Factors affecting the haemodynamic behaviour of patients undergoing pheochromocytoma and paraganglioma removal: A review

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Pheochromocytoma and paraganglioma are catecholamine-secreting tumours associated with major haemodynamic upheavals. The cardiovascular and other organ-related morbidity and even mortality has been ascribed to the major haemodynamic effects of these tumours. Many factors affect the nature and intensity of these haemodynamic changes. The rarity of these tumours as well as their extremely varied clinical presentation preclude conduct of randomized-controlled trials that may provide evidence in terms of these factors and the ways to predict and control them. Many retrospective studies and case reports, however, do provide some insight into their haemodynamic behaviour. Factors such as tumour pathology, associated genetic syndromes, anatomical attributes and perioperative drug therapy affect the haemodynamics of patients with these unique tumours. Knowledge of these factors and their presumed and known association with haemodynamic behaviour of the patients is important during the

perioperative care of these patients. The review focuses on the tumour-related, patient-related and the perioperative care-related factors that affect the haemodynamic behaviour of these patients during the surgical removal of these tumours. *Cardiovasc Endocrinol* 6:73–80 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Cardiovascular Endocrinology 2017, 6:73–80

Keywords: haemodynamics, paraganglioma, perioperative period, pheochromocytoma

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Received 1 March 2016 Accepted 24 June 2016

Introduction

Pheochromocytoma (PCC) and paraganglionoma (PGL) are tumours of neuroendocrine origin with the potential to cause acute hypertension and related end organ complications. The release of high amount of catecholamines from these tumours is known to cause hypertensive crises, severe cardiomyopathy and cardiogenic shock, which are the reasons for morbidity and mortality, especially in undiagnosed and untreated patients. Abraham Lincoln, the 16th President of America, was probably suffering from MEN2B syndrome, with clinical manifestations of marfanoid habitus and PCC, which was the cause of his extremely labile hypertension and his poor cardiovascular status [1]. Indeed, it has always been speculated that if the advancement in genetic testing and investigational evolution along with medical and surgical progress that is present in today's world was available during that time, the much-revered leader could have been treated for his condition.

The advancement in the medical and surgical techniques has significantly decreased the mortality associated with the removal of these tumours, but the surgery is still associated with considerable haemodynamic disturbances that contribute towards the perioperative morbidity of the patients. With the advancement in laparoscopic surgery and its widespread use for adrenalectomy and PGL

removal, the anaesthetic management has acquired a whole new dimension. Laparoscopic surgery provides the advantages of less postoperative pain, earlier ambulation and faster hospital discharge to patients, but is associated with its own set of unique anaesthetic implications, with pneumoperitoneum and hypercarbia adding to an already precarious haemodynamic status. PCC and PGL are rare tumours and very minimal evidence on their perioperative management is available in the form of randomized-controlled studies or what is known as level I evidence. A number of retrospective studies and case series do shed some light on the various factors affecting their haemodynamic behaviour. Many nonmodifiable factors such as tumour pathology, genetic association, size and site of the tumours and modifiable factors such as preoperative preparation, anaesthetic drugs and surgical approach may influence the perioperative haemodynamic status of these patients. Knowledge of these factors may aid the physicians, surgeons and anaesthesiologists in the perioperative management of these patients.

Many guidelines are already in place that provide endocrine surgeons and physicians recommendations on the diagnostic, operative and nonoperative medical management for PCC, PGL and adrenal incidentalomas [2–4]. This review, however, primarily aims to discuss and enumerate the above-mentioned factors and their contribution

towards the haemodynamic behaviour of patients with these rare tumours in the perioperative period.

