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REVIEW

Pharmacological management of intraoperative hypertensive crises in pheochromocytoma: A narrative review of esmolol, nicardipine, and sodium nitroprusside

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Management of pheochromocytoma, particularly in the perioperative period, requires a tailored pharmacological approach to address hemodynamic instability and hypertensive crises. This review evaluates the safety, efficacy, and clinical context of esmolol, nicardipine, and sodium nitroprusside in managing blood pressure and heart rate during pheochromocytoma resection. Esmolol, an ultra-short-acting β1-adrenergic antagonist, is essential in controlling tachyarrhythmias and myocardial stress in the perioperative period. Its rapid onset and short half-life enable precise titration, though continuous monitoring is required to mitigate the risk of bradycardia and hypotension. Nicardipine, a dihydropyridine calcium channel blocker, is effective in controlling acute hypertensive episodes and maintaining coronary perfusion. Its selectivity for vascular smooth muscle makes it an ideal agent for patients with low ejection fraction, minimizing cardiac depression. In contrast, sodium nitroprusside, a direct nitric oxide donor, provides immediate and reversible vasodilation, which is crucial for managing hypertensive crises during surgery. However, its use necessitates close monitoring due to the risk of cyanide and thiocyanate toxicity with prolonged use.

Choosing the most appropriate antihypertensive therapy depends on patient-specific factors such as comorbidities and the severity of hemodynamic changes. Each medication's therapeutic effect, side effects, and risk profiles should be carefully considered to optimize clinical outcomes in high-risk patients undergoing pheochromocytoma surgery. This review highlights the importance of understanding the pharmacodynamics and appropriate use of these agents in clinical practice to improve patient management and outcomes.

Keywords: pheochromocytoma, tumor, hypertensive crises, pharmacological management

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Introduction

Pheochromocytoma is a rare catecholamine-secreting tumor derived from chromaffin cells of the adrenal medulla, characterized by excessive synthesis and release of catecholamines, including norepinephrine, epinephrine, and dopamine. These catecholamines play a critical role in maintaining cardiovascular homeostasis, but their uncontrolled secretion can trigger severe hemodynamic disturbances, including paroxysmal or sustained hypertension, tachyarrhythmias, and end-organ complications [1,2].

Surgical resection remains the definitive treatment for pheochromocytoma, but intraoperative tumor manipulation frequently results in sudden catecholamine surges, posing a significant risk for hypertensive crises, cardiac arrhythmias, and myocardial ischemia. The perioperative management of these patients, therefore, requires precise pharmacological strategies aimed at controlling acute hemodynamic instability [1,4].

Pharmacologic agents with rapid onset, short half-life, and dose-titratable effects are preferred to ensure intraoperative cardiovascular control. Among these, esmolol, an ultra-short-acting beta-selective adrenergic antagonist, is particularly useful for rate control and myocardial protection. Nicardipine, a dihydropyridine calcium channel blocker, is widely used for its potent arterial vasodilatory effects without negative inotropy. Sodium nitroprusside, a direct nitric oxide donor, provides fast and reversible vasodilation, though its use requires careful monitoring due to potential cyanide toxicity [5].

This narrative review aims to critically evaluate the pharmacological profiles, indications, efficacy, and safety of esmolol, nicardipine, and sodium nitroprusside in the management of intraoperative hypertensive crises associated with pheochromocytoma, offering a comparative perspective for optimizing perioperative outcomes.

Hypertensive crises in pheochromocytoma: clinical features, catecholamine dynamics

Hypertensive crises encompass a spectrum of life-threatening conditions, including accelerated or malignant hypertension, hypertensive encephalopathy, acute left ventricular failure, aortic dissection, and pheochromocytoma crisis. Additional clinical scenarios classified under hypertensive crises include hypertensive emergencies precipitated by interactions between monoamine oxidase inhibitors and tyramine-rich foods or medications, eclampsia, drug-induced hypertension, and potentially intracerebral hemorrhage. These conditions necessitate urgent medical intervention due to the substantial risk of end-organ damage, hemodynamic instability, and adverse systemic outcomes. Prompt recogni-

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tion and targeted therapeutic strategies are essential to mitigate morbidity and mortality associated with hypertensive crises [6]. Hypertension occurs in roughly 80-90% of persons diagnosed with pheochromocytoma. Approximately 50% exhibit persistent hypertension, 45% have paroxysmal hypertension, and 5-15% maintain normotension [7]. The quintessential clinical manifestation of pheochromocytoma is defined by the triad of cephalalgia, palpitations, and diaphoresis. Other symptoms often seen in afflicted people could involve tachycardia, anxiety, and pallor [8].

