



Current Preoperative Preparation of Pheochromocytoma/Paraganglioma Syndrome

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Abstract

Pheochromocytomas and paragangliomas are catecholamine-producing neoplasms that can cause life-threatening hemodynamic instability, particularly intraoperatively, when the tumor is manipulated. Preoperative medical management reduces both preoperative morbidity and mortality. The current review discusses the latest literature on preoperative management. Preoperative strategies include a nonselective alpha-antagonist, selective alpha antagonists, calcium channel blockers, tyrosine hydroxylase inhibitors, and fluid and salt loading. Compared to selective alpha-antagonists, preparation with phenoxybenzamine prior to surgery is associated with superior intraoperative hemodynamic stability, but also more post-operative hypotension, adverse drug effects, and longer treatment period. No studies indicate a difference in clinical outcomes between phenoxybenzamine and selective alpha-antagonists. Calcium channel inhibitors have been shown in multiple studies to have similar hemodynamic stability and outcomes as patients with pre-operative alpha blockades, particularly in patients with smaller tumors. Metyrosine has been shown to attenuate intraoperative hemodynamic stability when used in conjunction with phenoxybenzamine or a selective alpha-antagonist. Magnesium-sulfate does not improve intraoperative hemodynamic instability when used in conjunction with nicardipine. Therefore multiple effective strategies exist to prevent morbidity and mortality associated with resection, however, a lack of preparation is not one of them.

Introduction

Pheochromocytomas (PCCs) are catecholamine-producing neoplasms arising from adrenal medullary chromaffin tissue. They are commonly characterized by episodic norepinephrine (NE) and epinephrine (E) hypersecretion. Extraadrenal PCCs are generally referred to as paragangliomas (PGLs). PPGL references both PCCs and PGLs. This review addresses the latest evidence regarding preoperative prep for patients with catecholamine-producing tumors.

The goal of preoperative care is to prevent a sudden release of catecholamines or attenuate the response to a release of catecholamines perioperatively. There are many ways to achieve this. Phentolamine was the first established preoperative pharmaceutical therapeutic, but many others have been developed and many recent studies have confirmed the efficacy of these therapies [1]. Pre-operative treatment can include the non-selective alpha-antagonists, selective alpha-antagonists, calcium channel blockers, inhibitors of catecholamine production, beta-blockers for reflex tachycardia, and others.

Preoperative preparation should be initiated, even in normotensive or asymptomatic patients. One 1997 study showed that two of seven patients with no preoperative therapy died of hypertensive crisis [2]. In a second study, two of five untreated patients required post-operative ventilation while only one of the other eighty-two patients, who were pre-treated, required it [3].

The length of time needed for a blockade is still controversial; however, it is common to be blockaded for 1-3 weeks. A 2016 study showed that of 381 patients with hormonally functional PPGLs, only 69.3% received adequate pharmacologic pre-treatment [4]. Patients with hypertension, evidence of metastatic disease, or were diagnosed by an endocrinologist, were significantly more likely to receive a proper blockade.

PCC Complications

PCCs are associated with several cardiovascular complications, due to overstimulation of

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adrenergic receptors. This includes cardiac hypertrophy, ischemic heart disease, myocardial infarction, cardiac arrhythmias, heart failure, Takotsubo syndrome, and shock. This leads to non-specific ST-T wave changes, an abnormal R wave, a prolonged QT interval, and symmetrically deep and wide inverted T waves on EKGs [5,6]. PCCs are also associated with hyperglycemia. In one study 31% of patients with PCCs had diabetes mellitus and 90% of these cases resolved after adrenalectomy [7].

Although no prospective studies have established optimal preoperative hemodynamic parameters, reports have suggested that patients should be treated until orthostatic hypotension is achieved [8]. Recent guidelines have recommended a target blood pressure of less than 130/80 mmHg while seated and greater than 90 mmHg systolic while standing with a target heart rate of 60-70 bpm seated and 70-80 bpm standing [9]. Additionally, it has been reported that ST-T changes on electrocardiogram should be absent for at least a week and patients should not have more than 1 premature ventricular contraction every 5 minutes [8,10,11]. Most studies are concordant that normotensive PCC patients should also be treated with preoperative alpha blockade because they have similar hemodynamic intraoperative instability compared to hypertensive patients [9,12,13]. The totality of evidence suggests that all patients received preoperative blockade until orthostatic hypotension is achieved.

