

Perioperative Management of Pheochromocytoma: Anaesthetic Implications

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Abstract

Pheochromocytoma is a catecholamine producing tumour that can cause severe hypertension and other systemic disturbances. The perioperative management of pheochromocytoma remains a complicated anaesthesia challenge requiring intensive preoperative preparation and vigilant intraoperative and postoperative care. In this article the perioperative management of pheochromocytoma is reviewed by first summarizing its pathophysiology, clinical aspects and diagnosis, then highlighting the preoperative optimization of the patient and finally describing the intraoperative and postoperative anaesthetic management in the light of the current information.

Introduction

Pheochromocytoma is a catecholamine secreting tumour that arises from the chromaffin cells of the sympathetic nervous system in the adrenal medulla and the sympathetic chain; however, it may arise anywhere in the body.¹ Patients present with a variety of symptoms which reflect excessive secretion of catecholamines (norepinephrine, epinephrine, or dopamine) into the circulation.² The released catecholamines cause significant hypertension, often severe and refractory to conventional treatment.¹⁻⁵

Early diagnosis and definitive treatment with surgical resection is important because the tumour may be fatal if undiagnosed, especially in patients undergoing surgery for other disorders or in pregnant women during delivery.^{1,4} Despite recent developments in technology, monitoring and pharmacology, perioperative management of pheochromocytoma remains a highly stressful situation for the anaesthesiologists.⁵ Appropriate preoperative medical management dramatically decreases morbidity and mortality during the operative management of this tumour.⁶ This article reviews the perioperative management of pheochromocytoma by first summarizing its pathophysiology, clinical aspects and

diagnosis, then highlighting the preoperative optimization of the patient and finally describing the intraoperative and postoperative anaesthetic management.

Pathophysiology

Pheochromocytomas arise in the chromaffin cells of neuroectodermal origin. During embryonic development the chromaffin cells settle mainly near the sympathetic ganglia, vagus nerve, paraganglia and carotid arteries but some chromaffin tissue may be present in the bladder wall, prostate, rectum, gonads, renal and hepatic hili.⁷ Thus pheochromocytomas can arise at any of these sites.¹ An understanding of biochemistry and functions of catecholamines is important for appreciating the pathophysiology of pheochromocytomas. The biosynthesis and metabolism of catecholamines is illustrated in Figure.

The actions of catecholamines are mediated by the alpha adrenergic and the beta adrenergic receptors.⁸ Alpha 1 receptors cause vascular constriction while alpha 2 receptors mediate the presynaptic feedback inhibition of norepinephrine release and decrease insulin secretion. Beta 1 receptors increase cardiac rate and contractility and beta 2 receptors lead to arteriolar and venous dilation and relaxation of tracheobronchial smooth muscle.^{1,8}

The symptoms caused by pheochromocytoma are due to the effects of a large amount of catecholamines, norepinephrine and epinephrine in the circulation.⁵ Most pheochromocytomas (more than 80%) mainly secrete norepinephrine, sometimes paroxysmally, but usually sustained.³ In rare cases, these tumours may produce epinephrine predominantly.¹ Some tumours may secrete dopamine and various peptides and ectopic hormones.⁹ Increased dopamine secretion by a pheochromocytoma may suggest malignancy.¹⁰

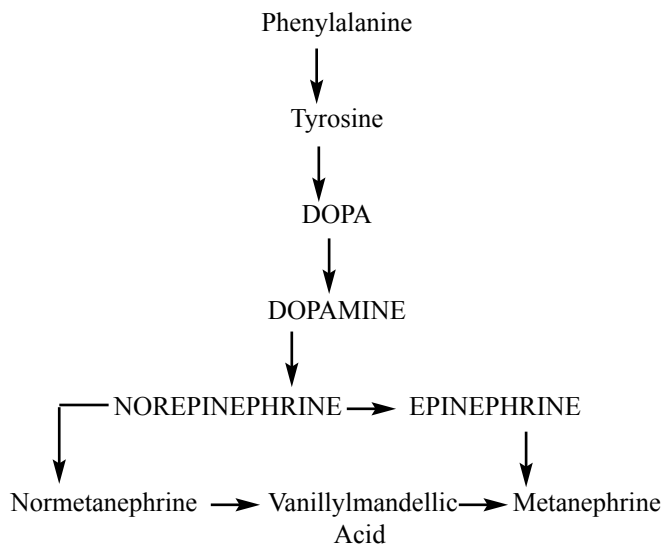


Figure. Biosynthesis and metabolism of catecholamines.