Historical background

The first adrenalectomy for PCC was described by Roux and colleagues in the year 1926 [5]. A mortality rate of up to 50% has been described in patients undergoing PCC and PGL removal until the late 1960s when the factors contributing towards mortality were searched for and being identified [6]. The phenomenal decrease in mortality rates to less than 1% at present is largely because of advances in perioperative care provided by the physicians as well as the anaesthesiologists. In one of earliest descriptions of how meticulous preparation and careful intraoperative monitoring and management results in decreased perioperative mortality in these patients, Ross *et al.* [7] published a detailed account of 27 patients who underwent surgery for PCC and PGL removal in 1967. Some of the patients in the series were prepared with phenoxybenzamine, either intravenous or oral, with or without propranolol. The series reported no mortality. The authors found that phenoxybenzamine led to more satisfactory α -receptor blockade than intraoperative intravenous phentolamine, with better control of intraoperative increases in blood pressure encountered during the operation. The authors also actively managed the intraoperative tachycardia and arrhythmia with appropriate β -blockers and antiarrhythmic drugs. Further studies have also elucidated minimal and no mortality with diligent perioperative practices [8–12]. Harrison and colleagues, in 1968, described the perioperative management of 14 patients with PCC. They had one fatality, and α - and β -blockade was not routinely used in all patients [13]. The cause of mortality in this patient was refractory hypotension in the postoperative period after the removal of an epinephrine-secreting PCC. It was thus evident that better control of haemodynamic status in the perioperative period with diligent management of both hypotension and hypertension was required to decrease morbidity and mortality in these patients.

Pathophysiology related to PCC and PGL

PCC have an estimated annual incidence of ~ 0.8 per 100 000 person years or an overall estimated incidence of 2–8 per million [14]. About 4% of adrenal incidentalomas are PCC [15]. Nearly 40% of these tumours are associated with known germline mutations that encompass five syndromes (Table 1). Patients with tumours associated with any of the genetic syndromes are more likely to have bilateral and/or extra-adrenal tumours. The catecholamine type and their secretory pattern have also been shown to be different depending on the genetic association. Patients with Von Hippel–Lindau (VHL)-associated PCC have increased levels of plasma normetanephrines, whereas those with MEN2-associated PCC have increased plasma levels of metanephrines [18]. This indicates that the tumours associated with VHL are

mainly norepinephrine (NE) secreting, whereas those associated with MEN2 are primarily epinephrine secreting. Patients with MEN2 syndrome produce more catecholamines and in an episodic manner compared with patients with VHL syndrome. This difference in tumour characteristics is mainly because of the differential expression of tyrosine hydroxylase, which is the rate-limiting enzyme in the catecholamine production and phenylethanolamine *N*-methyltransferase, which is the enzyme responsible for conversion of NE into epinephrine in the tumours [19]. The activity of both these enzymes is significantly increased in tumours occurring in patients with MEN2 compared with those with VHL syndrome. The differential catecholamine production in these two syndromes leads to a clinical different symptomatic profile of patients. Although patients with MEN2 are more likely to have paroxysmal and episodic symptoms of hypertension, diaphoresis, palpitations and anxiety compared with patients with VHL syndrome, patients with NF1 have tumours with a phenotype similar to that in patients with MEN2 and secrete epinephrine as the major catecholamine. However, patients with tumours associated with the SDHB and SDHD mutation are usually NE and dopamine (DA) secreting [20].

PCCs synthesize catecholamines at increased rates that may be up to 27 times the synthetic rate of the normal adrenal medulla. The signs and symptoms of the patient as well as the hypertensive crises encountered intraoperatively are because of the release of these catecholamines in the circulation. PCCs may secrete either NE or epinephrine or both, but never DA. PGLs predominantly secrete NE and rarely DA. The clinical presentation of the patient as well as the nature of haemodynamic changes observed during and after tumour removal depend on the amount and type of catecholamine secreted and the pattern of its release [21]. Catecholamines are produced in quantities that considerably exceed the vesicular storage capacity and accumulate in the cytoplasm. Catecholamines in the cytoplasm are subject to intracellular metabolism; the excess catecholamines and their metabolites diffuse out of the tumour cells into the circulation and are subject to enzyme-linked metabolism [22]. The levels of various end products of this metabolism and the catecholamines themselves can be measured in the plasma and the urine and form the basis of the diagnosis of PCC and PGL. The amount and type of catecholamines being secreted by the tumour can be useful in predicting the type and severity of haemodynamic upheavals expected during tumour manipulation (see below). NE acts on the α -1, α -2 and β -1 sympathetic receptors, whereas epinephrine acts on β -1 and β -2 receptors. Stimulation of α -1 receptors leads to intense vasoconstriction of both arterial and venous vascular beds, leading to severe hypertension with decreased organ perfusion. Stimulation of α -2 receptors causes a negative feedback effect, which decreases NE release from the

