Management of pheochromocytoma: Old ideas and new drugs

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Abstract

Pheochromocytoma presents a challenge to the surgery team because of its clinical features and implications. The patient must be treated before the surgery until a stable hemodynamically state is achieved. The preoperative treatment includes α 2-short acting adrenergic blocking and β -blocker agents. The most crucial intraoperative moments are induction of anesthesia and hemodynamic oscillations. An adequate preoperative preparation, modern anesthetic drugs, good collaboration between the surgeons and the anesthesiologists, and postoperative care decrease the rate of complications and improve the outcome. This review aims to discuss all the possible pharmacological strategies of perioperative management of phoechromocytoma, focusing on new drugs and treatments.

Key words: Adrenal gland, magnesium sulfate, pheochromocytoma, remifentanil, α 2–short acting adrenergic blocking agents, β –blockers

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Introduction

Pheochromocytoma presents a neuroendocrine tumor originated from chromaffin cells in the adrenal medulla. Recently it has been reported that pheochromocytoma is responsible for approximately 0.1% of all cases of hypertension.^[1-3] The secreted catecholamines (dopamine, norepinephrine, and epinephrine) explain all the clinical manifestations of this type of tumor. Paragangliomas are extra adrenal chromaffin tumors secreting norepinephrine.

Pheochromocytoma may also be presented in association with other neuroendocrine tumors composing multiple endocrine adenoma type IIa and type IIb. Type IIa consists of medullary carcinoma of the thyroid, parathyroid adenoma, or hyperplasia, and pheochromocytoma. Type IIb is pheochromocytoma in association with phakomatoses such as von Recklinghausen's neurofibromatosis and von Hippel-Lindau disease.^[2]

Address for correspondence: Dr. Rudin Domi, Str Rruga e Dibres, 370, Tirana, Durres-Albania. E-mail: rudilaureta@hotmail.com Pheochromocytoma management presents difficulties, because of the clinical features and complications such as hypertension, tachycardia and dysrhythmias, cardiac ischemia or myocardial dysfunction, hyperglycemia, intravascular volume depletion, and lactic acidosis. It has been reported that 25% to 50% of hospital deaths in patients with pheochromocytoma occur during induction of anesthesia,^[2:4] so the correct pharmacological perioperative management is of great importance. An epinephrine-secreting tumor is presented with palpitations, headedness, syncope, anxiety, hypertension crises, and hypergylemia, whereas the patients with norepinephrine-secreting tumor can manifest sweating, hypertension, and headache.^[5]

The pharmacological perioperative management includes preoperative preparation, suitable drugs for anesthesia, pharmacological control of hemodynamic, blood volume restoration, and postoperative care.



The Influence of Perioperative Hemodynamic Changes on Patient's Outcome

Hypertension is a common chronic disease encountered in perioperative period. Blood pressure (BP) elevation incidence varies from 3% to 75%.^[6] Hypertension can influence on exacerbating the current diseases or can cause new perioperative complications. The complications of poorly controlled hypertension include myocardial infarction, renal failure, arrhythmia, and cerebrovascular disease. Many conditions in hypertensive patients with coronary artery diease (CAD) expose the patients at high risk for perioperative cardiac events. Age, diabetes, stroke/transient ischemic attack, smoking, heart failure, renal impairment, MI, peripheral vascular disease, and revascularization are independently associated with increased risk. In general, the high risk associated with these conditions was reduced by achieving a SBP of 140 mm Hg.^[7]

Some authors conclude that isolated systolic hypertension is associated with a 40% increase in the likelihood of cardiovascular morbidity perioperatively in coronary aortic bypass graft (CABG) patients.^[8]

The predicted outcome of arrhythmias varies widely depending on the type of arrhythmia. Simple premature ventricular contractions (PVCs) and paroxystic atrial tachycardia (PAT) usually have a good outcome. Complex PVCs may result in no significant effect on survival if they are eradicated or well controlled by drugs. However, the underlying heart problem may affect survival. The onset of arrhythmia can cause stroke episodes as well.

Pharmacological Options of Perioperative Management of Pheochromocytoma

The main objectives of perioperative optimization of the patients suffering from pheochromocytoma are as follows: The control of BP, control of heart rate and arrhythmias, and finally restoration of blood volume.