Most individuals with pheochromocytoma have significantly high catecholamine ranges, with norepinephrine and epinephrine reaching 5 to 10 times the normal level. Normotension is often observed in individuals with reduced catecholamine levels, particulary in cases involving dopamine-predominant tumors, small or biochemically silent tumor variants, and genetic subtypes with atypical catecholamine secretion profiles which contribute to normotension despite the presence of a tumor.

The clinical manifestation of hypertension differs according to adrenal catecholamine levels and secretion patterns. Notwithstanding increasing cellular catecholamine levels, considerable quantities may be metabolized, resulting in normal or near-normal plasma catecholamines while metanephrines remain elevated [2]. Chronic hypertension is strongly linked to increased plasma norepinephrine concentrations, which are persistently secreted by the tumor. Furthermore, individuals with tumors that mostly release norepinephrine continuously have elevated 24-hour, daytime, and overnight blood pressure relative to individuals with tumors that largely secrete epinephrine [9].

Hypertensive crisis and cardiovascular complications in pheochromocytomas

Acute manifestations

Pheochromocytomas and hypertensive crises are associated with severe acute cardiovascular and cerebrovascular disturbances. Excess catecholamine secretion can induce severe labile hypertension, cardiovascular collapse, pulmonary edema, and acute respiratory failure. Early clinical reports have described cardiac symptoms with electrocardiographic abnormalities, including sinus tachycardia, wandering pacemaker rhythms, and generalized ST-segment and T-wave abnormalities. During surgical manipulation, intermittent dysfunction of the sinoatrial and atrioventricular nodes and premature contractions have been documented. Some patients exhibit electrocardiographic findings resembling ischemic heart disease, such as ST-segment elevations or depressions and T-wave inversions. Patients with pheochromocytoma are at elevated risk for ventricular arrhythmias, including torsades de pointes, potentially progressing to ventricular fibrillation and sudden cardiac death [10].

Chronic manifestations

Undiagnosed hypertension secondary to pheochromocytoma frequently leads to hypertrophic cardiomyopathy, representing a major chronic cardiac complication. Persistent catecholamine excess is associated with prolonged electrocardiographic alterations indicative of myocardial ischemia, strain, or catecholamine-induced myocarditis. In certain cases, repolarization anomalies such as peaked T-waves, large T-wave inversions, and prolonged corrected QT intervals are observed. After pharmacologic alpha-adrenergic inhibition or tumor removal, myocardial infarction-like electrocardiographic abnormalities generally resolve. Sinus node dysfunction and bradyarrhythmias, although infrequent, have been documented in the literature and often resolve following ablation [10].

Complications

Cardiac complications associated with pheochromocytomas include atrial and ventricular conduction disturbances, with rare cases of atrioventricular block. Many patients develop acute coronary syndrome presentations, including unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction, attributed to catecholamine-induced myocardial stress. Given the risk of life-threatening cardiovascular events, comprehensive management strategies incorporating continuous electrocardiographic monitoring and hemodynamic stabilization are essential to mitigate adverse outcomes and optimize prognosis. Figure 1 illustrates the multisystem complications related to pheochromocytoma, highlighting its extensive impact on multiple organ systems [10].

Preoperative optimization and management of hypertension in pheochromocytomas

Comprehensive preoperative planning has significantly reduced perioperative morbidity and mortality in patients with pheochromocytomas. Excess catecholamine secretion leads to widespread activation of alpha- and beta-adrenergic receptors, resulting in vasoconstriction, tachycardia, and hypertension. While the necessity of mandatory preoperative antihypertensive therapy remains a subject of debate, evidence supports its role in mitigating intraoperative and postoperative cardiovascular complications. The Endocrine Society recommends preoperative alpha-adrenergic blockade, accompanied by adequate fluid and sodium supplementation, to optimize hemodynamic stability. However, contemporary approaches advocate for a more individualized and flexible preoperative management strategy, tailored to each patient's clinical profile and hemodynamic parameters [11].