Table 1 Clinical features of genetic syndromes associated with pheochromocytoma and paraganglioma [16,17]

Syndromes	Gene defect	Inheritance pattern	Clinical features	Incidence of PCC/ PGL	Malignant potential
Neurofibromatosis type 1	NF1	Autosomal dominant	Cutaneous and plexiform neurofibromas Café-au-lait spots Lisch nodules Long bone dysplasia Optic gliomas Malignant peripheral nerve sheath tumours Chronic myelogenous leukaemia	PCC (possibly bilateral) Incidence: 5%	12%
Multiple endocrine neoplasia type 2A	RET	Autosomal dominant	Medullary thyroid cancer Hyperparathyroidism	PCC Incidence: 50% Bilateral: 25%	< 5%
Multiple endocrine neoplasia type 2B	RET	Autosomal dominant	Medullary thyroid cancer Marfanoid habitus Mucocutaneous neuromas Gastrointestinal ganglioneuromas	PCC Incidence: 50% Bilateral: 25%	< 5%
Von Hippel–Lindau disease	VHL	Autosomal dominant	Haemangioblastomas of the central nervous system Endolymphatic sac tumours Epididymal cystadenomas Renal cell carcinoma Renal and pancreatic cysts Pancreatic neuroendocrine tumours GI stromal tumours	PCC (possibly bilateral) Incidence: 10–20% PGL/HNPGL rare	5%
Hereditary paraganglioma syndrome (PGL syndromes 1–5)	SDHA	Autosomal dominant		PCC/PGL	Low
	SDHB	Autosomal dominant	Renal cell carcinoma GI stromal tumours Pituitary adenomas rare	PGL PCC and HNPGL possible	23%
	SDHC	Autosomal dominant	Renal cell carcinoma GI stromal tumours Pituitary adenomas rare	HNPGL PGL possible PCC rare	Low
	SDHD	Autosomal dominant	Renal cell carcinoma GI stromal tumours Pituitary adenoma rare	Multifocal HNPGL PCC/PGL	< 5%

HNPGL, head and neck paragangliomas; GI, gastrointestinal; PCC, pheochromocytoma; PGL, paraganglionoma; VHL, Von Hippel–Lindau.

sympathetic nerve endings. Stimulation of β -1 receptors on the cardiomyocytes leads to inotropic and chronotropic effects, leading to a clinical effect of hypertension (although not as intense as that found with α -1 stimulation) and tachycardia. However, stimulation of β -2 receptors in the smooth muscles of arteries leads to vasodilatation. High levels of NE, therefore, are seen clinically as severe hypertension, normal or increased heart rate, more propensity for end organ damage and orthostatic hypotension because of intense vasoconstriction and volume contraction. High levels of epinephrine, however, lead to

hypertension, severe tachycardia and more pronounced orthostatic hypotension because of β -2 stimulation. DA acts only on the DA receptors D-1 and D-2 in clinically observed levels that do not have much hypertensive or tachycardia effect. Only at very high doses, as may occur during paroxysms of increased release from a DA-secreting tumour, the catecholamine acts on the α -1 and β -1 receptors, causing hypertension and tachycardia.

Clinical cardiovascular presentation

Pheochromocytoma and PGL can present with a gamut of symptoms and signs. The most common triad of symptoms of headache, palpitation and diaphoresis is found in less than 40% of patients. Various common and uncommon clinical pictures of the tumour presentation are enumerated in Table 2. The type, quantity and pattern of catecholamines released by the tumours can affect the haemodynamic profile found in patients preoperatively and during surgery [5]. Primarily NE-secreting tumours, both PCC and PGL, will usually result in hypertension. If the tumours also show episodic release, the patients will usually have baseline hypertension along with paroxysms of hypertensive crises and associated symptoms. With primarily epinephrine-secreting tumours, hypertension may not be a prominent feature, but episodic features of diaphoresis, syncope and flushing are present, associated with the episodic release of epinephrine. Patients with

