

A practical approach to children with pheochromocytomas and paragangliomas

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Introduction

Pheochromocytoma (PCC) and paraganglioma (PGL) are rare chromaffin cell tumours which secrete catecholamines and form part of the family of neuroendocrine tumours. They are responsible for 0.5–2% of cases of secondary hypertension in paediatrics and although rare, are potentially lethal. The presentation of hypertension in these patients is characteristic, and the treatment is definitive.¹ Pheochromocytoma and paragangliomas (PPGLs) have a reported annual incidence of two to five cases per million, of which only 10% occur in children.²

Definition of pheochromocytoma and paraganglioma:

- A pheochromocytoma is a tumour arising from adrenomedullary chromaffin cells that commonly produces one or more catecholamines.
- A paraganglioma is a tumour derived from extra-adrenal chromaffin cells of either the sympathetic or parasympathetic ganglia. The sympathetic paravertebral ganglia are located in the thorax, abdomen and pelvis and the parasympathetic ganglia are located along the glossopharyngeal and vagal nerves in the neck and at the base of the skull.³

PCCs and PGLs have different catecholamine-secreting profiles. Tumours secreting epinephrine and frequently norepinephrine are generally from the adrenal gland while extra-adrenal tumours secrete norepinephrine and dopamine. The parasympathetic (head and neck) paragangliomas are non-functional and are usually only diagnosed once the mass effect of the tumour is apparent.¹

Characteristics of paediatric vs. adult pheochromocytomas and paragangliomas: PPGLs in children are often hereditary and may present with different characteristics compared with adults. The traditional 'rule of 10s' which refers to adults with PPGL states that 10% of PCC are extra-adrenal, 10% are malignant, 10% are bilateral, 10% are found in normotensive patients, and 10% are familial. This no longer holds true, as there appears to be a significantly higher proportion of tumours that are malignant, extra-adrenal and familial.⁴

Table 1.² Characteristics of paediatric versus adult pheochromocytomas and paragangliomas

	Paediatric tumours	Adult tumours
Hereditary	80%	52%
Extra-adrenal	66%	35%
Multifocal	32%	13%
Metastatic	49%	29%
Recurrent	29%	14%
Noradrenergic	93%	57%

These differences in disease presentation are important to consider in both pre- and postoperative management of children with PPGLs.²

Genetics of PCC and PGL

PPGL may occur as sporadic tumours but may also develop as part of hereditary tumour syndromes reflecting mutations in at least 14 different tumour susceptibility genes.² With recent advances in genetic medicine, the reported rate of inheritance in paediatric cases is now thought to be as much as 80%.¹ Genetic testing is therefore imperative for all children who present with a PCC or PGL. Major syndromes associated with PPGL include¹:

- Multiple endocrine neoplasia (MEN) type 2A and 2B
- Neurofibromatosis type 1
- Von Hippel-Landau type 2
- Carney's triad
- The paraganglioma-pheochromocytoma syndromes involving succinate dehydrogenase gene mutations¹

Clinical presentation

The average age at presentation of PCCs and PGLs in paediatrics is 11–13 years, with a male: female ratio of 2:1. The clinical presentation is variable but sustained hypertension is seen in 60–90% of cases. This is in contrast to adults who present predominantly with paroxysmal hypertension.¹ The clinical presentation of a functional PCC or PGL in childhood depends on differences in catecholamine secretion and release as well as individual patient sensitivity to catecholamines. Patients may