Table. Intraoperative Considerations.

An anxiolytic should be given preoperatively
Arterial catheter should be placed before induction
Intravenous catheter for antihypertensive and fluid administration should be placed before induction
Epidural (optional) to be placed before induction
Central venous catheter should be placed for intravascular volume monitoring
Haemodynamic fluctuations should be treated with antihypertensives and adrenergic antagonists
Hypotension and hypoglycemia should be monitored after tumor isolation

Clinical Aspects

Pheochromocytoma is a rare tumour with a reported incidence in the United States of 1.55 to 2.1 per million populations per year.¹¹ This tumour is also rare in the Pakistani population but its actual incidence is not yet reported. The greatest frequency occurs in the fourth and fifth decade of life, with a slightly higher female preponderance.³ About 90% of pheochromocytomas occur sporadically and are benign.¹² In 10% of patients with pheochromocytoma, the adrenal tumour is part of a familial disorder such as the multiple endocrine neoplasia (MEN) syndrome, von Recklinghausen disease or von Hippel-Lindau syndrome.¹³ Around 10% of cases occur in children or adolescents.¹

Hypertension is the commonest presenting sign in patients with pheochromocytoma as most of these tumours secrete predominantly norepinephrine.^{4,14,15} The classical symptoms are headaches, palpitations and episodic sweating.^{4,5} Central nervous system manifestations are anxiety, nervousness, psychosis, visual disturbance and tremors.

Cardiovascular symptoms include ventricular arrhythmias, cardiac failure with cardiomyopathy, and peripheral vasoconstriction with pallor.³ Acute pulmonary oedema may complicate pheochromocytoma at any time.¹⁶ Prolonged exposure of the circulation to high norepinephrine concentrations results in constriction of both arteriolar and venous circulation with a marked decrease in circulating blood volume.^{2,5}

Some patients present with increased blood glucose concentrations as a result of glycogenolysis and impaired insulin release by the islet cells of pancreas.^{2,17} The author was involved in the anaesthetic management of a patient who presented with severe uncontrolled diabetes mellitus and no history of hypertension. On abdominal computerized tomography (CT) he was found to have a right adrenal mass. The opinion of an endocrinologist was not in favour of a pheochromocytoma as none of the classical signs or symptoms were present. However, anaesthetic management for the resection of the mass was performed with full precautions as for a pheochromocytoma. The histopathological examination of the resected mass proved it to be one. The patient's glycaemic level normalized after removal of the tumour.

A small proportion of patients with pheochromocytoma present with paroxysmal symptoms which reflect excessive secretion of epinephrine and dopamine.¹ Excessive epinephrine secretion causes hypermetabolism with weight loss, paroxysmal tachycardia, palpitations, sweating and stimulation of insulin release through a beta 2 adrenoceptor mechanism.¹⁶ The overall picture depends upon the relative proportions of norepinephrine and epinephrine secreted by the tumour. Pheochromocytoma is an extremely rare tumour in children¹⁸ but should be searched for in children presenting with hypertension and especially those with family history of MEN syndromes.

Diagnosis

At the first presentation, the hypertension might not warn the treating physician about pheochromocytoma, but hypertension resistant to conventional treatment along with intermittent severe headache and palpitations should alert the physician about the presence of a pheochromocytoma. Once there is a suspicion, the best confirmatory test is to measure free catecholamines and their metabolites in a 24 hour urine collection.^{3,5} These measurements include epinephrine, norepinephrine, dopamine, metanephrine, and vanillylmandelic acid (VMA). Measurement of plasma catecholamines reflect only that single moment when the blood sample was collected. Twenty four hours urinary VMA is the only biochemical test currently available for confirming the diagnosis of pheochromocytoma.