Table 2 Symptoms and signs reported in patients with pheochromocytoma and paraganglioma

Symptoms	Signs
Headache ^a	Hypertension: episodic or continuous
Sweating ^a	Tachycardia
Palpitations ^a	Orthostatic hypotension
Flushing ^a	Features of heart failure
Anxiety	
Panic attacks	
Chest pain ^a	
Dyspnoea	
Syncope	
Abdominal pain ^a	
Diarrhoea	
Weakness and fatigue	
Anorexia and weight loss	
Polyuria and polydipsia	

^aSymptoms may occur episodically.

DA-secreting tumours usually have no hypertension, although paroxysms may be present. The above haemodynamic characteristics represent only a generalization and patients with PCC and PGL show a gamut of symptoms and signs, with many exceptions to the above description.

Anatomical considerations

The PCCs arise from the adrenal medulla, whereas the PGLs arise from chromaffin cells situated along the sympathetic and parasympathetic tissue between the head and the pelvis. The right and left adrenal glands are situated retroperitoneally superomedial to the respective kidneys surrounded by the fibrous capsule of the kidney (Gerota's fascia) and the perinephric and retroperitoneal fat. They have extensive blood supply from the inferior phrenic artery, aorta and the renal artery. The dissection of left adrenal is slightly easier than that of the right adrenal because of the proximity of the latter to the inferior vena cava and the longer vascular pedicle of the former. Manipulation of the gland during dissection is one of the factors implicated in the occurrence of hypertensive spikes during both open and laparoscopic surgery. It may thus be expected that PCCs with abnormal or complex anatomy and those with a larger size will lead to more hypertensive episodes intraoperatively. Paragangliomas arising from sympathetic tissue situated in the thoracoabdominal region secrete catecholamines, whereas those arising from parasympathetic tissue (commonly known as head and neck paraganglioma) usually do not secrete catecholamines. Head and neck PGLs can remain silent for many years because of their slow growth and minimal tendency to secrete catecholamines. The most common clinical symptomatology is because of their compression or infiltration of adjacent tissues, leading to hearing loss, tinnitus, dysphagia and cranial nerve palsy [23]. However, thoracoabdominal PGLs arising from the sympathetic tissue usually produce catecholamines and are thus associated with clinical symptoms of increased NE in more than 80% of the patients. The most common PGLs are those associated with the retroperitoneal organ of Zuckerkandl, the chromaffin para-aortic sympathetic tissue between the origin of the inferior mesenteric artery and the aortic bifurcation. The other common locations are the infra-diaphragmatic para-aortic region and the mediastinum. The urinary bladder is another common site of paraganglioma [24]. Their unique location and the proximity to the major vessels, especially the aorta, make them even more difficult to dissect compared with PCCs. They receive extensive blood supply from the surrounding organs as well as the aorta. These anatomical complexities mean that the surgical removal of these tumours involves increased operative time, increased risk and episodes of intraoperative hypertension as well bleeding from the surrounding vulnerable vasculature. Experience with minimally invasive surgery for removal of PGLs is

still limited because of its rarity and anatomically complex location. In a retrospective series analysis, Hattori and colleagues compared the intraoperative haemodynamic changes as well as the postoperative outcome in patients undergoing PGL and PCC removal by the minimally invasive approach. They reported that the operative time is longer and the intraoperative hypotensive episodes are significantly more in patients undergoing PGL removal than the patients who underwent PCC removal by a minimally invasive approach [25]. The reported hypertensive episodes and the maximal blood pressure during the tumour manipulation were the same between the two groups, although the operative time was significantly longer in the PGL group. The study was, however, a retrospective one and included only nine patients in the PGL group. The rarity of this tumour and the relative unpredictability of the haemodynamic effects of these tumours preclude adequately powered, prospective and well-controlled studies to conclusively make an inference on this issue.

