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Perioperative Management Of Blood Pressure In Pheochromocytoma

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IMPORTANCE: Pheochromocytoma (& paraganglioma) are rare neuroendocrine tumors with variable clinical manifestations, familial and genetic components, complex management, significant comorbidity, and mortality. Blood pressure and cardiac complications are the most important one which needs particular attention before operating on such cases. Adequate perioperative management of blood pressure, blood volume, and other associated cardiovascular issues can reduce mortality and morbidities. A multidisciplinary team approach involving endocrinologists interested in managing such cases and the endocrine surgical team experienced in operating such cases is vital.
This review will focus mainly on managing blood pressure in the perioperative period, various pharmacological options, and clinically relevant pros & cons of each therapy based on the available evidence from the literature.

KEYWORDS: Pheochromocytoma, Paraganglioma, Perioperative hypertension in Pheochromocytoma

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Review Article

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A rare neuroendocrine tumor of chromaffin cells in the adrenal medulla (pheochromocytoma) counts 80-85% of the cases, or paravertebral sympathetic chain (paraganglioma) is 15-20% of the cases. The annual incidence in the European population is 0.2 per 100,000 per year. The traditional rule of 10% (which states that 10% are malignant, 10% are bilateral, 10% are extra-adrenal, 10% are normotensive and 10% are familial) is not always true as 29% are malignant, 24 % are extra-adrenal and 32% are familial[1,2].

Symptoms: Classic manifestations are recurrent or chronic sympathetic over activity (Hypertension, weight loss, sweating, palpitations) and elevated catecholamines (CAs). Hypertension is present in around 90 % but maybe paroxysmal in 30%-50% of these cases. Vasoconstriction-related bowel ischemia can cause abdominal pain. Papilledema can cause visual symptoms. Almost one-third to one-half of patients are diagnosed incidentally on abdominal imaging.

DIAGNOSIS

Biochemical testing: It needs evidence of both excessive release of catecholamines (Cas) and anatomical localization of the CA secreting tumor. Biochemical tests include plasma CAs including Epinephrine (E), Norepinephrine (NE), Dopamine (DA), or their intermediate metabolites including metanephrine (MN) or normetanephrine (NMN), and terminal metabolites such as vanillylmandelic acid (VMA). Plasma levels of free metanephrine (MN) have a sensitivity of 97% and specificity of 93% and are the most reliable tests for the biochemical diagnosis of pheochromocytoma[3].

Imaging studies: Radiological tests needed to locate the PPGL includes CT chest/abdomen and pelvis as a first choice. MRI is preferred in those with contrast allergy, head and neck tumor, or those where radiation risk is unacceptable such as the reproductive age group. MRI is also superior for paraganglioma. Nuclear scans such as MIBG scintigraphy (I-Metaiodobenzylguandine, a functional analog of norepinephrine which is taken up the adrenergic tissues), FDG-PET scan, and/or Somatostatin receptor imaging are used for metastatic disease or occult lesions not detectable on CT / MRI or for preoperative staging of extra-adrenal tumors[4].

Genetic testing: It is recommended for all patients. PPGL can be part of various syndromes such as MEN2, von-Hippel-Lindau (VHL) syndrome, Succinate Dehydrogenase Enzyme mutation, and NF1. Also, one-third of the cases have germline mutation, which is mainly autosomal dominant inheritance[5].

TREATMENT OF BLOOD PRESSURE

Surgery is the mainstay of treatment unless contraindicated. Release of excessive CAs during surgery

can cause fatal cardiovascular complications such as malignant Hypertension with end-organ damage, such as heart failure, arrhythmia, acute coronary syndrome, stroke, renal failure, etc.

Receptors and catecholamines: Alpha 1 is present on arteries, pupillary smooth muscles, and urinary sphincter. These are excitatory receptors and stimulate smooth muscle contraction, leading to vasoconstriction, pupillary dilatation, and the urinary sphincter's contraction. Beta-1 receptors are present on cardiac tissue and cause increased heart rate, myocardial contractility, and impulse conduction. Beta-2 receptors are present on bronchioles, blood vessels, the biliary system, and uterine smooth muscles. When stimulated, these receptors relax the smooth muscles in the bronchioles, blood vessels & uterus). Beta receptors on liver cells induce glycogen breakdown. Alpha 2 receptors present at pre-synaptic sympathetic nerves and have an inhibitory role in controlling sympathetic outflow [Table 1]