Hypertension control

In pheochromocytoma individuals, paroxysmal, chronic, or intermittent hypertension might strike. The first-line therapy for alpha-receptor activation is alpha-blockers. Commonly recommended is phenoxybenzamine; treatment usually begins with 10 mg twice daily and progressively increases to 20-30 mg twice daily over 10-14 days until blood pressure is controlled using beta and calcium

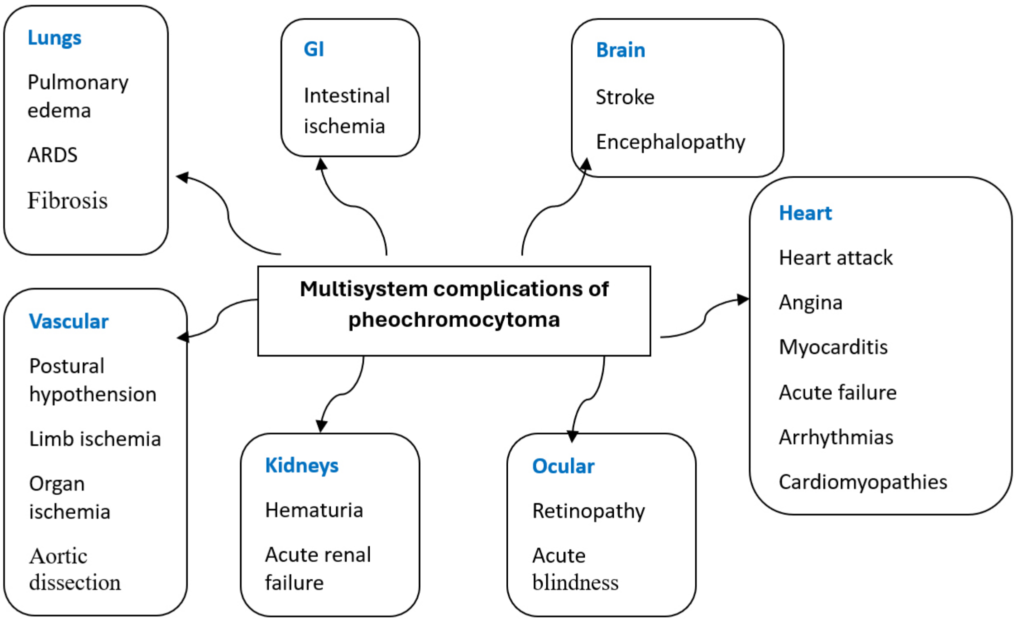

Fig. 1. Multisystem complications of pheochromocytoma.

channel blockers as adjuncts. Only after alpha blockade can beta blocking be started; otherwise, it might lead to abrupt cardiac failure or pulmonary edema, severe vasoconstriction, or both. Calcium channel blockers reduce norepinephrine-mediated calcium influx into smooth muscle cells, therefore causing vasodilation. Amlodipine is taken 10 to 20 mg/day. The table I summarizes the treatment lines for intraoperative hypertensive crisis in pheochromocytoma along with their mechanisms of action [11].

Alpha-Receptor blockers

Alpha-adrenergic antagonists inhibit alpha-adrenergic receptor activation by endogenous catecholamines, modulating vascular tone and sympathetic activity. Alpha$_1$-adrenergic receptors, coupled to Gq proteins, mediate vasoconstriction via phospholipase C activation, increasing intracellular calcium. Alpha$_2$-adrenergic receptors, linked to Gi proteins, inhibit adenylyl cyclase, decreasing cyclic adenosine monophosphate and modulating neurotransmitter release. Nonselective agents (e.g., phenoxybenzamine) block both alpha$_1$- and alph$_2$-receptors, with phenoxybenzamine irreversibly inactivating receptors, providing sustained catecholamine blockade but increasing the risk of reflex tachycardia and postoperative hypotension. In contrast, selective α_1-antagonists (e.g., prazosin, doxazosin) selectively inhibit α_1-mediated vasoconstriction, offering more predictable blood pressure control and fewer adverse effects. Clinically, alpha-adrenergic antagonists are essential in the preoperative management of pheochromocytomas to prevent hypertensive crises, as well as in the treatment of hypertension and benign prostatic hyperplasia. Careful titration is necessary to avoid orthostatic hypotension and syncope, especially upon treatment initiation [11].

Antagonists of beta-recepter

To prevent acute cardiac decompensation, beta-adrenergic blockade should be initiated only after adequate alpha-blockade. This strategy effectively controls tachycardia resulting from excessive catecholamine secretion or alpha-blockade-induced vasodilation. Cardioselective beta-blockers, such as metoprolol and bisoprolol, are preferred due to their reduced incidence of adverse effects compared to nonselective agents. While labetalol possesses both alpha- and beta-adrenergic blocking properties, it should not be used as a substitute for dedicated alpha-blockade, as its beta-antagonistic effects may precipitate unopposed alpha-adrenergic vasoconstriction. Proper preoperative pharmacologic preparation remains a cornerstone of successful surgical management in patients undergoing resection of pheochromocytomas and paragangliomas [11].