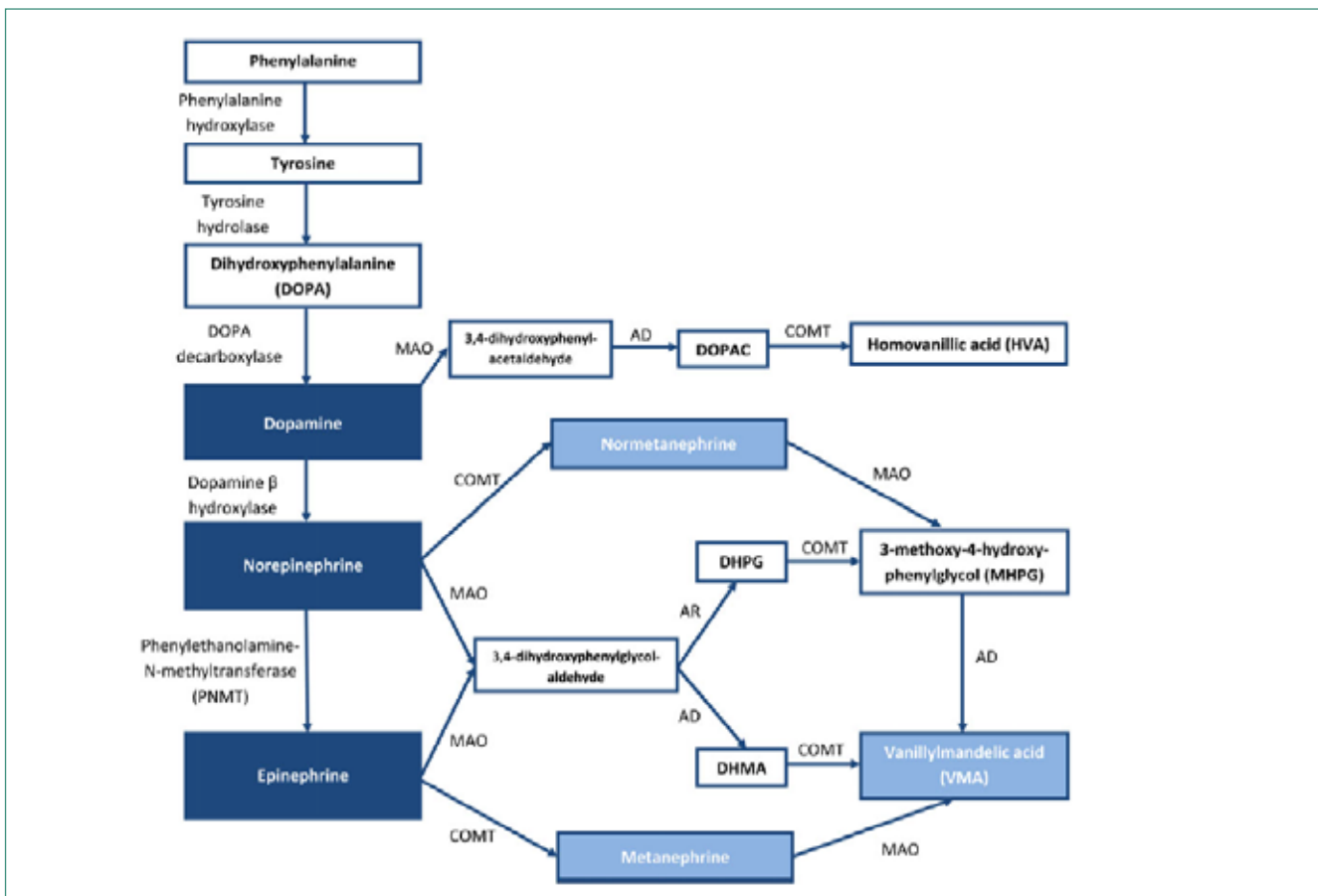


Fig 1 Catecholamine metabolism. COMT, catechol-O-methyltransferase; DOPAC, 3,4-dihydroxyphenylacetic acid; AD, aldehyde dehydrogenase; AR, aldehyde reductase;

Figure 1. Catecholamine metabolism. 3,4-dihydroxyphenylglycol; DHMA 3,4-dihydroxymandelic acid.

present with the classic triad of headaches, palpitations and sweating as well as other symptoms of catecholamine excess such as pallor, tremor, anxiety, orthostatic hypotension and syncope. Symptoms can also be nonspecific and include blurred vision, abdominal pain, diarrhoea and other gastrointestinal symptoms, weight loss, hyperglycaemia, polyuria, polydipsia, low-grade fever and behavioural problems. In children, a complaint of nausea is particularly common.⁵ Symptoms are often episodic and may occur spontaneously or be provoked by typical physical actions, surgery, anaesthesia or certain drugs. Occasionally patients may also present with complications of catecholamine excess such as a cardiomyopathy, hypertensive crisis, stroke, seizures or even multi-organ failure and death.

The mass effect from non-functional head and neck PGLs can lead to dysphagia, hoarseness, hearing disturbances and pain. These tumours may also present as an incidental radiographic finding or because of family screening for one of the hereditary syndromes described above.