Sympathetic Receptors	Location	Functions	Symptoms	Antagonistic Drugs
Alpha-1	Arteriolar smooth muscles Urinary sphincter Radial smooth muscles of pupil	Vasoconstriction Urinary retention & prevention of retrograde ejaculation Pupillary dilatation	Hypertension Urinary retention Mydriasis and worsening of narrow angle glaucoma	Prazosin Terazosin Doxazocin Phenoxybenzamine
Alpha-2	Central sympathetic system Sympathetic nerve endings	Inhibit sympathetic outflow	Reduced sympathetic outflow	Phenoxybenzamine
Beta-1	SA & AV Node Myocardial cells Conduction system of the heart.	Increase heart rate & conduction Increase force of contraction	Tachycardia Hypertension Tachyarrhythmia	Metoprolol Bisoprolol Atenolol Esmolol
Beta-2	Smooth muscles of bronchioles, arterioles and uterus. Hepatocytes	Bronchodilatation Vasodilatation Uterine relaxation Glycogenolysis	Hypotension Tocolytic affect Hyperglycemia	Propranolol Nadolol Timolol

Table 1: Sympathetic receptor and related antihypertensive drugs

Abbreviations: AV Node: Atrio-ventricular node, SA: Sino-atrial node.Note all beta-2 blockers are also beta-1 blockers, but selective beta-1 blockers don't block beta-2 receptors at pharmacological doses.

Dopamine causes renal vasodilation, systemic vasoconstriction, and negative ionotropic effect.

NE has predominant Alpha 1 effect, hence Hypertension. Epinephrine (having more methylation has more affinity for beta receptors) at medium dose has a dominant beta impact. Therefore, hypotension and at high doses have an alpha effect too, hence Hypertension. Similarly, DA can have a variable effect on BP. So, BP depends on the type and quantity of chemicals secreted by the tumor[6].

Perioperative BP control: Target BP is <130/80 sitting and no less than 80/45 while standing. A heart rate of 60-70 sitting and 70-80 standing. Anti-hypertensive is started early for adequate control of BP. Even asymptomatic cases should have a perioperative assessment about BP control to avoid Intra op surge. Alpha 1 blocker are the first-choice drug, whereas beta-blockers are added after adequate alpha blockade to prevent vasospasm. Other options include calcium channel blockers and CAs synthesis inhibitors which can be used/added if needed[7].

Alpha antagonists: Common side effects include orthostatic hypotension, fluid retention, retrograde ejaculation, and may also worsen narrow-angle glaucoma. Selective & non-selective both works well for blood pressure control. The choice depends on side effects, institutional preference, and CVS risks. Few studies showed alpha blockade is unnecessary as many other effective drugs are available, which can help avoid alpha-blockers-related side effects and minimize the time needed for alpha-blockers to optimize blood pressure.

Alpha 1 blocker such as Doxazocin, 2-8mg/day (long-acting, once a day dose can be used. Another selective alpha-1 blocker is the short-acting drug Prazosin: 0.5-1mg three times a day, max dose: 15mg/day. Terazosin is also a short-acting alpha-1 blocker with 2-10mg/day. Short-acting drugs have the advantage of no postoperative hypotension, but they may not provide a good cover during operation. Alpha 1 blocker has no crossing of BBB and can avoid many side effects such as sedation. Non-Selective Alpha-Blockers: Phenoxybenzamine can be used at a dose of 10mg twice a day (maximum dose is 1mg/kg/day). Infusion 0.5mg/kg/day 3-5 days before operation can also be used. Long-acting (cover per op period, post-op hypotension). As it can cross BBB, hence sedation is a common side effect. Alpha2

blockage causes side effects such as tachycardia, nasal congestion[8]. [Table 2].

Drug	Class	Dose	Comments
Doxazocin	Alpha-1 Blocker	2-8mg/day, OD	Long acting
Prazocin	Alpha-1 Blocker	0.5-1mg TDS, Max dose: 15mg/day	Short acting
Terazocin	Alpha-1 Blocker	2-10mg/day, OD	Long acting
Phenoxybenzamine	Alpha 1&2 blocker	10mg BD Max 1 mg/kg/day. Infusion0.5mg/kg/day	Short acting
Amlodipine	CCA	5-10mg OD	Long acting
Nifedipine	CCA	20-120mg/day, (divided doses)	Short acting
Nicardipine	CCA	60-120mg/day	Short acting
Metyrosine	CA Synthesis Inhibitor	500 mg/day Max dose: 2gm/day	Long acting.
Nitroprusside	Vasodilator	0.5-10 mcg /kg/min infusion	Infusion. Used for hypertensive emergency only.
Phentolamine	Alpha-blocker (non-selective)	2.5-5 mg at 1mg/ min & if needed repeat every 3-5 minutes	IV Boluses or infusion. Used for hypertensive emergency only.
Mg Sulphate	Vasodilator	loading dose: 40-60mg/kg, then infusion 1-2gm/hour	Infusion. Used for hypertensive emergency only.

Table 2: Various drugs used and their dosage.

