnostic issues, preoperative optimization, and anesthesia management of pheochromocytoma. It describes advanced imaging and biochemical techniques for diagnosis and localisation. Once considered nightmare by anaesthesiologist, pheochromocytoma have improved outcome nowadays due to widely available vasoactive drugs, monitors and perioperative care. Also, availability of laparoscopic and robotic adrenal-sparing adrenalectomy has reduced hospital stay and hastened recovery.

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INTRODUCTION

Pheochromocytoma is a tumor that originates from

either chromaffin cells in adrenal medulla or in other paraganglia tissues of the sympathetic nervous system. Adrenal is the origin for majority of tumor accounting 80% and rest are from extra adrenal site[1]. Majority of them are benign and may be associated with familial syndromes like multiple endocrine neoplasia (MEN) syndromes, von Recklinghausen disease or von Hippel-Lindau (VHL) syndrome in 10% of the patients. In a few patients pheochromocytoma have been found arising from atypical sites like head and neck, pericardium, inferior mesenteric artery (the organ of Zuckerkandl), aortic bifurcation, other chromaffin tissue in the abdomen, pelvis, and thorax[2,3].

GENETIC MUTATIONS AND PHEOCHROMOCYTOMA

The formerly used rule of 10 for pheochromocytoma (10% of tumors are malignant, bilateral and extra adrenal) is not convincing with present evidence[4]. Pheochromocytoma may occur sporadically in majority of cases but as high as 40% children and 25% adults may have an associated gene mutation[5,6]. Hereditary pheochromocytoma may be associated with MEN type 2 with RET proto-oncogene mutation, VHL syndrome with *VHL* gene mutations, von Recklinghausen disease with *NF1* gene mutation and succinate dehydrogenase subunit D genes mutation in familial non-syndromic pheochromocytoma[5-7]. Despite multiple gene mutations have been associated with pheochromocytoma, the testing for gene mutations in all the cases is not considered appropriate and is not cost effective.

CLINICAL PRESENTATION

The presenting signs and symptoms are primarily due to release of catecholamine or their metabolites in the body[1,8-12]. Most of the pheochromocytoma sites except head and neck tumors (less than 5%) produce, store, metabolize and secrete catecholamines or their metabolites[8]. The usual symptoms include hypertension, palpitations, headache, sweating, fatigue, nausea, weight loss, constipation, flushing, fever and pallor. The prolonged exposure of increased concentrations of catecholamines may result in dilated cardiomyopathy, ventricular failure, myocardial infarction, arrhythmia, stroke or other vascular ischemic symptoms. The classical triad of headache, sweating and palpitations may be seen in up to 40% of patients[9,10]. Headache and hypertension occur in predominantly norepinephrine secreting tumors whereas other symptoms like palpitations, sweating, anxiety, panic etc suggest epinephrine or dopamine secretion[11]. Stimulation of sympathetic nervous system may release neither excessive quantities of norepinephrine into the synaptic cleft. Due to proximity of norepinephrine to its receptors, the response is exaggerated even with small increments and patient may present hypertensive crises.

In addition a number of metabolic derangements like diabetes (decreased insulin and increased hepatic glucose output), lactic acidosis, hypercalcemia (parathyroid adenomas), diarrhea and fluid and electrolyte imbalance (vasoactive intestinal peptide secreting tumors) may also be seen in some patients with pheochromocytoma[10-12]. Some patients may be asymptomatic due to receptor down regulation. In such patients, the sympathetic reflexes may be blunted, leading to severe hypotension and shock during unrelated surgery. The symptoms of pheochromocytoma may also be mimicked by many endocrine (hyperthyroidism, menopausal syndrome, carcinoid), cardiovascular (heart failure, arrhythmias), ischemic heart disease and neurological (migraine, stroke) diseases. So, we need to confirm the diagnosis with further testing[12].