Table I. Treatment. Line class of medication

Treatment Line	Class of medication	Mechanism of action
First line	Alpha blockers Ex.: Phenoxybenzamine; Prazosin; Doxazosin	Inhibit alpha-adrenergic receptors, leading to vasodilation and reduced blood pressure
Second line	Beta blockers Ex.: Propanolol; Metoprolol; Atenolol; Labetolol	Block beta-adrenergic receptors, decreasing heart rate and contractility
Third line	Calcium channel blockers Ex.: Nifedipine, Amlodipine, Verapamil, Diltiazem	Inhibit calcium influx in vascular smooth muscle, causing vasodilation

Calcium channels blockers

Catecholamine-induced vasoconstriction leads to a contracted intravascular volume, necessitating volume expansion to mitigate the risk of severe orthostatic hypotension following α-blockade. To achieve this, patients are advised to increase oral fluid intake to 2-3 liters per day and sodium consumption to 5-10 grams per day. In cases where oral intake is insufficient, intravenous crystalloids or colloids may be administered to ensure adequate volume restoration. Serum hematocrit levels serve as a key indicator of volume expansion, with a 5-10% decrease suggesting effective intravascular replenishment. Preoperative optimization generally spans 5-15 days and incorporates alpha-adrenergic blockade, volume expansion, and metabolic stabilization to enhance perioperative outcomes [11].

Preoperative optimization

Preoperative management aims to achieve optimal hemodynamic stability, including blood pressure control (targeting <130/80 mmHg in the seated position while maintaining systolic blood pressure >90 mmHg when standing), intravascular volume expansion, and metabolic stabilization. Alpha-adrenergic blockade remains the cornerstone of therapy, ensuring adequate vasodilation and prevention of intraoperative hypertensive crises. Beta-blockers are introduced subsequently to control reflex tachycardia, while calcium channel blockers serve as adjuncts for blood pressure management. In select cases, tyrosine hydroxylase inhibitors, such as metyrosine, may be employed to suppress catecholamine synthesis. Given the risk of catecholamine-induced hyperglycemia, glycemic control through insulin or oral hypoglycemic agents is essential. Furthermore, a comprehensive cardiac assessment is warranted to evaluate for catecholamine-induced cardiomyopathy or myocardial ischemia, ensuring perioperative cardiovascular risk stratification and optimization [12].

Intraoperative administration

Anesthetic management in pheochromocytoma surgery focuses on maintaining hemodynamic stability, particularly during critical events such as laryngoscopy, peritoneal insufflation, and tumor manipulation, which can precipitate catecholamine surges. Sevoflurane is the preferred inhalational anesthetic due to its favorable cardiovascular profile, while propofol or etomidate are recommended for induction, particularly in patients with catecholamine-induced cardiomyopathy, due to their minimal hemodynamic impact [13]. Ketamine is strictly contraindicated due to its sympathomimetic effects, which can exacerbate hypertension and tachycardia. Intraoperative invasive hemodynamic monitoring, including continuous arterial blood pressure measurement and central venous access, is essential for real-time cardiovascular assessment and prompt intervention. Additionally, early ligation of the adrenal vein is strongly recommended to minimize intraoperative catecholamine release, thereby reducing the risk of hypertensive crises and improving perioperative hemodynamic control . The table II provides a detailed overview of the pharmacological agents used, including their respective drug classes, mechanisms of action and relative potency [14].

Postoperative management

Postoperative critical care monitoring is essential for the early detection and management of hemodynamic instability following pheochromocytoma resection [15]. Hypotension may result from residual α-adrenergic blockade, intravascular volume depletion, or intraoperative blood loss, necessitating prompt fluid resuscitation and, if required, the administration of vasopressors to maintain adequate perfusion. In cases of persistent hypertension, further evaluation is warranted to assess for fluid overload, autonomic dysfunction recovery, renal artery involvement, or residual tumor presence. Endocrine complications, such as hypoglycemia due to sudden withdrawal of catechola-

Table II. Pharmacological management of hypertensive crisis in pheochromocytoma patients