Another anatomical factor presumably related to increased intraoperative hypertensive episodes is the size of the tumour. Increasing tumour size was associated with more hypertensive episodes in patients undergoing PCC and PGL removal in a retrospective study that included data from 91 patients (relative risk 1.40) [26]. Larger tumours may be associated with increased incidence of postoperative morbidity as well, that is, prolonged mechanical ventilation and vasopressor use in the postoperative period [27]. Another multicentric retrospective study reported an increase in the incidence of hypertensive episodes and conversion to an open approach intraoperatively in patients undergoing laparoscopic removal of large (>6 cm) PCCs compared with patients with smaller tumours, but the difference was not statistically significant [28]. Cardiovascular complications associated with hypertensive emergencies have not been reported in any of these studies. It is thus reasonable to assume that although larger tumours will cause more episodes of hypertensive emergencies, these are amenable to standard vasodilator therapy and are usually not associated with major cardiovascular adverse effects. In a recent and only prospective study related to the matter, Wang *et al.* [29] compared the efficacy of laparoscopic surgery with open approach in patients with PCC more than 6 cm in size. The frequency of intraoperative blood pressure fluctuation (any marked change in blood pressure requiring a therapeutic intervention or interruption of the operative procedure) was more in the laparoscopic approach, but was statistically insignificant (34.8 vs. 21.4%). Conversion to an open approach was, however, required in two patients. Larger-sized tumours may, however, be associated with a higher risk of malignancy and local recurrence that may preclude the use of minimally invasive techniques [30].

Preoperative preparation

Preoperative preparation is known to decrease the perioperative hypertensive spikes significantly. Adequate optimization of blood pressure with α - and β -blockers has decreased the perioperative morbidity and mortality to less than 3% in these patients [31]. The choice of α -blockade is between the nonselective, noncompetitive α -blocker that is, phenoxybenzamine and selective, competitive α -blocker that is, prazosin, doxazosin and terazosin. Phenoxybenzamine acts by binding covalently to the α -receptors (both α -1 and α -2) and rendering them inactive. The recovery of receptor function occurs by the formation of new receptors that may require 8–12 h. Theoretically, the hypotension after tumour removal may thus be more sustained in patients who have been optimized with phenoxybenzamine. However, the intraoperative hypertensive crisis during tumour handling is much less in these patients. Selective and competitive α -blockers, alternatively, lead to lower incidences of postoperative hypotension, but may not provide adequate control of intraoperative hypertensive emergencies. Phenoxybenzamine has been in clinical use for α -blockade in patients with PCC and PGL for more than 50 years now. Recently, however, the increasing unavailability of the drug, along with the fact that the drug has a very unfavourable side-effects profile, has led to physicians favouring the α -blockers [32,33]. Many studies have attempted to explore the difference in the haemodynamic profile proffered by selective and nonselective α -blockers. In one of the largest, albeit retrospective, studies that looks at this aspect, Weingarten and colleagues compared the haemodynamic behaviour of 87 patients with PCC and PGL at two different medical centres with either a predominantly phenoxybenzamine-based or selective α -1 blocker-based pretreatment protocol. They found that patients who underwent surgery at the latter centre had a greater maximal systolic blood pressure intraoperatively ($P=0.011$) and received significantly greater volume of intravenous fluids. However, more number of patients who received phenoxybenzamine-based treatment needed phenylephrine after removal of tumour ($P=0.009$) [34]. This notion, however, may not be always observable as the perioperative haemodynamic behaviour of patients with these tumours is known to be inconsistent. Multiple other retrospective and prospective studies have reported conflicting results on this issue [35–40]. Many centres (including ours), however, do favour the use of shorter acting and more titrable selective α -blockers. In a recent prospective study that included 27 patients who received either phenoxybenzamine or prazosin for preoperative α -blockade, the authors found that patients on prazosin pretreatment required more antihypertensive drugs during surgery. However, more vasopressors were required in patients who received phenoxybenzamine. Both these differences, however, did not reach statistical significance ($P=0.16, 0.19$, respectively) [40].