Physiological Basis

The goals of preoperative management are to reduce the possibility of a catecholamine surge and its effect on target organs upon anesthesia induction and tumor manipulation while insuring stability in postoperative care [14]. The following discussion summarizes the physiology relevant to biochemical testing, functional imaging, and pharmacological intervention for PPGL.

Preganglionic sympathetic nerves synapse with acetylcholine on the chromaffin cells in the adrenal medulla which release epinephrine and norepinephrine. Chromaffin cells have their embryologic origin in neural crest cells. Neural crest cells also migrate throughout the body forming ganglions. Acetylcholine synapses on nicotinic receptors on chromaffin cells leading to calcium channels opening and subsequent E and NE release.

The production of E and NE are important in the biochemical screen and clinical complications of PCCs. Tyrosine, the amino acid from which they are derived, is actively transported into chromaffin cells then hydroxylated to 3,4-dihydroxyphenylalanine (L-dopa) by tyrosine hydroxylase, the rate limiting enzyme in the production of catecholamines. Tyrosine hydroxylase is the target of the drug metyrosine. L-dopa is then converted to dopamine by aromatic L-amino acid decarboxylase. Dopamine is transported into secretory vesicles and then hydroxylated by dopamine β -hydroxylase to form norepinephrine. Norepinephrine is methylated by phenylethanolamine N-methyltransferase to create epinephrine in the cytosol, both of which are stored in the secretory vesicles, ready to be released. They are transported into the vesicles by the vesicular monoamine transporter. Metaiodobenzylguanidine (MIBG) is a radiolabeled molecule similar to norepinephrine and can be taken up into chromaffin cells through the norepinephrine transporter. A cell membrane transporter, the norepinephrine transporter, assists in reuptake of NE from the synaptic cleft and is a target of amphetamines, methylphenidates, and cocaine.

E and NE are metabolized by catecholamine-O-methyltransferase

into metanephrine and normetanephrine in the chromaffin cells. This is important because while E and NE are released episodically from PCCs, the metabolites, metanephrine and normetanephrine, are continuously leaked into the blood. This along with the evidence that they stay in circulation longer than catecholamines makes them a much better clinical marker for PCCs [15]. Alternatively, E and NE are metabolized by monoamine oxidase into dihydroxyphenylglycol which is converted to vanillylmandelic acid. Monoamine oxidase inhibitors for depression can therefore lead to hypertensive crisis in PCC patients. Normally intra-adrenal O-methylation of E and NE is not the major route of metabolism. The adrenals produce 90% of metanephrine and 23% of normetanephrine (the largest source) that are in the blood [16]. When a patient has a PCC this becomes the major mechanism of E and NE degradation [17].

E and NE activate three families of receptors. Alpha-1 adrenergic receptors operate postsynaptically to signal cells to open calcium ion channels. Alpha-2 adrenergic receptors operate on the presynaptic membrane to negatively regulate catecholamine release as well as post-synaptically. Together the alpha-adrenergic mediated reactions lead to vasoconstriction, bronchoconstriction, cardiac contractility, hepatic glucose production, decreased insulin release, and more. Beta-adrenergic receptors stimulate cAMP release in the affected cells as opposed to a calcium ion channel mediated system. This leads to cardio acceleration, increased myocardial strength, glycogenolysis, lipolysis, and increased glucagon release.

Preoperative Medications

Phenoxybenzamine

Phenoxybenzamine is an irreversible nonselective alpha-antagonist with a half-life of 24 h. The non-competitive nature of the drug allows it to maintain its alpha blockade during a catecholamine surge and the long half-life of the drug makes it easy for patients to be compliant [8]. Patients are usually started at 10-mg dose twice daily and increased by 10 mg per day at night to avoid injuries related to the orthostatic hypotension [18]. One study looking at Phenoxybenzamine use at a single medical center showed that, over the past two decades, the average phenoxybenzamine dose increased from 59 mg to 106 mg and intraoperative hemodynamic stability improved significantly [19]. The subsequent alpha-2 receptor blockade results in reflex tachycardia due to increased NE release by cardiac sympathetic nerve endings [18,20]. Phenoxybenzamine is started 7-21 days before the surgery and once the alpha blockade is established beta receptor blockers (propranolol or atenolol) can be used to reduce the resultant tachycardia or for patients with tachyarrhythmias [21]. Beta-blockers may be dangerous in patients with catecholamine-related cardiomyopathy and it is suggested to use beta-1 selective blockers such as atenolol and metoprolol for them [5]. The long-acting nature of phenoxybenzamine can prolong hypotension postoperatively [20].