Perioperative hemodynamic control

The aims of preoperative preparation are to prevent an acute hypertensive crisis in the operating room and then to minimize catecholamine-induced hemodynamic changes during anesthesia and surgery. Preoperative hemodynamic treatment consists of the combination of an α -adrenergic blocker and a β -blocker. Phenoxybenzamine, a nonselective, noncompetitive, long-acting α -adrenergic blocker for many years, has been a mainstay of therapy.^[1,9-14] Phenoxybenzamine acts on α -adrenergic receptors, causing alkylation of receptor's complex by a reactive carbonium ion.^[11,12] Persistent hypotension and peripheral edema are the most common side effects. Because some patients may be very sensitive to the effects of phenoxybenzamine, it should be given initially in doses of 20–30 mg/70 kg orally once or twice a day. Most patients usually require 60–250 mg/day. The efficacy of therapy should be judged by the reduction of symptoms (especially sweating) and stabilization of BP. The optimal duration of α -blockade therapy may last from 3 days to 2 weeks. Because of its prolonged effect on α -receptors, it has been recommended to discontinue it 24 to 48 hours before surgery, in order to avoid refractory or severe hypotension after the adrenal gland has been removed. Short-acting, selective, competitive α 1-adrenergic receptors blockers (e.g., doxazosin 2-6 mg daily) have been used to prepare patients for surgery.^[10,11] Doxazosin, a quinazoline derivate, acts as selective α 1-adrenoreceptor. This nonlipophilic drug acts mostly in α_{1A} -receptor subtype, having no effects on presynaptic α 2-adrenoreceptors. This phenomenon is associated with neutral effect on norepinephrine reuptake and release, making not necessary for the β -blockers. A potential advantage of competitive, selective α 1-blockade is that once the tumor has been resected and excess catecholamine release eliminated, α -adrenergic receptors return quickly to normal function, leading to less hypotension. Prys-Roberts reported that effective preoperative BP was achieved using doxazosin without postural hypotension and central signs, so characteristic for phenoxybenzamine.^[11] Table 1 summarizes all the potential advantages and side effects of doxazosin and phenoxybenzamine.

Tachycardia as a consequence of elevated catecholamine levels must be treated with β -blockers. The β -blockade must not be instituted before initiation of α -blockade so that α -adrenergic activation would be unopposed in the vasculature. Propranolol, a nonselective $\beta_{1,2}$ -blocker with a half-life greater than 4 hours, is most frequently used. Most patients require 80 to 120 mg/day. Some patients with epinephrine-secreting pheochromocytomas may need doses up to 480 mg/day.

Several authors suggest the use of calcium channel

Table 1: The differences between doxazosin andphenoxybenzamine		
Doxazosin	Phenoxybenzamine	
Selective and effective α 1-adrenoreceptor	Not selective	
Not necessary β -blockers	β -blockers always necessary	
No central sign (headache, nasal stuffiness)	Central signs present	
No postural hypotension	More postural hypotenstion	
No peripheral edema	More peripheral edema	
No intraoperative significant hypotension	After the gland removed significant hypotension	
During the first postoperatively day, α1-adrenoreceptor blockade was reversed	Long postoperative α -adrenoreceptor blockade	

blockers (verapamil 120–240 mg every day, nifedipine 30–90 mg, diltiazem 180 mg daily) to prepare the patient in preoperative period. These agents do not cause postoperative hypotension and can control the rhythm and heart rate.^[15] These drugs reduce arterial pressure by inhibiting norepinephrine-mediated transmembrane calcium influx in vascular smooth muscle and not by decreasing catecholamine synthesis.^[15,16] It has been reported that calcium channel blockers can prevent the cathecholamine coronary spam as well.^[16]

Other drugs, including clonidine (0.1-1.2 mg), dexmedetomidine,^[17] and magnesium,^[18-22] have also been used to achieve suitable degrees of α -adrenergic blockade before surgery. Clonidine is a well-known presynaptic α 2-adrenoreceptors agonist. Its main pharamacological actions include reduced sympathetic tone, reducing anesthetic requirements, and sedation. Clonidine reduces BP through reduced sympathetic tone. Dexmedetomidine is a selective α 2-adrenoceptor agonist and has sedative and analgesic properties. The decreased BP and heart rate are attributed to the low catecholamine level. It can blunt sympathoadrenal responses to tracheal intubation and surgical stimuli.^[23,24]

The role of magnesium sulfate has been re-evaluated.^[18-22] It can decrease catecholamine release, reducing anesthetic drugs, and dilate the bronchial tree. Magnesium is predominantly an arteriolar dilator, reducing afterload but with minimal effects on venous return and preload. Magnesium has also been shown to be effective in controlling a postdelivery hypertensive crisis with pulmonary edema and encephalopathic signs.