Medication	Drug class	Mechanism of action	Relative potency
Phentolamine	non-selective alpha blocker	block both alpha-1 and alpha 2 adrenergic receptors, reducing vasoconstriction and lowering blood pressure	very high
Phenoxybenzamine	non-selective alpha blocker	irreveribly blocks alpha 1and alpha 2 adrenergic receptors, decreasing vaso-constriction and blood pressure	high
Prazosin	selective alpha -1 blocker	selectively blocks alpha -1 adrenergic receptors leading to vasodilation and reduced blood pressure	moderate
Esmolol	cardioselective beta blocker	selectively blocks beta -1 adrenergic receptors, decreasing heart rate and myocardial contractility	low
Nicardipine	calcium channel blocker	inhibits calcium influx into vascular smooth muscle, causing vasodilation and lowering blood pressure	low
Nifedipine	calcium channel blocker	inhibits calcium influx into vascular smooth muscle, leading to vasodilation and decreased blood pressure	low
Nitroprusside	direct vasodilator	relaxes vascular smooth muscle through nitric oxidee release, leading to reduced blood pressure	very high
Labetolol	combined alpha and beta blocker	blocks both alpha and beta-adrenergic receptors reducing heart rate and peripheral vascular resistance	high
Nitroglycerin	nitrate vasodilator	dilates veins and arteries, decreasing preload and afterload thus lowering blood pressure	moderate
Propanolol	non-selective beta blocker	blocks both beta1 and beta 2 adrenergic receptors decreasing heart rate and myocardinal contractility	low

mine-induced insulin resistance and cortisol insufficiency in patients with bilateral adrenalectomy or underlying adrenal insufficiency, require close metabolic monitoring and appropriate management [16].

Long-term surveillance is crucial to detect recurrence or metastatic disease. Annual fractionated plasma or urinary metanephrine testing is recommended to screen for biochemical recurrence, ensuring early detection and timely intervention in affected individuals [15].

Role of Esmolol in hemodynamic stabilization. Pharmacological properties

Esmolol is a short-acting, cardioselective beta-adrenergic blocker with low partial agonist action and no membrane depressive effects [16]. Esmolol lowers heart rate, myocardial contractility, and oxygen consumption by blocking beta receptors with competition. Rapid metabolism by red blood cell esterases shortens its half-life, enabling accurate titration and hemodynamic parameter modification [17].

Clinical uses

Esmolol is used to treat supraventricular tachycardias such atrial fibrillation and flutter and endotracheal intubation-related hypertension in the short term. Manage hypertensive crises, aortic dissection, acute coronary syndromes, thyrotoxicosis, refractory ventricular arrhythmias, and catecholamine surges during electroconvulsive treatment off-label. Perioperative and critical care settings need precise hemodynamic management, which is useful due to its safety and quick start [17].

Esmolol is indicated intraoperatively for the regulation of catecholamine-induced tachycardia during pheochromocytoma resection. Its administration is appropriate only after the establishment of adequate alpha-adrenergic blockade, thereby mitigating the risk of unopposed α-receptor-mediated vasoconstriction. Owing to its ultra-short half-life and rapid onset of action, esmolol permits precise and dynamic modulation of heart rate during the operative course [18].

Safety and efficacy

Esmolol treats supraventricular tachycardia, intraoperative hypertension, and postoperative care, according to clinical research. It is well-tolerated, with hypotension being the most prevalent side effect. Esmolol increases stroke volume and reduces norepinephrine dependency in septic shock without affecting organ function. Its short half-life permits fast dosage modifications, making it useful in perioperative and critical care [17].

Advantages and drawbacks

After early fluid resuscitation, esmolol regulates heart rate, stabilizes hemodynamics, and may lower 28-day mortality in sepsis and septic shock. It also lowers serum troponin I, suggesting cardioprotection. Its use in pediatric patients remains unapproved due to insufficient clinical data supporting its safety and efficacy. Current research has not demonstrated a significant impact on intensive care unit length of stay or oxygenation parameters in patients with sepsis. Additionally, variability in cardiac response and treatment protocols highlights the need for larger, well-controlled studies to refine dosing strategies and establish long-term clinical outcomes. Further investigation is necessary to optimize therapeutic approaches and ensure evidence-based application in critically ill populations [19].

Dose: Esmolol, a highly selective beta1-adrenergic receptor antagonist, is characterized by a rapid onset of action and a short elimination half-life, rendering it particularly advantageous for intraoperative management in this context. The standard dosing regimen consists of an initial bolus of 500 μg/kg administered over one minute, followed by a continuous infusion at a rate of 50 μg/kg/min for four minutes, with subsequent titration guided by the patient's clinical response [20].