Diagnosis

Initial biochemical tests are done to establish and confirm excess secretion of catecholamines and/or their metabolites. This is followed by radiographic studies to identify the location of the tumour. In the paediatric population thorough imaging is particularly important due to the increased incidence of multifocal, extra-adrenal and metastatic tumours.⁶ Genetic testing is also indicated in all paediatric cases.

Biochemical tests

Measurements of plasma and 24 h urinary catecholamines (epinephrine, norepinephrine and dopamine) and urinary vanillylmandelic acid (VMA) have fallen out of favour due to lower sensitivity and specificity. The measurement of catecholamine metabolites is now recommended. These include plasma-free metanephrines and 24 h urinary fractionated metanephrines.¹

Table II. Sensitivity and specificity of biochemical tests used in the diagnosis of paediatric pheochromocytoma¹

Biochemical test	Sensitivity (%)	Specificity (%)
Plasma normetanephrine and metanephrine	100	94
Plasma norepinephrine and epinephrine	92	91
Urinary norepinephrine and metanephrine	100	95
Urinary norepinephrine and epinephrine	100	38
Urinary vanillylmandelic acid	63–75	94

Imaging

Radiographic studies should be performed once the biochemical diagnosis of catecholamine excess is established. The initial test of choice is cross-sectional imaging of the abdomen and pelvis using either CT or MRI which have similar diagnostic sensitivities. Imaging of the neck and chest is indicated if the initial studies are negative.⁷ MRI may be preferable in the paediatric population

due to the radiation exposure with CT. MRI also has better sensitivity than CT to locate extra-adrenal tumours and is superior in evaluating the extent of invasion into the spinal canal and major vessels.¹ Functional testing using nuclear scintigraphy with I-labeled metaiodobenzylguanidine (MIBG) is a highly specific test that can confirm the catecholamine-secreting nature of a tumour as well as localise tumours not seen with cross-sectional imaging and may identify other sites of disease. It may be indicated in certain cases.

Management

Preoperative preparation

Adequate preoperative evaluation and management of these patients is crucial before surgery and has led to a remarkable reduction in perioperative mortality over the last 60 years. Early phaeochromocytoma surgery saw mortality rates of up to 45%.⁴ The surgical mortality associated with catecholamine-secreting tumours is now of the order of 0–3%.⁸ This is largely attributed to the advent of preoperative α blockade. Given the rarity of neuroendocrine tumours in paediatric and even in adult patients, there are no randomised controlled trials looking at the various therapeutic options. The presentation of these tumours may also vary greatly which once again makes scientific comparisons challenging. Therefore, many aspects of the perioperative management of PCC and PGL remain contentious as well as being dependent on drug availability within a given clinical environment. In a recent editorial James suggests that “perhaps the best course of action is not to adopt a rigid protocol but rather to use a more tailored preoperative management strategy to suit the individual needs of the patient”.⁸

The objectives of preoperative preparation include⁴:

- Arterial pressure control
- Reversal of chronic circulating volume depletion
- Heart rate and arrhythmia control
- Assessment and optimisation of myocardial function
- Reversal of glucose and electrolyte disturbances

Arterial pressure control

Preoperative α blockade is standard practice and is commenced at least 7–14 days prior to surgery. The aim is to provide preoperative arterial pressure control with subsequent restoration of blood volume. Commonly used α blockers include phenoxybenzamine and doxazosin.

Phenoxybenzamine has not been available in SA for more than 20 years. It is a non-selective, non-competitive α blocker which has a sustained effect lasting up to 24–48 hours after the last

dose. It should therefore be stopped 24–48 hours before surgery. Its α_2 blockade causes a reflex tachycardia as well as side-effects of nasal congestion, headaches and somnolence. Its use may also be implicated in postoperative refractory hypotension. The advantage of phenoxybenzamine is that it may reduce the effects of catecholamine surges intraoperatively due to its non-competitive mechanism of action.

Doxazosin is a competitive, selective α_1 blocker. It therefore does not cause a reflex tachycardia or sedation. Some studies also suggest a reduced incidence of postoperative hypotension.⁴ The main disadvantage of doxazosin is that due to its competitive antagonism, breakthrough hypertension occurs with intraoperative catecholamine surges.

Prazosin, another selective α_1 blocker is favoured by some clinicians. It has a very short half-life however, which requires frequent dosing and may cause profound rebound hypertension if a dose is missed. It may also be relatively ineffective in the intraoperative control of blood pressure especially if the last dose was given the night before surgery. Symptomatic postural hypotension may be seen at the beginning of therapy with these agents, so it is important to start at low doses and titrate upward.⁷

Calcium channel blockers are an additional class of drug that may be used to further improve blood pressure control in those already α blocked.