Selective alpha-1 receptor antagonists

Doxazosin, Prazosin, and Terazosin are short acting competitive antagonists of alpha-1 adrenergic receptors with minimal alpha-2 receptor effects [18,21]. These drugs have a shorter half-life, shorter duration of action, less reflex tachycardia by preserving the alpha-2 effect, and a lower incidence of postoperative hypotension than phenoxybenzamine. Their shorter half-life means that these drugs require more frequent dosing to sustain a blockade. The competitive nature of these drugs means that they are more susceptible to be overcome by a surge of catecholamines [20,22]. Doxazosin

is popular due to its longer plasma half-life of 22 h resulting in daily dosing [18,20,23]. Doxazosin is less effective at crossing the blood-brain barrier and therefore causes less central sedation than phenoxybenzamine [20,24]. One study of Doxazosin showed that of 48 patients with PCCs who were treated with doxazosin intraoperative hypertensive crises were observed in 15% (all treated with no aftermath) and postoperative hypotension was observed in 8% [22]. Urapidil is another alpha-1-receptor selective antagonist that can be administered intravenously with the blockade being set up 3 days prior to surgery. In one study this led to a reduction in days in the hospital and reduced health care costs while maintaining the same level of safety and efficacy as phenoxybenzamine [25].

Phenoxy vs. Doxazosin

Many studies have been published recently comparing the efficacy of selective alpha-1 antagonists versus phenoxybenzamine. All of them concluded that both sets of drugs were effective at perioperative blood pressure management in patients with PCCs [3,20,22-30]. Due to the rarity of the disease a clinical trial would be difficult and these studies are mainly single-center retrospective chart reviews spanning many years and contain a limited number of patients. The main difference found in these studies is that systolic blood pressure is more likely to spike with selective inhibitors than phenoxybenzamine; however, this is controversial because one study showed fewer systolic blood pressures above 200 mmHg in the group treated with Doxazosin [28]. Another point of controversy is that two studies showed no difference in intraoperative hemodynamic stability [24,29,30] while three more recent studies concluded that selective inhibitors were associated with significantly more episodes of intraoperative hypertension [3,26,27]. Since none of the studies showed a difference in clinical outcomes, they noted that selective antagonists tend to be associated with fewer side effects and shorter treatment periods [20,28].

Availability and physician experience may play a role in which medication is given as well. Many physicians prefer selective alpha inhibitors such as prazosin because phenoxybenzamine can be difficult to titrate and the complications associated with alpha inhibitors are less severe with selective blockers [23,31]. Due to recent changes in pharmaceutical pricing and availability, phenoxybenzamine is often prohibitively expensive, while many selective blockers are available and financially feasible.

Calcium Channel Inhibitors

Dihydropyridine calcium channel blockers such as amlodipine, nifedipine or nicardipine are a low-cost and widely available arterial vasodilator. They work by blocking the NE mediated calcium influx in smooth muscle cells [5,32]. Some authors have suggested that they prevent catecholamine induced spasms of the coronary arteries [33,34]. A 2005 study retrospectively reviewed 105 PCC patients who were treated with nicardipine [35]. They showed that 13% of patients had systolic blood pressures greater than 220 mmHg, 10% of patients had postoperative complications and 3% of patients died. A 2012 study comparing patients treated with nicardipine versus phenoxybenzamine showed no difference in hemodynamic stability and outcomes particularly for patients with PCCs smaller than 3 cm [36]. A 2014 study directly compared preoperative alpha and calcium channel blockades and found that calcium channel blockades produced less intraoperative severe hypotension, thus reducing the amount of intraoperative vasoactive drugs used and the fluid volume required [32]. However, the incidence and duration of hypertensive

episodes was significantly greater. A previous article suggested that these could play an important role in preoperative treatment of normotensive patient's with PCCs to avoid the orthostatic hypotension associated with alpha-blockers [5]. A 2015 study showed that there was no difference in postoperative morbidity in patients treated with calcium channel blockers versus alpha-blockers [37]. The totality of evidence in the literature suggests that calcium channel blockers are effective at managing intraoperative hemodynamic fluctuations, particularly in smaller tumors.