Monitoring Esmolol use

Esmolol therapy requires vigilant monitoring to ensure both safety and efficacy. Continuous assessment of blood pressure, heart rate, and electrocardiographic parameters is essential from baseline through post-dose adjustments. Once hemodynamic stability is achieved, monitoring intervals may be extended to every five hours. Each infusion bag change necessitates precise dosage verification to prevent administration errors. At infusion rates exceeding 200 mcg/kg/min, patients must be closely observed for signs of hypotension, bronchoconstriction, and heart failure, necessitating prompt intervention if adverse effects occur. A structured monitoring protocol ensures optimal dose titration while minimizing the risk of hemodynamic compromise [21].

Esmolol side effects

Esmolol causes dose-dependent hypotension and bradycardia, especially in hemodynamically unstable individuals. At dosages over 200 mcg/kg/min, severe hypotension might cause syncope, heart failure, or death, requiring close monitoring. Conduction problem patients had greater bradycardia, including sinus halt and heart block. Reduced doses or infusion stoppage usually reverse symptoms within 30 minutes. Esmolol and neostigmine improve surgery-caused hypotension and bradycardia, according to studies [22].

Nicardipine: a distinctive calcium channel blocker in cardiovascular therapy-mechanism, clinical application and hemodynamic impact

Nicardipine, a dihydropyridine calcium channel antagonist, exerts its pharmacologic effects by inhibiting calcium influx through voltage-gated L-type calcium channels in vascular smooth muscle cells. It has demonstrated efficacy and favorable tolerability in the management of stable exertional angina, vasospastic angina due to coronary artery spasm, and mild to moderate hypertension. While its precise mechanisms in these conditions are not fully elucidated, its potent vasodilatory effects on both coronary and peripheral arteries play a pivotal role in optimizing myocardial oxygen supply-demand balance and reducing systemic vascular resistance, thereby alleviating ischemic burden and hypertensive stress [23].

Nicardipine's distinct chemical structure differentiates it from other calcium channel blockers, imparting clinically advantageous properties for the management of acute cardiovascular conditions, including hypertensive crises, myocardial ischemia, congestive heart failure, and cerebrovascular disease. Its rapid onset, dose-dependent vasodilation, and minimal negative inotropic effects make it a preferred agent in critical care settings where precise blood pressure control is essential [24].

In patients with coronary artery disease, intravenous administration of nicardipine reduces myocardial oxygen demand through afterload reduction while concurrently enhancing myocardial oxygen supply via coronary vasodilation. Preliminary evidence suggests that nicardipine also exhibits cardioprotective effects and may mitigate vascular spasms [24].

Clinical investigations have demonstrated that nicardipine is effective in the management of chronic stable angina induced by physical exertion and may also provide benefit in resting angina associated with coronary vasospasm. Its therapeutic efficacy in stable angina has been shown to be comparable to nifedipine; however, hemodynamic and clinical assessments suggest that nicardipine may offer an additional advantage. Unlike some other calcium channel blockers, it does not significantly depress cardiac conduction or impair left ventricular function, even in patients with preexisting myocardial contractility impairment, making it a well-tolerated option in individuals with compromised cardiac function [24].

In the treatment of hypertension, nicardipine is recognized as a valuable antihypertensive agent, suitable for use either as initial monotherapy or in combination with other antihypertensive agents. Compared to other vasodilators, it is less frequently associated with adverse effects such as fluid retention or weight gain, enhancing its tolerability profile. Short-term studies have demonstrated that its antihypertensive efficacy is comparable to that of hydrochlorothiazide, cyclopenthiazide, propranolol, and verapamil, further supporting its role as an effective and well-tolerated therapeutic option in the management of hypertension. However, further long-term studies are required to establish its sustained effectiveness and role in chronic hypertension management [24].

Nicardipine is employed intraoperatively as a continuous intravenous infusion for the prevention and management of hypertensive crises induced by tumor manipulation. Owing to its potent arteriolar vasodilatory properties and absence of direct adrenergic receptor interaction, it enables precise and controlled blood pressure reduction while maintaining compatibility with concurrent α-adrenergic blockade. Its administration is particularly indicated in clinical scenarios requiring progressive, sustained vasodilation with minimal induction of reflex tachycardia [25].