In paediatric patients the goal is a blood pressure reduction to < 50 percentile for age and height.¹ Alpha-methylparatyrosine (Metyrosine) is an inhibitor of the tyrosine hydroxylase enzyme. It can reduce catecholamine production by 50–80% but, unfortunately, its side-effects have limited the use of this drug except in malignant and inoperable tumours.

Reversal of chronic circulating volume depletion

Chronic catecholamine excess leads to a contracted intravascular volume. In addition to pharmacological control, a high sodium diet and increased fluid intake are indicated to restore normal circulating blood volume. This is imperative in order to avoid intraoperative haemodynamic instability and particularly postoperative hypotension. Fluid intake of at least 1.5 times maintenance rates is suggested in the preoperative period.¹

Heart rate and arrhythmia control

A tachycardia may be the result of an epinephrine- or dopamine-secreting tumour or may be a reflex tachycardia secondary to α_2 -receptor blockade. The choice and timing of β blockade is important. β blockers should not be given prior to adequate α blockade. Blockade of vasodilatory β_2 receptors leads to

Table III. Pharmacokinetic properties of α receptor antagonists used for preoperative control of hypertension in patients with phaeochromocytoma and paraganglioma⁹

Drug class	Drug	Half-life (h)	Doses/day
Nonselective α receptor antagonist	Phenoxybenzamine	24*	2–3
Selective α_1 receptor antagonist	Prazosin	2–3	4–6
	Doxazosin	20–22	Once daily
	Terazosin	12	1–2

* Effect of drug is sustained up to 24–48 h after stopping until new α receptors are generated.

Table IV. Drugs used in preoperative blockade of paediatric catecholamine-secreting tumours¹

Class of drug/drug name	Starting dose	Maintenance dose	Common side-effects
Non-selective alpha blocker Phenoxybenzamine	0.2 mg/kg/day (max. 10 mg/dose)	Increase by 0.2 mg/kg/day every 4 days to goal 0.4-1.2 mg/kg/day ÷ every 6-8 h (max. 2-4 mg/kg/day)	Orthostatic hypotension Tachycardia Nasal congestion
Selective alpha-1 blocker Doxazosin	1-2 mg/day	Increase to 4-16 mg, daily or ÷ 2 times daily	Orthostatic hypotension Dizziness
Non-selective beta blocker Propranolol	1-2 mg/kg/day, ÷ 2-4 times daily	4 mg/kg/day, up to 640 mg/day, ÷ 2-4 times daily	Dizziness Fatigue Asthma exacerbation
Selective beta-1 blocker Atenolol	0.5-1 mg/kg/day, daily or ÷ 2 times daily	2 mg/kg/day, up to 100 mg/day, daily or ÷ 2 times daily	Oedema Dizziness Fatigue
Alpha and beta blocker Labetalol	1-3 mg/kg/day, ÷ 2-3 times daily	10-12 mg/kg/day, up to 1 200 mg/day, 2-3 times daily	Dizziness Fatigue Asthma exacerbation
Tyrosine hydroxylase inhibitor Metyrosine	20 mg/kg/day, ÷ every 6 hrs OR 125 mg daily	Increase up to 60 mg/kg/day ÷ every 6 hrs OR Increase by 125 mg every 4-5 days to max 2.5 g/day	Orthostatic hypotension Diarrhoea Sedation Extra-pharyngeal symptoms Crystalluria

unopposed alpha mediated vasoconstriction and worsening of the hypertension. The removal of β_1 stimulation following β blockade also means the heart has to cope with an increased afterload with less ability to contract. This can precipitate heart failure in patients with myocardial dysfunction and is another important reason why β blockers should only be started after appropriate arteriolar dilatation has been achieved with α blockers. There is no evidence to support the preference of β_1 selective adrenergic receptor blockers over non-selective β adrenergic receptor blockers.³ Selective β_1 blockers include atenolol and bisoprolol. Popularly used non-selective β blockers include propranolol. β blockers with additional α blocking properties such as labetalol and carvedilol are synergistic with α blockers in reducing blood pressure.