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Once the diagnosis has been established, the tumour must be localized to facilitate its surgical removal. Although larger tumours may be located with ultrasonography, most tumours require CT scanning or magnetic resonance imaging (MRI) especially when located outside the adrenal gland.¹ CT and MRI both provide an accurate identification of the majority of pheochromocytomas.¹⁹ Tumours in unusual sites and metastases may have to be identified with metaiodobenzylguanidine (MIBG) scintigraphy, which has a high specificity for pheochromocytoma as MIBG is concentrated by the tumour's avid uptake of precursor amines.²

Preoperative Assessment

Surgical resection of the tumour is the only curative procedure. Prior to surgery it is imperative to control arterial pressure, heart rate and arrhythmias and to restore the blood volume to normal.^{1-5,14,15,17} The anaesthesiologist should take relevant history, assess the severity of hypertension and look for any end-organ damage, especially catecholamine induced cardiomyopathy and cardiac failure, which is associated with a high mortality.^{3,20}

For a detailed assessment of cardiovascular status electrocardiography (ECG), chest X-ray and M-mode echocardiography should be advised. ECG might show hypertrophy, arrhythmias, cardiomyopathy, ischaemia or infarction. Chest X-ray may reveal cardiomegaly or pulmonary oedema.⁵ M-mode echocardiography should be used to assess left ventricular dysfunction, evaluate improvement after alpha adrenergic blockade, and determine the optimal timing of surgery.^{5,21}

A baseline full blood count and haematocrit followed by serial monitoring provides an assessment of the adequacy of volume expansion when alpha adrenergic blockade has been started.¹⁷ An assessment of renal function should be carried out by biochemical investigations such as urea, creatinine and electrolytes. Insulin therapy may be required if hyperglycaemia is present. If hypercalcaemia is present, the presence of MEN type 11 should be suspected.³

Preoperative Management

Adrenergic crisis leading to an uncontrollable situation may occur at induction of anaesthesia, intubation, and during tumour handling.¹ Appropriate preoperative medical management dramatically decreases morbidity and mortality during the operative management of pheochromocytoma.⁶ Therefore it is important to adequately optimize the patient before surgery. There has been a decrease in mortal-

ity associated with its resection from 40-60% to 0-6% over the last 50 years.²² There should be close cooperation between the cardiologist, endocrinologist, surgeon and the anaesthesiologist for an uneventful outcome.

Preoperative preparation is conventionally done with alpha adrenergic blockade over a period of 10-14 days and subsequently, additional beta adrenergic blockade is required to treat any associated tachyarrhythmias.⁵ Patients can usually be safely prepared for surgery on an outpatient basis. Alpha blockade is commonly achieved with oral phenoxybenzamine 20mg three times daily, which is a non-competitive, non-selective alpha adrenergic blocking agent.²³ It also permits spontaneous volume expansion but this occurs gradually and takes two to three weeks. Half-life of phenoxybenzamine is more than 24 hours. Noninvasive blood pressure monitoring should be done in the supine and standing positions during therapy.²⁴

Selective competitive alpha 1 adrenergic antagonists are preferred by some anaesthesiologists because they do not produce reflex tachycardia, have a shorter duration of action, can be adjusted rapidly before surgery and the duration of postoperative hypotension is decreased.²³ Prys-Roberts used doxazosin preoperatively in 20 patients with pheochromocytoma or paraganglioma in doses of 2 to 8mg daily and noted that preoperative blood pressure was controlled as well as with phenoxybenzamine.²

Other selective competitive alpha 1 adrenergic antagonist like prazosin can also be used. It has a short elimination half life of two to three hours and requires more frequent dosing⁵ starting at 1mg three to four times daily and gradually increased up to 12mg daily.^{17,23} Its blood concentration may decrease to ineffective levels at the time of surgery if the last dose was given on the night before surgery.²⁴ Terazosin is a similar alternative selective alpha 1 adrenergic antagonist. The choice of drug will depend not only on the physician's preference but also upon availability and cost effectiveness. Whichever drug is used, it is important to introduce it cautiously starting with small doses and increasing gradually until orthostatic hypotension develops indicating adequate alpha blockade.³ Despite preoperative alpha blockade, significant increases in blood pressure still occur intraoperatively, especially during tumour manipulation.²⁴