Hemodynamic data indicate that nicardipine significantly inhibits vascular smooth muscle contraction, reducing systemic vascular resistance by approximately 42%, while preserving calcium-dependent catecholamine release. Given these properties, nicardipine is also considered a viable option for perioperative and intraoperative blood pressure control in patients with pheochromocytomas, potentially serving as an alternative to conventional alpha-adrenergic blockade [26].

Nicardipine, a calcium channel antagonist, exerts potent arterial vasodilation and can be administered intraoperatively via infusion at an initial rate of 3-5 mg/h for 15 minutes, with gradual increments of 0.5 to 1 mg/h every 15 minutes as needed. Once the target blood pressure is reached, the infusion rate should be reduced to 2-4 mg/h. Hypertensive crises can also be managed with boluses of 1-2 mg. Unlike sodium nitroprusside, nicardipine does not induce reflex tachycardia and maintains cardiac output, making it a preferred choice for some clinicians. A limitation of nicardipine is its half-life of 40-60 minutes, which may result in prolonged hypotension [20].

Sodium nitroprusside: pharmacological profile, clinical applications, and toxicity considerations

Sodium nitroprusside is both an arterial and venous vasodilator that effectively reduces preload and afterload. Unlike calcium channel blockers, sodium nitroprusside primarily dilates large-capacitance vessels. It decreases cerebral blood flow and raises intracranial pressure, making it unsuitable for use in patients with hypertensive encephalopathy or those recovering from a cerebrovascular accident. In individuals with coronary artery disease, sodium nitroprusside may reduce coronary perfusion pressure through the proposed coronary steal phenomenon, rendering it inappropriate in the context of acute myocardial infarction. The drug has a rapid onset and offset of action, which is particularly beneficial when immediate blood pressure reduction is required, such as in the perioperative period. Due to its potency, rapid effects, and potential for tachyphylaxis, intra-arterial blood pressure monitoring is strongly recommended when administering sodium nitroprusside [27].

Sodium nitroprusside is indicated intraoperatively for the management of acute, severe hypertensive crises that may arise during pheochromocytoma tumor manipulation. Its potent and rapid-onset vasodilatory effects, coupled with its extremely short half-life, facilitate precise and immediate control of blood pressure fluctuations induced by catecholamine release [28] [29].

Mechanism of action and hemodynamic effects

Sodium nitroprusside is a water-soluble complex composed of ferrous iron, nitric oxide, and five cyanide ions. As a prodrug, it undergoes biotransformation upon interaction with sulfhydryl-containing molecules, such as erythrocytes and albumin, leading to the release of nitric oxide. This nitric oxide-mediated activation of guanylate cyclase results in an increase in intracellular cyclic guanasine monophosphate, which subsequently activates protein kinase G . Protein kinase G phosphorylates target proteins, leading to the inactivation of myosin light chains, thereby inducing vascular smooth muscle relaxation and potent vasodilation [30].

Unlike nitroglycerin, which primarily acts on venous circulation, sodium nitroprusside exerts balanced vasodilatory effects on both arterial and venous vasculature, leading to a marked reduction in systemic vascular resistance (afterload), ventricular filling pressures (preload), and overall blood pressure. These pharmacokinetic properties, characterized by a rapid onset within two minutes and a short half-life approximately 10 minutes, make sodium nitroprusside a critical agent in the acute management of severe hypertension, heart failure, and perioperative hemodynamic control [30].

Clinical Indications and Applications

It is approved for use in acute hypertensive crises, acute decompensated heart failure, and controlled perioperative hypotension. These indications target rapid blood pressure reduction, improved cardiac output, and reduced intraoperative blood loss.

Additionally, sodium nitroprusside has been explored for off-label uses, including hypertension management in acute ischemic stroke, afterload reduction in acute mitral regurgitation, and augmentation of cardiac output in cardiogenic shock with elevated systemic vascular resistance. It has also been considered for acute preload reduction in select cases of valvular aortic stenosis.

Emerging research suggests sodium nitroprusside may have potential roles in preventing the "no-reflow" phenomenon during percutaneous coronary intervention and as an adjunct therapy for schizophrenia-related vasospastic dysfunction [30].

Sodium nitroprusside induces a more rapid reduction in arterial pressure and is considered the first-line vasodilator for pheochromocytoma surgery. In contrast, nitroglycerin is preferred in patients with ischemic heart disease, as it enhances coronary blood flow by dilating collateral vessels and preventing coronary vasospasm. However, sodium nitroprusside may diminish coronary perfusion due to its pronounced effect on diastolic arterial pressure and its potential to induce intracoronary steal. Sodium nitroprusside infusions can be initiated at a rate of 0.5-1.5 μg/kg/min, with the dosage increased to a maximum of 4 μg/kg/min as necessary, carrying a very low risk of cyanide toxicity for intraoperative infusions lasting less than 12 hours in patients with normal renal and hepatic function [20].