DISCUSSION

Once the signs and symptoms are suggestive of pheochromocytoma, the diagnosis can be confirmed by plasma epinephrine, norepinephrine and urinary catecholamine metabolite [vanillyll mandelic acid (VMA)][1,8,11,13-15]. But since the catecholamines may be released sporadically, these tests have low sensitivity and low specificity. The excessive production of catecholamines is metabolized in the tumor by catechol-o-methyl transferase to metanephrins which can be measured in the plasma[8]. They have a sensitivity of 99% (negative tests rule out pheochromocytoma) and should be carried out as the first test in patients with clinical symptoms and normal catecholamines[11,13]. Also high plasma metanephrin to epinephrine and normetanephrine to norepinephrine ratios are suggestive of pheochromocytoma. The 24 h urinary metanephrins has been found to have high sensitivity (97%) for pheochromocytoma. The product of normalised metanephrin and normetanephrine (100% sensitive and 99% specific) and serum chromogranin A have also been used for diagnostic purpose[14,15].

The other tests reported include clonidine suppression test glucagon stimulation test and selective adrenal vein sampling (not done now days)[13-15]. In clonidine suppression test, plasma epinephrine and norepinephrine are measured before and 3 h after 0.3 mg clonidine. In pheochromocytoma there will be less than fifty percent reduction in epinephrine and norepinephrine and less than 40% reduction plasma metanephrin values[14].

LOCALIZATION

Once the diagnosis is confirmed by history and biochemical testing, we need to localize the tumor to decide the treatment plan[1,8,9,16]. Surgical resection is the only curative procedure for these tumors. Both magnetic resonance imaging (MRI) and computerized tomography (CT) provide accurate and consistent anatomical identification of adrenal tumors as small as

1 cm in the majority of cases[16]. Contrast enhanced CT further increases its sensitivity but MRI is slightly better than CT. Gadolinium enhanced MRI can be used in children, pregnancy and patients with contrast allergy. In extra adrenal, metastatic and recurrent tumors, the sensitivity of both MRI and CT decreases (< 90%)[9,16]. Such cases need to be identified with radio nucleotide [meta-iodobenzyl guanidine (MIBG)] testing. MIBG has specificity as high as 100% but it may be taken up by neuroblastomas, medullary carcinoma thyroid, carcinoid and small cell carcinomas of lung. Also certain drugs like labetolol, reserprine, calcium channel blockers and some tricyclic antidepressants may interfere with uptake of MIBG and give false negative tests.

The positron emission tomography scan are nowadays available and become important in cases where conventional imaging is unable to detect the tumor in patients with positive biochemical testing[16].

PREOPERATIVE PHARMACOLOGICAL CONTROL

The control of symptoms due to excessive release of catecholamines are essential as preoperative pharmacological preparation reduces the mortality to less than 3%[9,10,13,16-23]. The surgery is rarely an emergency and anesthesiologist has time to optimize to control blood pressure, heart rate and arrhythmias. The advantages of preparation are: (1) Decreased vasoconstriction and restoration of vascular volume; (2) Normalization of hematocrit; (3) Symptom control; (4) Reversal of myocardial ischemia; and (5) Reduced intraoperative hemodynamic fluctuations.

Pharmacological agents

Various drugs have been used to achieve the optimal status prior to surgical intervention[16-23]. These include:

Alpha blockers: Phenoxybenzamine is a non-selective α blocker and is considered the main stay of perioperative control. It has a long duration of action and allows twice daily ingestion[16]. It can be administered orally (10 mg twice a day upto 1 mg/kg per day) or intravenous (0.5 mg/kg per day over 5 h for 3 d). It takes 2-3 wk for treatment to be effective. It produces a non-competetive blockade of the receptor that prevents the effects of surges of catecholamines during preoperative period. This also blocks the α2 adrenoreceptor and prevents feedback inhibition exercised by presynaptic adrenergic neurons leading to uninhibited release of norepinephrine at the cardiac sympathetic nerve endings and consequent undesirable chronotropic and inotropic side effects. Also, it is a non competitive blocker and has a long duration of action. Beta-blockers are given to control tachycardia. It may also lead to side effects due to central α2 blockade like somnolence, peripheral edema, headache, stuffy nose, *etc*.