During alpha receptor blockade tachycardia and arrhythmias can occur due to resultant unopposed beta receptor activity.^{1,8} The tachycardia and arrhythmias are controlled by carefully introducing beta adrenergic blockers. Beta blockade should never be instituted until alpha adrenergic blockade is fully established as unopposed alpha stimulation may lead to severe hypertension.²³

Caution is also required in patients with cardiomyopathy who may develop pulmonary oedema due to withdrawal of beta stimulation.²⁵ Thus, beta adrenergic blockade should be avoided in patients with catecholamine induced cardiomyopathy as it can lead to development of intractable hypotension, bradycardia and asystolic arrest.^{5,26} Selective beta I adrenoceptor antagonists such as atenolol (100 mg day-1) or bisoprolol (10-20 mg day-1) should be used in order to minimize undesirable side effects in the bronchi or peripheral vasculature.² Non-selective beta 1 antagonists such as propranolol (40-240 mg day-1) or metoprolol (50-200 mg day-1) can also be used³ but care must be taken in patients with history of obstructive airway disease or peripheral vascular disease. Calcium channel blockers (27) have also been employed in the preoperative and intraoperative haemodynamic control, such as nifedipine 30-90 mg day-1 and nicardipine infusion starting at 5 mg hour-1, increasing by 2.5 mg hour-1 every 5 minutes to a maximum of 15 mg hour-1.

Preoperative sedation and anxiolysis, preferably with a benzodiazepine, and assurance by the anaesthesiologist will decrease anxiety and prevent marked haemodynamic fluctuation in the immediate preoperative period.⁵ Patients often develop hypertensive swings during surgical manipulation of the tumour despite complete pharmacological blockade. Therefore medication for alpha and beta blockade should be continued until the day of the operation except phenoxybenzamine which may be stopped the day before surgery as it has a long half life and can cause post-operative hypotension.²

Intraoperative Management

Close communication between the surgeon and the anaesthesiologist is absolutely crucial to the success of intraoperative management of patients undergoing resection of pheochromocytoma. Preoperative discussion of anticipated problems is important and guides the anaesthesiologist in making adequate preparation for the anaesthetic management.

Various anaesthetic techniques have been successfully employed for the resection of pheochromocytoma.^{2,3,5,17} Regional anaesthesia has been used alone or in combination with general anaesthesia and neurolept technique.²⁸ The choice of anaesthesia does not influence the outcome of the operation.³ and a rational anaesthetic technique based on sound pharmacologic principles should be selected. Based on 32 years of experience with this surgery, Prys-Roberts has suggested a practical rational anaesthesia technique consisting of a mid to low thoracic epidural combined with adequate general anaesthesia and selective adrenergic antagonists to control haemodynamic surges in

response to tumour manipulation.² Many drugs have been suggested for the control of intraoperative haemodynamic surges^{1-3,5,17}, but the choice of drugs used for this purpose, especially in the developing world, will depend upon the availability of the drugs in addition to patient's requirements.

Anaesthetic Management

Perioperative management of pheochromocytoma remains an anaesthetic challenge even in the best of centers²⁹ and involvement of experienced surgeon and anaesthesiologist is mandatory. The patient should be transferred cautiously to the operating table to avoid any straining which may cause catecholamine release.³ After connecting ECG and pulse oximeter and assessing blood pressure non-invasively, central venous and arterial catheters should be placed under local anaesthesia to establish haemodynamic monitoring. This could be easily achieved with a gentle technique and reassurance of the patient and allows immediate identification of haemodynamic fluctuations during induction and maintenance of anaesthesia and surgical manipulation of the tumour, and also guides for pharmacologic intervention.⁵ If the patient is nervous the central venous catheter could be placed immediately after induction. Pulmonary artery catheter is not an absolute requirement and should be reserved for patients with severe left ventricular dysfunction and preoperative cardiovascular compromise.³⁰ Routine monitoring should include ECG, capnography, inspired oxygen concentration (FiO₂), pulse oximetry, neuromuscular blockade, temperature and urine output.¹⁷

Preferably two large bore intravenous catheters should be placed, one of them before induction under local anaesthesia, for administration of medications and fluids. The patient can then be positioned gently for insertion of the epidural catheter at the T10-11 to T12-L1 level.² In the author's institute it is a common practice to insert the epidural catheter before the induction of anaesthesia. The epidural could be used for both intraoperative and postoperative analgesia or an intravenous opioid agent like fentanyl can be used intraoperatively and an epidural bolus followed by continuous infusion can be used for postoperative analgesia.