Assessment and optimisation of myocardial function

Children with a catecholamine induced cardiomyopathy present with a wide spectrum of clinical severity. They may not display any signs or symptoms except for perhaps palpitations or arrhythmias.⁵ It is therefore crucial that a thorough search for any evidence of cardiac dysfunction is performed pre-operatively. An ECG may reveal ventricular hypertrophy, tachyarrhythmias or myocardial ischaemia. Echocardiography is considered mandatory.⁴ Various forms of cardiomyopathy have been described. It is usually of a dilated type but may also occur rarely in an obstructive form.⁵ Atypical Takotsubo's cardiomyopathy has also been described.⁴ Making the diagnosis of a cardiomyopathy is important for several reasons⁵:

- There is an increased morbidity and mortality in these patients
- The myocardial dysfunction may be reversible
- The diagnosis has important implications for the child's subsequent management including the anaesthetic technique and intraoperative monitoring

Reversal of glucose and electrolyte disturbances

A significant number of children with PPGL will be found to have abnormalities of glucose tolerance. Chronically elevated catecholamine levels elevate plasma glucose levels through a number of different mechanisms. All children should therefore have at least a random blood glucose test and, if indicated, a fasting blood sugar or glucose tolerance test performed.⁵

Electrolyte measurements are necessary to identify catecholamine-induced renal impairment. Cases of severe hypokalaemia, due to hyperreninaemia and secondary hyperaldosteronism have been reported in children with PPGL.⁵ Hypercalcaemia may occur when a neuroendocrine tumour is associated with a parathyroid adenoma as in MEN 2A. In addition, a full blood count and cross match should be done and any abnormalities investigated and corrected preoperatively.

Intraoperative management

An experienced endocrine surgeon and anaesthetist are crucial to the safe management of these patients given the potential complications of resecting these tumours.¹ Close communication amongst team members is also important to anticipate and treat periods of instability. The Endocrine Society Clinical Practice Guidelines³ recommend minimally invasive adrenalectomy (laparoscopic) for most adrenal pheochromocytomas. Open resection is recommended for large (> 6 cm) or invasive pheochromocytomas to ensure complete tumour resection, prevent tumour rupture, and avoid local recurrence. Open resection is also recommended for most paragangliomas, unless they are small, non-invasive and in favourable locations.

Monitoring and vascular access

- ECG
- Pulse oximeter
- Capnography
- Temperature probe
- Arterial line
- CVP

- Large bore peripheral venous access
- Urinary catheter
- Cardiac output monitoring in patients with cardiomyopathy

Due to the sudden and sometimes unexpected changes in haemodynamics in these patients, both standard and invasive monitoring is mandatory. In older children, as in adults, the arterial line and central venous catheter can be inserted under a combination of local anaesthesia and sedation. In younger children this is not an option.⁵ Cardiac output monitoring may be invaluable in the context of cardiomyopathy. The use of pulmonary artery catheters in children remains a contentious issue. The relative lack of experience in the use of pulmonary artery catheters by most paediatric anaesthetists would be associated with an increased risk of complications.⁵ Transoesophageal echocardiography can be used to guide fluid management and titration of vasodilators. Oesophageal Doppler has been used in the paediatric population and a prospective study investigating its efficacy is currently being undertaken in Austria.⁴ Devices relying on arterial pulse contour analysis have never been formally evaluated in phaeochromocytoma surgery.⁴

The chosen anaesthetic technique should⁴:

- Avoid drug-induced catecholamine release
- Avoid catecholamine release induced by anaesthetic or surgical manoeuvres
- Minimise haemodynamic responses to tumour handling
- Treat episodes of hypotension, particularly after tumour devascularisation

Avoid drug-induced catecholamine release

Table V. Drugs to consider avoiding on the basis of drug-induced catecholamine release⁴

• Desflurane	• Succinylcholine
• Ketamine	• Ephedrine
• Morphine	• Droperidol
• Pethidine	• Metoclopramide
• Atracurium	• Cocaine
• Pancuronium	

Avoiding catecholamine release induced by anaesthetic or surgical manoeuvres

Catecholamine release may be provoked by anaesthetic induction and tracheal intubation, surgical incision, abdominal exploration and tumour manipulation, as well as raised intra-abdominal pressure associated with capnoperitoneum or coughing. The following drugs are useful to ameliorate catecholamine release in response to these stimuli⁴:

- Magnesium sulphate
- Remifentanyl
- Dexmedetomidine

Magnesium sulphate (MgSO₄) has been shown to inhibit the release of catecholamines from both the adrenal medulla and peripheral adrenergic nerve terminals. It reduces alpha adrenergic receptor sensitivity to catecholamines as well as exerting anti-arrhythmic effects via antagonism of L-type calcium channels. Magnesium also has direct dilator action on predominantly arteriolar vessel walls. In a case series by James,¹⁰

3–5 ug/kg fentanyl combined with 40–60 mg/kg of MgSO₄ before intubation followed by an infusion of 1–2 g/h (with further boluses if required) provided good control of systolic arterial pressure before tumour handling.