Selective α1 blockers: Doxazosin, prazosin and tetrazosin are also used for optimization and lack reflex tachycardia[16,17]. They may produce profound hypotension due to uninhibited norepinephrine reuptake and its inhibition at postsynaptic α1 receptors. They are usually administered at bedtime with adequate hydration. Doxazosin is administered as a single dose (1-16 mg); prazosin and tetrazosin are administered 4-6/h. A preoperative blockade of 2-3 wk is required to optimize myocardial function.

Beta blockers: β blockers given in perioperative period limit the signs and symptoms due to increased circulating catecholamines (supraventricular and ventricular arrhythmias) and control tachycardia due to α blockade[16]. If a β blocker is started before effective α receptor blockade, the vasoconstrictor effects of α receptor go unopposed may produce dangerous hypertension[19]. Cardio selective agents like atenolol (25-50 mg) and metoprolol (50 mg) are preferred drugs. Labetalol β blockade capability is more than α blockade capability (1:7) and it also interferes with imaging by preventing uptake of ^{131}I MIBG.

Calcium channel blockers: (Amlodipine 10-20 mg/d, nicardipine 30-90 mg/d or verapamil 180-240 mg/d) inhibit NE-induced intracellular calcium influx and prevent catecholamine-induced coronary spasm, myocarditis, and attenuate hypertensive responses to noxious stimuli. They do not produce hypotension and are preferred in normotensive patients with occasional episodes of paroxysmal hypertension[16]. Clevidipine butyrate is an intravenous an ultrashort-acting, third-generation dihydropyridine calcium channel blocker that inhibits calcium influx in arterial smooth muscle, causes arterial vasodilation and decreases in peripheral vascular resistance. It is a novel agent for hemodynamic control in the management of pheochromocytoma before a tumor resection[20]. Clevidipine has a fast onset (1-2 min), is rapidly titratable, has a fast offset (5-15 min), and has proven safety and efficacy for acute perioperative hypertension. Since its preparation contains soybean oil and egg yolk phospholipids, it is contraindicated in patients with soybean, soy product, egg, or egg product allergies and in patients with lipid metabolism deficiencies[20].

Alpha-methylpara tyrosine: Methyl-para-tyrosine (MPT) is a competitive inhibitor of tyrosine hydroxylase (rate-limiting step in catecholamine biosynthesis)[16,18]. This reduces catecholamine stores and their release on stimulation of the tumor. In MPT is especially useful in extensive metastatic disease to control refractory blood pressure or in patients in which conventional drugs are not tolerated due to side effects (heart failure: β blocker and tachycardia: α blocker). Its use in combination with α blocker has shown to result in a better blood pressure control and less need for use of antihypertensive

medication or pressors during surgery. However, its usefulness is limited due to associated side effects like diarrhea, crystalluria, depression, galactorrhea, anxiety and extra pyramidal symptoms.

Magnesium sulfate: It inhibits the release of catecholamine, directly inhibits catecholamine receptors, and is a calcium antagonist. It attenuates catecholamine release due to noxious stimuli (*e.g.*, endotracheal intubation) and abolishes the arrhythmias induced by epinephrine. It also profoundly dilates the arterioles, reduces the peripheral vascular resistance (after load), and exerts minimal effect on venous return (preload)[16,22]. The beneficial effects are more pronounced during the peri-operative period and thus, can be considered an attractive option for catecholamine blockade in patients undergoing tumor resection[22]. It has been found effective for resection of pheochromocytoma in children, during pregnancy and patients presenting with arrhythmias[23]. Its use is associated with sedation, prolonged neuromuscular blockade and muscle weakness.

α2-agonists: Clonidine is a well-known presynaptic α2-adrenoreceptors agonist. It reduces sympathetic tone reduces blood pressure and anesthetic requirements[16]. Dexmedetomidine is a selective α2-adrenoceptor agonist and has sedative and analgesic properties. The decreased BP and heart rate are attributed to the decreased catecholamine levels. It can blunt sympatho-adrenal responses to tracheal intubation and surgical stimuli[21].