Metyrosine

Metyrosine, a tyrosine hydroxylase inhibitor, has also been used as a preoperative therapy for pheochromocytomas. A 1997 study showed that metyrosine in combination with phenoxybenzamine or prazosin greatly decreased the use of intraoperative vasopressors and phentolamine over just the alpha blockade alone [2]. A 2015 study from a center that primarily used phenoxybenzamine in combination with metyrosine for preoperative management showed that when phenoxybenzamine was used without metyrosine cardiovascular specific complications (such as arrhythmias) increased 16% and intraoperative hemodynamic variability (heart rate and systolic blood pressure) was significantly greater [38]. However, metyrosine caused a number of side effects such as somnolence, depression and galactorrhea [2,5]. Due to the potential side effects and few studies supporting its use, metyrosine is reserved for patients cannot tolerate alpha blockers or whose hypertension is refractory to alpha-receptor and calcium channel blockade. One cautionary case report highlighted the failure of metyrosine as a monotherapy to control preoperative and intraoperative hypertension, particularly during tumor manipulation for a patient [39].

Other Preoperative Therapeutics

There are a few case reports of other therapies that have been successfully used to prepare PCC patients for surgery. One physician treated a patient with a PCC at the carotid bifurcation with octreotide and labetalol for three months to control the symptoms before performing surgical resection with minimal blood pressure fluctuations [40,41]. Another report of four cases from Oman showed the successful use of labetalol in preoperative management of PCCs in the absence of phenoxybenzamine [40]. This is commonly discouraged due to only having a 1:7 alpha to beta blocker ratio which results in paradoxical hypertension [9,33,42]. Beta-blockers can be used but only after alpha blockade is effective in order to prevent unopposed alpha activation. Unopposed alpha-adrenergic agonism can lead to vasoconstriction increasing blood pressure. The same report suggested that magnesium sulfate infusion during surgical preparation assisted in the intraoperative hemodynamic stability. However, a study on nicardipine as a preoperative therapy also showed that magnesium sulfate did not have an effect on the intraoperative hemodynamic stability [36]. As previously stated, even normotensive patients should be treated with preoperative blockade to reduce perioperative morbidity and mortality [32].

Fluid Preparations

Although no studies have specifically addressed the practice of fluid and electrolytes resuscitation in preparation for surgery, many highly recommend it. Chronically high levels of catecholamines from PPGLs contracts intravascular volume. Salt or saline loading should be instituted in preoperative patients to expand the intravascular volume [43]. It also allows patients to increase their pre-operative

alpha-blockade further before achieving orthostatic hypotension and it may reduce post-operation hypotension [9]. Some surgeons admit patients the day before the surgery to increase their intravascular volume with isotonic intravenous fluids while others encourage preoperative salt ingestion [8,44,45].

Anxiety Preparation

Reducing anxiety prior to induction is crucial to prevent apprehension from causing catecholamine surges [46]. Long-acting benzodiazepines the night prior and IV midazolam prior to transfer on the day of surgery can reduce the risk of hypertensive crises during induction. H2 blockers may also be used, but with caution as some antiemetics can trigger a crisis. Vasodilators should be available and ready to administer for various purposes: nitroglycerin, nitroprusside, nicardipine, diltiazem, magnesium sulfate, and vasoconstrictors when indicated as well as esmolol for heart rate control.

Summary of Preoperative Preparation

Multiple successful strategies exist for the preoperative management of PPC patients. Even when patients are normotensive, preoperative preparation is required. Phenoxybenzamine effectively controls intraoperative hemodynamics but leads to prolonged postoperative hypotension. It also can lead to reflex tachycardia, central sedation and orthostatic hypotension. Selective alpha inhibitors such as urapidil, prazosin, terazosin, and doxazosin have less intraoperative hemodynamic control but also less postoperative hypotension and a decreased side effect profile. They have varying half-lives which are shorter than phenoxybenzamine, making them easier to titrate. Selective alpha inhibitors are currently more cost effective and are more widely available than phenoxybenzamine in many regions. Reflex tachycardia after the initiation of alpha-blockade may require beta-blockers such as metoprolol or atenolol. Dihydropyrimidine calcium channel blockers (i.e. amlodipine, nifedipine, and nicardipine) are widely available and effective at controlling intraoperative hemodynamics, particularly in smaller and less active tumors. They also can be added to an alpha-blockade for patients with poorly controlled hypertension. Metyrosine, while it should not be used as a monotherapy, is an excellent additional therapy that has been shown to reduce complications.

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