Beta-Blockers: Beta-blocker is used as add-on therapy to avoid alpha blockade-related tachycardia or CAs related cardiomyopathy, or CAs related tachycardia. One needs to be careful about the beta-blocker-related risk of hypotension, bradycardia, or cardiac arrest, especially in patients who have CAs related cardiomyopathy (CMP). B1 selective drugs such as atenolol or metoprolol can be used. B1 & Alpha 1 blocking drugs such as labetalol or carvedilol can also be used. Still, the beta effect is more potent than alpha. Hence it can't replace the regimen of alpha-blocker followed by beta-blocker[9].

Calcium Channel Blockers (CCB): CCB is used as alternative therapy when alpha-blockers can't be used due to contraindications or add-on therapy when alpha-blockers are not enough or as monotherapy for mild Hypertension. CCB can avoid many side effects of the alpha blockade and help reduce CAs related cardiomyopathy and coronary spasm. Monotherapy may not be enough for most cases except those who have mild Hypertension or are only biochemically active. Drugs includes Amlodipine (5-10mg/day), Nifedipine 30-120 mg/day, Nicardipine 60-120 mg/day[10], [Table 2].

CAs synthesis Inhibitors (Metyrosine): Metyrosine blocks Tyrosine Hydroxylase and prevents tyrosine conversion to DOPA. As it can cross BBB, hence side effects such as sedation, depression, extrapyramidal side effects due to lack of catecholamine in the brain. Also, it may not be commonly available in many countries. It's not enough when used alone but works better when combined with alpha-blockers. Dose is 500 mg/day (maximum dose is 2gm/day). It usually needs 3-5 days to kick in and reduces 50-60% of CAs. Hence it needs to be started 2-3 weeks before surgery. It is beneficial in those with metastatic disease or add-on therapy when other drugs are not enough[11].

CVS Evaluation: CAs related to cardiomyopathy (CMP), arrhythmia, coronary spasm, arteriosclerosis, left ventricular hypertrophy are the risks associated with excessive catecholamine exposure.

History, examination, ECG & Echocardiogram should be done to assess the cardiac functions. Arrhythmias risk can be reduced by using beta-blockers[12].

Correction of Hypovolemia: It is due to prolonged vasoconstriction. It can be managed by increasing sodium and fluid intake to avoid sudden hypotension during or after surgery. Saline infusion day before surgery and during the perioperative period is helpful. Cautions need to be exercised for those with heart failure or renal failure. Metabolic control, especially any hyperglycemia, is also essential for such cases [9,13].

Avoid precipitants: Norepinephrine & Epinephrine release is provoked by steroids, glucagon, vasopressin, Angiotensin II receptor blockers. Similarly, sympathomimetic drugs such as cocaine, amphetamine, phentermine, phenylethylamine should be avoided. NE Reuptake Inhibitors, including TCAs, SnRI are avoided. Avoid strenuous physical activity, alcohol, and smoking as all of these causes increased release of Cas[9, 12, 14].

Clinically or Biochemically silent Tumours: The clinically silent but biochemically active tumor should receive alpha

blockade or CCB preoperatively to avoid per op hypertensive issues. Biochemically silent tumors: may receive pre-op medication depends on CVS risk assessment[8,9,15].

Hypertensive Crisis: Precipitant factors include stress, postural change, activity, operative manipulation, drugs, & beta-blockers without alpha-blockers. It is usually defined as BP > 180/120 with or without end-organ damage [16]. Drugs needed to treat includes Sodium Nitroprusside Infusion (0.5-10 mcg /kg/min). Other options are Phentolamine boluses: 2.5-5 mg at 1mg/ min & if needed repeat every 3-5 minutes. Mg Sulphate infusion can also be used if the above does not work (loading dose: 40-60mg/kg, then infusion 1-2gm/hour). It is arteriolar and also inhibits CAs release[13, 17], [Table 2].

Peri-operative Hypotension: It is also expected due to intravascular hypovolemia, anaesthetics-related drop in blood pressure, the effect of the anti-hypertensive drugs used, &/or loss of catecholamines once a tumor is resected[18]. Additionally, any cardiac decompensation can add to hypotension. Chronic high catecholamine exposure can also cause downregulation of autonomic receptors, making this hypotension resistant to vasopressors [19]. Initial management includes adequate IV fluid replacement, optimizing anti0hypertensive drugs being used, and, if needed using vasopressors. It's important to exclude and manage any cardiac decompensation [12,13, 20].

CONCLUSION

Adequate management of pheochromocytoma patients during the perioperative period is crucial, mainly focusing on control of blood pressure, cardiac complications, intravascular hypovolemia, hypertensive crisis, and postoperative hypotension. Adequate cardiovascular assessment is needed before surgery. Many drug options are available, which can be used based on the severity of Hypertension, associated comorbidities, and drug side effects. Alpha-blockers are the cornerstone of blood pressure management in such cases. Other medications such as beta-blockers, calcium channel blockers, Metyrosine, etc., are often used as add-on therapy. Per operatively and postoperatively, a drop in blood pressure should also be managed vigilantly.

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