PREOPERATIVE MANAGEMENT

The objectives of preoperative evaluation are to ensure adequate α blockade, assess myocardial function, minimize organ complications, ensure normovolemia and correct hyperglycemia and electrolyte abnormalities. Adequacy of blockade is assessed using Roizen's criteria[24]: (1) BP < 160/80 mmHg; (2) Orthostatic hypotension not less than 80/60 mmHg; (3) No more than 1 ventricular premature contractions (VPC) in 5 min; and (4) No new ST-T changes on the ECG over the last week.

The achievement of these parameters suggests an optimization of the patient with regards to effect of catecholamine. Also, the cardiovascular evaluation needs to be done and includes a baseline ECG for evaluation of any myocardial ischemic changes, left ventricular hypertrophy and/or strain. An echocardiogram may further detect ventricular dysfunction, evaluate improvement with therapy and diagnose dilated cardiomyopathy.

ANESTHETIC MANAGEMENT[25-29]

The anesthetic management and monitoring during surgery will depend upon the extent of surgical approach. Traditionally the surgery is performed in open lateral retroperitoneal approach but sometimes transabdominal approach may be required. Recently laproscopic transperitoneal resection of the tumor is being done. Anesthetic plan will depend upon the surgical approach and patient positioning. Good communication between anesthesiologist and surgeon is important during the perioperative period[25].

Premedication

Preoperative sedation and good communication by the anesthesiologist help in decreasing anxiety and prevent marked hemodynamic fluctuations in the immediate perioperative period. Oral benzodiazepines and H2 receptor antagonist can be given. Short acting selective α-1 adrenergic blockers should be administered in the morning of surgery but longer acting drugs (Phenoxybenzamine/doxazosin) should be stopped 12-24 h prior to schedule surgery[25] (Table 1).

Operating room preparation

The infusions of hypotensive drugs [sodium nitroprusside (SNP) 0.01%, nitroglycerine (NTG) 0.1%, esmolol 1 mg/mL and norepinephrine 40 mcg/mL] and vasoactive drugs (magnesium sulfate, labetalol, diltiazem, nicardipine and lidocaine 2%) needs to be prepared in the operating room. Fluids in form of colloids, crystalloids, blood and blood products should be readily available (Table 2).

Anesthesia induction and maintenance

Two large bore (14G) peripheral intravenous access should be secured. The pain and anxiety associated with these procedures can lead to sudden hypertensive response. Invasive lines like radial artery and central venous cannulation should be secured under local anesthetic infiltration supplemented with intravenous midazolam. The monitoring includes continuous electrocardiogram, pulse oximeter, capnograph, temperature and urine output. The invasive monitoring includes central venous pressure and invasive arterial blood pressure monitoring.

Anesthesia induction and tracheal intubation must be smooth and hemodynamic response to intubation should be avoided. Various drugs/techniques have been used to blunt sympathetic response such as nitroprusside, nitroglycerin, magnesium sulfate, urapidil, opioids (fentanyl, remifentanyl), esmolol, nicardipine, and lidocaine have been described.

Induction of anesthesia

Almost all induction agents have been used safely and the choice of drugs depends upon institutional and individual practice. Both thiopentone and propofol are the commonly used drugs during induction of anesthesia. Propofol is preferred because it produces vasodilatation and blunts to the hypertensive response to laryngoscopy and intubation[26]. Etomidate is also recommended due to its cardiovascular stability[27,28]. The use of all the drugs that increase sympathetic tone