Remifentanyl is very effective in blunting haemodynamic responses to intubation or pain. Its pharmacokinetic profile facilitates rapid titration to effect. It is however inadequate in preventing hypertension associated with tumour manipulation when used as a single agent.⁴

Dexmedetomidine is a centrally acting selective α₂ receptor agonist with sedative and analgesic properties. The central sympatholytic effects result in substantial reductions in plasma catecholamine levels, making it a potentially very attractive agent in this setting. However, the relatively few case reports describing its use in phaeochromocytoma surgery have still required additional vasodilators, particularly during tumour handling.⁴

Minimise haemodynamic responses to tumour handling

Tumour manipulation during surgery can result in profound hypertension, bradycardia (with norepinephrine), and tachyarrhythmias (with epinephrine). Hypertensive crises are usually managed with a vasodilator, while tachyarrhythmias are controlled with β blockers. Agents that have been used successfully include⁴:

- Phentolamine
- Sodium nitroprusside
- Glyceryl trinitrate
- Nicardipine
- Esmolol
- Labetalol

Phentolamine is a competitive non-selective α receptor antagonist. It results primarily in vasodilatation and can cause a reflex tachycardia. It has a very short duration of action with a half-life of only 19 minutes. It is commonly administered to control hypertensive surges whilst establishing desired infusion rates of other drugs.⁴ Tachyphylaxis is common.

Sodium nitroprusside (SNP) is a potent direct vasodilator with an immediate onset and short duration of action. It causes predominantly arteriolar vasodilatation. SNP infusions should be started at 0.5–1.5 ug/kg/min and may be increased up to 4 ug/kg/min. The risk of cyanide toxicity is very low at these doses.

Glyceryl trinitrate (GTN) is principally a venodilator. GTN infusions are usually titrated within the range of 0.5–5 ug/kg/min. A reflex tachycardia often occurs and can be problematic.

Nicardipine is a dihydropyridine calcium channel antagonist. It is a potent arterial vasodilator and is administered by infusion intraoperatively. A reflex tachycardia does not occur, making it the preferred choice by some authors. It has an elimination half-life of 40–60 minutes which can result in persistent hypotension. Clinical experience is still limited.

Esmolol is a selective β₁ antagonist with a rapid onset and a short duration of action, making it the ideal β blocker in these cases. The initial loading dose is 500 ug/kg over one minute, followed by a maintenance infusion of 50 ug/kg/min titrated to effect.

Labetalol is predominantly a β blocker with some α blocking effects. It may be used to control blood pressure as well as tachycardias. It has a much longer half-life (5.5 h) than esmolol and is therefore less titratable.

Treating hypotension after tumour devascularisation

Hypotension seen after devascularisation of the tumour is relatively common. It may be both profound and catecholamine-resistant. The underlying mechanisms of this hypotension are still debated and are usually multifactorial including:

- Residual α blockade, particularly with the use of phenoxybenzamine
- Abrupt catecholamine deficiency after tumour resection
- Catecholamine receptor down-regulation caused by chronically elevated catecholamine levels
- Catecholamine-induced myocardial dysfunction
- Hypovolaemia from blood and fluid loss
- Suppression of the normal contralateral adrenal gland from excessive catecholamines

Appropriate management includes stopping any hypotensive agents and optimising fluid balance taking into account the possibility of ongoing haemorrhage and myocardial dysfunction. Norepinephrine is a very useful agent to increase peripheral vascular resistance and vasopressin should be considered if hypotension is refractory. Vasopressin causes systemic vasoconstriction and pulmonary vasodilatation by acting on V_1 receptors. It also increases circulating volume by acting on V_2 receptors in the distal convoluted tubule and collecting ducts of the kidney, thereby increasing water reabsorption. There have been several case reports of the successful use of vasopressin after phaeochromocytoma resection, although dosing practices varied widely.⁴ Other possible treatment options include adrenaline and phenylephrine. One should consider glucocorticoids if hypoadrenalism is suspected or if bilateral adrenalectomy is performed.