The combination of labetalol (5-10 mg q 5 min) with magnesium sulfate is an effective combination for resistant cases.^[25] Labetalol selectively blocks α -1 receptors and nonselectively blocks beta receptors decreasing BP, heart rate, and myocardial oxygen demand. The ratio β/α is 7/1 when administered intravenous and 3/1 when orally given. Labetalol also reduces pulmonary vascular resistance and blunts the reflex increase of heart rate. Jankovic^[26] described a patient who was prepared with a regimen consisted in the combination with urapidil infusion (10–15 mg/h) and magnesium sulfate (1 g/h). Urapidil, a competitive and selective short-acting α -1 blocker is also an agonist at central serotoninergic receptors. After an i.v. bolus dose of 25 ± 50 mg, it acts within 5 ± 10 min. This drug has high bioavailability (72%), high clearance $(1.8 \pm 3.8 \text{ ml min} \pm 1 \text{ kg} \pm 1)$ and short elimination half-life $(2 \pm 4.8 \text{ h})$. These features make urapidil a suitable choice.^[27]

Table 2 summarizes the drugs used to prepare the patient suffering from pheochromocytoma.

Table 2: The common drugs used to prepare thepatient before pheochromocytoma's resection (maint:Maintaining; q: Every)

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Drug's name	Daily dose	Comments	
Phenoxybenzamine	60–50 mg	Central signs, peripheral edema, severe, and prolonged hypotension	
Doxazosin	2–6 mg	Short acting, no prolonged hypotension	
Propranolol	80–120 mg	Caution in asthmatic pts,	
Metoprolol	50–100 mg	conduction disturbances,	
Labetalol	5–10 mg q 5 minutes	severe heart failure	
Verapamil	120–240 mg	Caution in AV blocks,	
Diltiazem	180 mg	hypovolemia, sinus sick	
Nifedipine	30–90 mg	syndrome, and heart failure. Side effects: Elevated liver enzymes, headache, dizziness, fatigue, edema	
Clonidine	0.1–1. 2 mg	Rebound hypertension	
Dexmedetomidine	1 mg/kg in 10 minutes, 0.7 mg/kg/h infusion	side effects:depression, nightmares, anxiety, dry mouth, bradycardia	
Urapidil	10–15 mg/h	Caution because of severe hypotension	
Magnesium sulfate	1–8 mg loading dose, 1-4 mg/h maint. dose	Potentiates neuromuscular blockade, caution in heart block and renal failure	

Anesthetic considerations

The rigorous preoperative treatment minimizes the hemodynamic oscillations during surgery. Of course the strong collaboration between the surgeon and the anesthesiologist is of great importance. Nevertheless several drugs or anesthesia technique can be used. The use of all the drugs that increase sympathetic tone, such as ketamine, ephedrine, pancuronium, and desflurane, must be avoided.

Anesthesia induction and tracheal intubation must be smooth to avoid hypertension and tachycardia. Several drugs or techniques are proposed to blunt sympathetic response such as nitroprusside, nitroglycerin, magnesium sulfate, urapidil, esmolol, [28] nicardipine, [29] remifentanil, and propofol.^[30] Opioids are hemodynamically safe, do not alter cardiac output, and decrease heart rate in a dose-dependent manner. This last effect is mediated by the stimulation of the central vagal nuclei. Remifentanil is an ultrashort-acting opioid and used by infusion (0.05 μ g/kg/min) causes bradycardia and hypotension. It acts through binding μ -receptors in brain, spinal cord, and peripheral neurons. Its effect peaks 1.5-2 minutes after the bolus dose. Abrupt discontinuation induces hyperalgesia, so it must be associated with morphine, sufentanil, or fentanyl. Propofol is another anesthetic, a hypnotic drug with a short-acting effect. It increases the activity at inhibitory γ -aminobutyric (GABA) synapses. The second mechanism is realized by inhibition of glutamate (N-metil-D-aspartate) known as NMDA receptors. Propofol used as an infusion $(25-75 \mu g/kg/min)$ alone or in combination with remifentanil decreases the homodynamic response during pheochromocytoma resection. The pharmacological profile of these drugs makes total intravenous anesthesia (TIVA) a modern and safe anesthetic choice. Another modern option is dexmedetomidine. As mentioned above, dexmedetomidine has several features, making it a suitable choice. Its unique pharmacology profile provides a satisfactory preoperative sedation and control of intraoperative hemodynamic control while reducing anesthetic requirements and enhancing postoperative analgesia.^[31,32] Dexmedetomodine attenuates the sympathetic response to tracheal intubation, pediatric cardiac surgery, emergence from anesthesia, and recently described for pheochromocytoma resection in an adult.^[17,33]

Table 3 summarizes the most commonly used anesthestic drugs in daily practice.