Table 1 Drugs commonly used in preoperative preparation of pheochromocytoma

Drug name	Dosages	Additional information
Phenoxybenzamine	60-50 mg	Dizziness, headache, nasal stuffiness peripheral edema and prolonged hypotension (long postoperative blockade)
Doxazosin	2-6 mg	Short acting, no prolonged hypotension
Beta blockers		
Propranolol	80-120 mg	Careful in patients with asthma, conduction disturbances, severe heart failure. May cause severe bradycardia and postural hypotension
Metoprolol	50-100 mg	
Labetalol	5-10 mg q5 min	
Calcium channel blockers		
Verapamil	120-240 mg	Careful in patients with n AV blocks, hypovolemia, sinus sick syndrome, and heart failure
Diltiazem	180 mg	
Nifedipine	30-90 mg	Side effects: Elevated liver enzymes, headache, constipation, dizziness, fatigue, edema
Clonidine	0.1-1.2 mg	
Dexmedetomidine	1 mg/kg in 10 min, 0.7 mg/kg per hour infusion	Dizziness, rebound hypertension side effects: depression, anxiety, dry mouth, bradycardia
Magnesium sulfate	1-8 mg loading dose, 1-4 mg/h maint	Potentiates neuromuscular blockade, caution in heart block and renal failure
Urapidil	10-15 mg/h	Caution because of severe hypotension
Alpha methyl-p-tyrosine	1-4 g/d	Crystaluria, extra-pyramidal and psychic disturbances

Table 2 Commonly used drugs during resection of pheochromocytoma

Drug	Dosages	Additional information
Fenoldopam	0.2 mg/kg per minute	Tachycardia, hypokalemia Cautions in patients with CVA
Sodium nitroprusside	1-2 mg/kg per minute	Cyanide toxicity, reflex tachycardia, severe hypotension
Nitroglycerine	25-250 mg/min	Reflex tachycardia, tachyphylaxis Methemoglobinemia, cerebral vazodilation
Nicardipine	5.0 mg/h	Hypotension, bradycardia, heart failure, WPW syndrome
Phentolamine	1-5 mg	Minimum side effects
Beta blockers		Careful in patients with asthma, conduction disturbances, severe heart failure. May cause severe bradycardia and postural hypotension. May potentiate effect of other drugs (like CCB)
Esmolol	5-10 mg × 3 min	
Metoprolol	2.5-5 mg × 2 min	
Labetalol	5-10 mg	
Epinephrine	1-20 mg/min	A and β agonist, positive inotropic, chronotropic effect and increases BP
Norepinephrine	1-30 mg/min	α/β1 agonist, decreases organ blood flow
Dopamine	5-20 mg/kg per minute	α/β/dopamine dose dependent agonist, may cause tachycardia and dysrthymias
Vasopressin	0.1-0.4 units/min	May cause MI

or may precipitate hypertensive crisis, such as ketamine, ephedrine, pancuronium and metoclopramide must be avoided[27,28]. Droperidol may cause hypertensive crisis and should be avoided[29].

Inhalation agents

Sevoflurane is preferred because it is cardio-stability and lack of arrhythmogenic potential[30]. Isoflurane lowers peripheral vascular resistance and blood pressure and can be used[31]. Halothane (arrhythmia potential) and desflurane (sympathetic stimulation) are not preferred in pheochromocytoma[32].

Muscle relaxants

During induction, use of succinylcholine can be hazardous as it may stimulate the autonomic ganglia (cause arrhythmia) and fasciculations due to succinylcholine may squeeze the gland and precipitate hypertensive crisis[33]. Atracurium and tubocurarine release histamine and should be avoided[34]. The recommended drugs are vecuronium, rocuronium and cisatracurium[27,28].

Total intravenous anaesthesia

Propofol and remifenatnyl are hemodynamically safe and decrease heart rate (central vagal nuclei stimulation). Remifentanil is an ultrashort acting opioid and acts by binding to μ-receptors in brain, spinal cord, and peripheral neurons[35]. Propofol is also a short acting drug which acts by increasing inhibitory γ-aminobutyric (GABA) synapses and inhibiting glutamate. Both the drugs together decrease the hemodynamic response during pheochromocytoma resection. The pharmacological profile of these drugs makes total intravenous anesthesia a safe anesthetic choice for such patients[36]. Recently, dexmedetomidine has also being used to provide a satisfactory preoperative sedation and intraoperative hemodynamic control. It also reduces anesthetic requirements and improves postoperative analgesia. Dexmedetomidine has been described recently for pheochromocytoma resection in an adult[27].