Postoperative management

Decision for postoperative extubation or elective ventilation depends on haemodynamic stability and other vital parameters. Postoperative ICU care is necessary for close monitoring of potential complications.¹¹ All patients should receive invasive arterial pressure monitoring for at least 24 hours after the procedure.⁴ The mechanism and management of postoperative hypotension has been discussed above. Hypertension after surgery may be due to:

- Pain
- Urinary retention
- Fluid overload
- Inadvertent ligation of the renal artery precipitating hyperreninism
- Incomplete tumour resection
- Metastatic disease

Analgesia in children can be provided by either intravenous opioids or via epidural analgesia. Postoperative morbidity associated with laparoscopic surgery may be significantly reduced.⁵

Severe hypoglycaemia has been reported following phaeochromocytoma removal and regular blood glucose

monitoring and appropriate titration of dextrose infusions is therefore recommended.⁵ Following removal of the tumour, the rapid fall of circulating catecholamines leads to a disappearance of their hyperglycaemic effects. There can also be an increase in insulin secretion leading to hypoglycaemia. The use of β blockers may compound this effect. Lifelong steroid replacement is indicated if a bilateral adrenalectomy has been performed, but steroid supplementation is rarely required otherwise.⁴

Follow up

Lifelong follow-up to detect recurrent or metastatic disease is recommended by the Endocrine Society Clinical Practice Guideline.³ Recurrence has been noted to occur anywhere between one and 14 years after the initial presentation.¹ There are no reliable markers to distinguish a benign lesion from a malignant one and malignant PCCs and PGLs are defined by the World Health Organization classification as the presence of metastases that do not include local invasion of the tumour.¹ Long-term follow-up on patients with hereditary PCCs and PGLs cannot be stressed enough given the lifelong risk of recurrence and metastatic disease.¹

Conclusion

The anaesthetic management of a child with either a phaeochromocytoma or a paraganglioma presents a unique challenge to the anaesthetist. An in-depth knowledge and understanding of the underlying pathophysiology and pharmacology is necessary in order to formulate a safe anaesthetic plan tailored to suit each patient. Good communication between an experienced multidisciplinary team comprised of surgeons, endocrinologists and anaesthetists is recommended for the safe perioperative management of these patients.

References

1. Bholah R, Bunchman TE. Review of Pediatric Pheochromocytoma and Paraganglioma. *Frontiers in Pediatrics*. 2017;5(155).
2. Pamporaki C, Hamplova B, Peitzsch M, et al. Characteristics of pediatric vs adult pheochromocytomas and paragangliomas. *The Journal of Clinical Endocrinology and Metabolism*. 2017;102(4):1122-32.
3. Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology and Metabolism*. 2014;99(6):1915-42.
4. Connor D, Boumpfrey S. Perioperative care of phaeochromocytoma. *BJA Education*. 2016;16(5):153-8.
5. Hack HA. The perioperative management of children with phaeochromocytoma. *Pediatric Anesthesia*. 2000;10(5):463-76.
6. Naranjo J, Dodd S, Martin YN. Perioperative management of pheochromocytoma. *Journal of Cardiothoracic and Vascular Anesthesia*. 2017;31(4):1427-39.
7. Waguespack SG, Rich T, Grubbs E, et al. A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. *The Journal of Clinical Endocrinology and Metabolism*. 2010;95(5):2023-37.
8. James M. The impact of changes in drug availability for hemodynamic management in pheochromocytoma: prêt-à-porter or tailor-made? *Canadian Journal of Anesthesia/Journal canadien d'anesthésie*. 2015;62(12):1244-7.
9. Ramachandran R, Rewari V. Current perioperative management of pheochromocytomas. *Indian Journal of Urology : IJU : Journal of the Urological Society of India*. 2017;33(1):19-25.
10. James MFM. Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma: a review of 17 anaesthetics. *British Journal of Anaesthesia*. 1989;62(6):616-23.
11. Rajappa GC, Anandaswamy TC. Laparoscopic cortical sparing adrenalectomy for pediatric bilateral pheochromocytoma: anesthetic management. *Anesthesiology and Pain Medicine*. 2014;4(2):e15460.