Intraoperative hemodynamic management

During the surgical manipulations, brisk hemodynamic changes may happen. The hypertension control is often attained by nitropruside, nicardipine, nitroglycerine, magnesium, and/or by deepening the anesthesia. The hemodynamic changes are well treated by the combined use of nicardipine and esmolol. Nicardipine is a titrable short-acting calcium channel blocker without any effect on preload, and esmolol is a titrable ultrashort-acting β-adrenergic blocking agent. Esmolol is a selective β 1-receptor antagonist, with ultrashort duration because of rapid metabolization by esterases. It is a preferred drug because of fast onset, short action, and can be used in asthmatic patients. Fenoldopam stimulates dopamine 1 receptors, causing peripheral vasodilation and reducing BP. The common dose is 0.2 mg/kg/min. Its short duration makes fenoldopam a suitable, titratable drug. Tachycardia is often controlled by β -adrenergic blocking agents such as esmolol or metoprolol. Antihypertensive drugs are presented in Table 4.

After the adrenal gland has been removed, the hypotension may be severe and it can be controlled by epinephrine, norepinephrine, neosynephrine, ephedrine, dopamine, vasopressin,^[34] especially in the patients receiving phenoxybenzamine. This hypotension can be a consequence of blood volume depletion (because of diuretics), and long-acting non-specific α -adrenergic blocking agents. The vasopressor drugs are presented in Table 5. If the clinical situation is dominated by hypotension, pure α -adrenergic agonist (neosynephrine) is preferred. If the clinical situation is dominated by hypotension and bradycardia, a both α and β adrenergic agonist agents (epinephrine) may be a suitable choice. Vasopressin use merits a special attention. It acts on V1, V2, and V3 receptors, but only V1 receptor is responsible for hemodynamic parameters. Acting V1, it binds G- protein coupled receptors and activates phospholipase C. This leads to increased intracellular calcium. Vasopressin use is found

Table 3: Anesthetic drugs used in pheochromocytoma resection

Intravenous	anesthetic	drugs
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	Bolus dose	Infusion rate	Comments
Fentanyl	2–5 mg/kg	0.01 mg/kg/min	Respiratory depression,
Remifentanil	1 mg/kg	0.05 mg/kg/min	nausea, vomiting, hyperalgesia, urinary retention,
Propofol	2–2.5 mg/kg	25–75 mg/kg/min	Venous irritation, pain after injection, myoclonus, propofol infusion syndrome

Table 4: Antihypertensive medicaments used duringpheochromocytoma's resection

Antihypertensive drug	Dose	Comments
Fenoldopam	0.2 mg/kg/min	Tachycardia, hypokalemia
Nitroprusside sodium	1–2 mg/kg/min	Cyanide toxicity, reflex tachycardia, severe hypotension if not proper use.
Nitroglycerine	25–250 mg/min	Reflex tachycardia, tachyphylaxis, methemoglobinemia production, cerebral vazodilation.
Nicardipine	5.0 mg/h	Can exacerbate hypotension, bradycardia, heart failure, and Wolff-Parkinson-White syndrome
Phentolamine	1–5 mg	Short acting, no side effect reported
Hydralazine	2.5–20 mg q4h	Reflex tachycardia, rennin- angiotensine system activation
Esmolol	5–10 mg q3 min	Different grades of bronchial
Metoprolol	2.5–5 mg q2 min	hyperactivity, bradycardia
Labetalol	5–10 mg metabolic acidosis, pot the other drugs' effect	and AV block, osmolar gap metabolic acidosis, potentiate the other drugs' effect e.g. calcium channel blockers

Table 5: The most commonly used vasopressors inclinical practice

Vasopressor drugs	Dose	Mechanism of action
Epinephrine	1-20 mg/min	α/β agonist, in low dose more $\beta,$ increases inotropy, chronotropy, and BP
Neosynephrine	10-100 mg/min	$\alpha\text{-}1$ agonist, increases preload and afterload
Ephedrine	5-10 mg	synthetic noncatecholamine, causes release of norepinephrine, increases preload
Norepinephrine	1-30 mg/min	$lpha/\beta 1$ agonist, natural neurotransmitter, decreases organ blood flow
Dopamine	5-10 mg/kg/min	$\alpha/\beta/D$ dose-dependent agonist, precursor of norepinephrine, causes tachycardia and dysrthymias
Vasopressin	0.1-0.4 units/min	V1/V2/V3 receptors, can cause myocardial ischemia and infarction

suitable for treating sepsis induced hypotension.^[34] Several authors^[35] reported its usefulness in pheochromocytoma patients.

Conclusion

As a conclusion, the availability of new and short-acting anesthetic drugs, good pharmacological knowledge, and liberation by old and long-acting drugs are new concepts and weapons in the anesthesiologist's challenge to pheochromocytoma.

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