Although various anaesthetic drugs and techniques have been used for this purpose, the author, after review of literature^{2-6,17,31} has endeavored to describe a practical and safe approach for the induction and maintenance of anaesthesia for pheochromocytoma resection in the following section. This technique is equally applicable for both open and laparoscopic surgical approaches.

After initiation of monitoring and preoxygenation anaesthesia is induced with fentanyl 2-5 mcg kg-1 and

propofol 1-2 mg kg⁻¹. Thiopentone has been widely used without adverse effects³¹ but can cause histamine release, which need to be avoided in these patients.³ Etomidate provides cardiovascular stability but causes pain on injection and involuntary movements which are undesirable. Midazolam could be used to facilitate co-induction.³ Other opioids like alfentanil or sufentanil could also be used in place of fentanyl. Remifentanil infusion has also been used and has shown good results³¹ and could be considered if availability and cost permits.

When the patient no longer responds to commands neuromuscular blocking agent is administered. Suxamethonium has been used successfully for rapid sequence induction in a pregnant patient with pheochromocytoma undergoing caesarean section under general anaesthesia³¹, but it should be best avoided as the muscular fasciculation may mechanically squeeze the tumour. Atracurium and mivacurium have been shown to release histamine, but Prys-Roberts² has used atracurium regularly for patients with pheochromocytoma since 1984 without any unfavorable effects. Vecuronium, rocuronium and cisatracurium have shown cardiovascular stability and release the least histamine and appear to be suitable agents for this purpose. After administering neuromuscular blocking agent, the lungs are manually ventilated with isoflurane 1-2% in oxygen for 3-5 minutes followed by tracheal intubation. The patient's lungs are ventilated through a nasogastric tube with a tidal volume of 7-10 ml kg⁻¹ and a rate of 10-12 breaths/min⁻¹ to maintain the end tidal CO₂ (PETCO₂) around 35 mmHg. The patient is then cautiously positioned for the planned surgical approach.

Anaesthesia is maintained with isoflurane 1-2% in an air-oxygen mixture with FiO₂ of around 0.5. Isoflurane is preferred because, unlike halothane, it does not sensitize the myocardium to catecholamines.¹⁷ Sevoflurane has also been used successfully.³² and can be used depending upon its availability and economic issues. Its rapid uptake and elimination allows easier control of depth of anaesthesia and haemodynamics of the patient.³² Nitrous oxide is also not contraindicated and could be added if preferred. Boluses or infusion of neuromuscular blocking drug are used to maintain good surgical conditions.

If epidural infusion is being used intraoperatively, further doses of fentanyl or any other opioid are usually not required. To achieve adequate intraoperative and postoperative analgesia with the epidural, infusion of bupivacaine 0.1-0.125% with fentanyl 2 mcg ml⁻¹ at the rate of 6-12 ml hour⁻¹, is administered after an initial bolus of 8-10 ml of 0.25% bupivacaine in divided doses.^{2,5}

For reversal of neuromuscular blockade, a combination of neostigmine and glycopyrrolate is used, as the tachy-

cardia associated with atropine can lead to a hypertensive spike.³ The decision to reverse neuromuscular blockade at the end of surgery or electively ventilating the patient in ICU until stability is achieved depends upon the preoperative state of the patient and the intraoperative course. Even if the trachea is successfully extubated at the end of surgery, the patient is kept in the ICU or high dependency unit at least for the first twenty four hours and closely monitored for haemodynamic instability.^{2-6,17,31}