Intra operative hypertensive crises

During the intraoperative period, hypertension can occur

during induction, insertion of central lines, intubation, surgical incision, creation of pneumoperitoneum and tumor manipulation[37]. Risk factors for intraoperative hemodynamic instability include large tumor, baseline mean arterial pressure more than 100 mmHg and a high plasma norepinephrine concentration. Hemodynamic crisis may be due to epinephrine or norepinephrine release. Epinephrine induced crisis will present with tachyarrhythmia (paroxysmal supraventricular tachycardia, VPCs and ventricular arrhythmias) with increased systolic blood pressure and diastolic blood pressure (> 100 mmHg)[26,27,37]. Drugs like esmolol (0.5-1 mg/kg intravenous bolus or infusion), labetalol 5-10 mg intravenous, adenosine or intermittent boluses of metoprolol (1-2 mg intravenous) will help in controlling the crises. Amiodarone or lidocaine may be required in patients with poor left ventricular function. Norepinephrine crises are more common and characterized by severe bradycardia with profound hypertension. Rapid intravenous infusion of SNP through the central vein is usually effective, but esmolol needs to be added to control resultant tachycardia. The hypertension can also be controlled by deepening the anaesthesia or use of drugs like nicardipine, NTG, magnesium, *etc*. A combination of nicardipine (titrable short-acting calcium channel blocker) and esmolol (titrable ultrashort acting selective β1-receptor antagonist) can be used as an alternative especially in asthmatic patients[26,27]. Fenoldopam (dopamine1 receptors agonist) is a suitable titrable drug (dose of 0.2 mg/kg per minute) and causes peripheral vasodilatation and reduces blood pressure[37].

After the adrenal gland has been removed, severe hypotension may be result due to blood volume depletion (because of diuretics), residual action of vasodilators, bleeding, catecholamine withdrawal, adrenoceptor down regulation and steroid withdrawal (bilateral adrenalectomies)[26,27]. Initial treatment should be volume replacement upto 2-4 L to restore CVP to 10-12 mmHg. If ineffectivewe may require combination of multiple inotropes like epinephrine, norepinephrine, neosynephrine (pure α-adrenergic agonist), ephedrine, dopamine and vasopressin.

ANALGESIA

Epidural analgesia and spinal anesthesia have been used in patients planned for open procedures with large incisions[26,27]. However, a combination of central neuraxial block with general anaesthesia must be balanced against the risk of hypertension during its placement and possibility of post-excision hypotension[38,39]. Drugs like morphine (histamine release) and pethidine (sympathetic stimulation) are not preferred in pheochromocytoma. Fentanyl is a potent opioid and can be used as bolus (3-5 μg/kg) or infusion (1-2 μg/kg per hour)[27]. Non-steroidal anti-inflammatory drugs provide analgesia in patients with laparoscopic and robotic-assisted adrenalectomy.

Now days, laparoscopic arenalectomy and more recently, robotic-assisted adrenalectomy is being done[40-42]. These may be associated with reduced blood loss and vasodilator use, due to decreased/delicate tissue handling. It also produces less postoperative pain, decreases hospital stay and recovery period. Laparoscopic approach may not be feasible in cases of invasive carcinoma also. Carbon dioxide pneumoperitoneum can induce catecholamine release by a pheochromocytoma, leading to increase mean arterial pressure and central venous pressure[43,44].

POSTOPERATIVE MANAGEMENT

Approximately half of patients remain hypertensive for a few days due to elevated catecholamine stores in adrenergic nerve endings, which tend to persist for 1 wk after resection[26,27]. Persistent hypertension may indicate fluid excess, return of autonomic reflexes, inadvertent ligation of a renal artery, or presence of residual tumor.

Some patients may have persistent hypotension due to blood loss, altered vascular compliance, and residual preoperative adrenergic blockade. Postoperative blood glucose monitoring should be done because hypoglycaemia has been reported. Patient operated for arenalectomy may have postoperative drowsiness/unconsciousness and may be related to hypoglycemia, depletion of CNS catecholamine and multiple episodes of hypertensive crises intraoperatively may lead to cerebrovascular accident[44].

To conclude, pheochromocytoma is a challenging in view of the impact of excessive and depleted catecholamines in the perioperative period. It requires although preoperative evaluation and optimization with meticulous intraoperative management. The postoperative period requires vigilance to prevent any untoward complication.

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