Toxicity and safety considerations

Despite its clinical efficacy, the use of sodium nitroprusside is constrained by the generation of toxic metabolites, primarily cyanide and thiocyanate, as well as the risk of severe hypotension and methemoglobinemia. Prolonged or high-dose administration increases the likelihood of cyanide accumulation, which can impair cellular respiration by inhibiting cytochrome c oxidase, leading to lactic acidosis, altered mental status, and hemodynamic instability [31].

To mitigate these risks, continuous arterial blood pressure monitoring is essential, along with frequent assessment of venous oxygen saturation and serum bicarbonate levels to detect early signs of cyanide toxicity, such as metabolic acidosis and increased venous oxygen content due to impaired oxygen utilization [31].

Cyanide toxicity

The metabolism of sodium nitroprusside leads to the release of cyanide ions, which are typically detoxified in the liver by rhodanese through their conversion into thiocyanate. However, excessive doses or prolonged infusions may surpass the body's detoxification capacity, resulting in cyanide accumulation. Patients with hepatic impairment, malnutrition, vitamin B12 deficiency, or those undergoing therapeutic hypothermia or cardiopulmonary bypass are at greater risk. Cyanide toxicity manifests clinically as metabolic acidosis, refractory hypoxemia, bradycardia, neurological dysfunction (including confusion and seizures), and cardiovascular collapse. If toxicity is suspected, immediate discontinuation of SNP is imperative, alongside prompt administration of antidotal therapy, preferably hydroxocobalamin, which binds intracellular cyanide, and sodium thiosulfate, which serves as a sulfur donor for rhodanese. In high-risk individuals, a preventive approach involves co-administering sodium thiosulfate in a 10:1 ratio with sodium nitroprusside, although the potential for thiocyanate accumulation remains a concern [31].

Methemoglobinemia

Excessive doses of sodium nitroprusside (>10 mcg/kg/min) can lead to methemoglobinemia, a condition characterized by impaired oxygen delivery despite normal arterial oxygen tension. Clinically, this manifests as cyanosis, hypoxia, and fatigue. Symptomatic patients or those with methemoglobin levels exceeding 30% (or 10% in individuals with compromised oxygenation) should receive immediate treatment with methylene blue [31].

Increased intracranial pressure

Sodium nitroprusside-induced cerebral vasodilation can elevate intracranial pressure, making it a suboptimal choice for patients with acute neurological pathology, such as traumatic brain injury or stroke [31].

Conclusion

The management of intraoperative hypertensive crises associated with pheochromocytoma requires a personalized pharmacological approach, given the significant hemodynamic risks. The comparative study of esmolol, nicardipine, and sodium nitroprusside highlights the importance of selecting the optimal antihypertensive agent based on the patient's profile and clinical specifics. Esmolol, with its rapid action and beta$_1$ cardioselectivity, is effective in controlling tachyarrhythmias and myocardial stress but requires careful monitoring to prevent bradycardia and hypotension. Nicardipine, through its selective arterial vasodilation, allows for blood pressure reduction without compromising cardiac function, making it a safe option for patients with reduced ejection fraction. In contrast, sodium nitroprusside, while providing rapid and reversible blood pressure control, raises concerns regarding its potential toxicity due to cyanide and thiocyanate accumulation. The choice of the optimal agent must consider patient comorbidities, the risk of hemodynamic instability, and the need for precise blood pressure control during surgery. A detailed understanding of the pharmacological mechanisms and adverse effects of each agent can significantly improve perioperative prognosis and minimize cardiovascular risks associated with hypertensive crises in pheochromocytoma.

Future research in pheochromocytoma management could focus on personalized pharmacological treatments, including the identification of biomarkers to tailor therapies like esmolol, nicardipine, and sodium nitroprusside. Additionally, advancements in non-invasive monitoring techniques and the development of new pharmacological agents may improve perioperative management and reduce complications. Investigating long-term outcomes and recurrence prevention strategies, particularly in hereditary cases, would further enhance patient care.

Authors' Contribution

S.G- Conceptualization; Writing - original draft.
B.M- Supervision Writing - review & editing.

Conflict of interest

None to declare.

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