Control of perioperative catecholamine release

As mentioned above, manipulation of the tumour causes a significant haemodynamic response and both systolic and diastolic blood pressures increase briskly. Sodium nitroprusside (SNP), phentolamine, prazosin, nitroglycerine and various other agents like magnesium sulphate, nicardipine, diltiazem, esmolol etc, have been used to control intraoperative rises in blood pressure.^{2,5,6,14,15,17} In the author's institute sodium nitroprusside is preferred for this purpose. It is a potent arterio-venodilator with a rapid and brief action and is used as a titratable intravenous infusion [around 0.5 mcg kg⁻¹ min⁻¹].¹⁷ With the small quantity used, cyanide toxicity is not a problem. Intravenous nitroglycerine can also be employed for this purpose. It is a rapid acting agent that mainly affects capacitance vessels.³⁰ Similar to SNP, its onset and duration are rapid.⁵ The competitive alpha adrenergic blocking agent phentolamine can also be used intraoperatively as an infusion or in incremental doses of 1 to 2 mg to control acute hypertensive crises because it acts fast and has a short half-life.³ It is associated with tachycardia but in patients receiving beta adrenergic antagonists, tachycardia attributable to phentolamine is not typically seen.²

Intraoperative use of beta adrenergic antagonists can help control tachycardia and tachyarrhythmias. Esmolol has haemodynamic effects that may be uniquely suited for the intraoperative management of pheochromocytoma.³³ Its rapid effect and short duration makes it easily titratable, both to control heart rate and blood pressure. The author has used metoprolol 1-2 mg IV boluses intraoperatively with good results.

Magnesium sulphate inhibits catecholamine release from chromaffin cells and alters the adrenergic receptors response.³⁴ James describes a series of 17 patients in whom intraoperative haemodynamic control was achieved with a loading dose of 40 - 60 mg kg⁻¹ followed by an infusion of 1-2 g h⁻¹.³⁴ Additional doses of magnesium sulphate were required in all patients at the time of tumor manipulation. Calcium channel blockers e.g. nifedipine and nicardipine have also been used for intraoperative haemodynamic control.²⁷

It is difficult to comment on the best medication to be used for haemodynamic control during resection of pheochromocytoma as it is not possible to conduct properly designed randomized trials because of the rarity of the condition. It has been suggested¹⁷ for the anaesthesiologists to rely on their familiarity of particular drugs or methods. In a developing country, the availability and affordability also becomes an issue of major consideration.

Postoperative Management

After the adrenal veins are ligated, there is a sudden decrease in the circulating catecholamines which may lead to hypotension. At this point the vasodilators and blocker should be discontinued and a modest fluid bolus should be given. An eye must be kept on the blood loss and blood given if required. Infusion of a vasopressor such as norepinephrine or phenylephrine may be required temporarily.⁵

The three most important complications in the immediate postoperative period are hypertension, hypotension and hypoglycaemia.³ Approximately 50% of patients remain hypertensive for a few days, most likely related to elevated catecholamine levels which may persist for one week after pheochromocytoma resection.³⁰ Therefore restarting or continuation of antihypertensive medication may be required for a few days. Presence of residual tumour must be considered in cases of persistent hypertension and catecholamine levels should be repeated. Persistent hypotension may be due to residual effects of preoperative adrenergic blockade.¹⁷ There should also be a high index of suspicion for intra-abdominal bleeding.

After removal of the tumour the pancreatic beta cell suppression is no longer present and insulin levels increase. The lipolysis and glycogenolysis is also absent due to removal of tumour and alpha blockade.¹⁷ This may lead to hypoglycaemia which may be associated with encephalopathy and the residual adrenergic blockade may mask its signs and symptoms.³⁵ Therefore blood glucose levels should be monitored in the perioperative period and glucose containing intravenous fluids should be started after tumour removal.⁶

Conclusion

The anaesthetic management of patients with pheochromocytoma remains a challenge to even the most experienced of anaesthesiologist, although the perioperative mortality has reduced remarkably. Surgical resection is the definitive treatment. Preoperative control of hypertension with alpha adrenergic blocking agents followed, where required, by beta adrenergic blocking drugs and adequate volume expansion is important for reducing the morbidity and mortality associated with this surgery. Patients with pheochromocytoma should ideally be managed by an expe-

rienced team of endocrinologist, endocrine surgeon and anaesthesiologists. Different anaesthetic techniques and medications have been used successfully and various combinations of vasodilating and antihypertensive drugs have been used intraoperatively during the resection of pheochromocytoma with good results. The pathophysiology of the disease is complex and anaesthetic care must be tailored in accordance with each patient's situation.

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