As catecholamines act on both α - and β -receptors, the clinical effects of β -receptors also need to be controlled. β -Blockers are, however, never started before α -blockade has been instituted. The haemodynamic effects of activation of β -1 receptors include tachycardia, whereas β -2 receptors lead to vasodilation. Initiation of nonselective β -blocker therapy without preceding α -blockade in a patient with PCC may lead to loss of β -2 receptor-mediated vasodilatation and unopposed effects of α -receptors, leading to severe vasoconstriction and associated life-threatening complications of hypertensive emergency including myocardial dysfunction and pulmonary oedema [41,42]. It is thus important to avoid β -blockers, especially nonselective β -blockers, in patients with PCC and PGL without initiation of an α -blockade.

Calcium channel blockers (CCB) are the other class of antihypertensives that have found an important place in the preoperative and intraoperative management of patients with catecholamine-releasing tumours. CCBs inhibit NE-mediated calcium ion influx into vascular smooth muscle. This leads to vasodilatation, resulting in control of blood pressure, tachyarrhythmias and catecholamine-associated coronary spasm. They can be used either as an adjunct to α - and β -blockers [43–45] or as primary antihypertensive therapy [46]. Brunaud and colleagues compared the effect of preoperative α -blockers (phenoxybenzamine) and CCBs (nicardipine) on intraoperative haemodynamic instability during PCC and PGL removal in 155 patients. The mean maximal systolic blood pressure of the patients was lower after α -blockade ($P<0.0001$) as was the incidence and duration of severe hypertension ($P<0.01$); however, severe hypotensive episodes were also more frequent ($P<0.001$) and longer ($P<0.0001$) with α -blockade. The type of preoperative drug used (α -blocker vs. CCB), however, was not an independent predictor of intraoperative haemodynamic instability [46]. CCBs have also been found to be useful in patients who are otherwise normotensive and/or experience intermittent spikes of hypertension [27].

Metyrosine, a tyrosine hydroxylase inhibitor, is another drug that has been used either alone [47] or as an adjunct to α -blockers in preoperative antihypertensive regimens in these patients [48]. Its use as an adjunct to phenoxybenzamine significantly decreased the intraoperative cardiovascular-related complications in a recent retrospective study [48]. Its use as a primary antihypertensive agent is not as well accepted because of its low availability, high incidence of side-effects and inability to control breakthrough hypertension in some patients [47–49].

Anaesthetic management

Anaesthetic drugs

The unique haemodynamic problems associated with these tumours in the perioperative period has for years perplexed the anaesthesiologists in the choice of

anaesthetic techniques and drugs. Many drugs have traditionally been considered unsafe to use because of their histamine-releasing properties (Table 3). Drugs such as ketamine and anaesthetic agents such as desflurane have intrinsic sympathomimetic activity and hence may be considered detrimental to the haemodynamic stability in these patients. The choice of anaesthetic drugs, however, plays a smaller role in the overall perioperative haemodynamic stability, which depends more on the tumour properties and the surgical handling rather than the individual anaesthetic drugs. The diligent and prompt management of hypertensive episodes associated with a good plane of anaesthesia (as is required in any surgery) can lead to a stable intraoperative course during removal of most of the tumours [50].

There still are anaesthetic agents that are favoured more by the anaesthesiologists because of their minimal effect on the sympathetic stimulation. Thiopentone and propofol have been used routinely without any report of unduly different haemodynamic changes as is seen with other patients. Etomidate has also been used in patients with PCC and may be a choice of an induction agent in patients with catecholamine-induced cardiomyopathic changes [51,52]. Most opioids have been found to be safe for use intraoperatively and fentanyl, sufentanil [53], remifentanyl [54,55] and alfentanil [56,57] have all been used safely in these patients. Remifentanyl, because of its high potency, rapid onset and a short duration of action, has been recommended for rapid control of hypertensive crisis as well as effective surgical analgesia in patients undergoing laparoscopic removal of PCC [54], although significant bradycardia and hypotension can be problematic with its use [58]. It is recommended that morphine be avoided in these patients because of its purported histamine release, which can lead to the release of catecholamines from the tumour. It has, however, been used safely in many patients intraoperatively, thus indicating that the histamine release induced may not be significant enough to cause catecholamine-induced hypertensive crisis [59]. Concerns of histamine release leading to a hypertensive crisis because of muscle relaxants atracurium and cisatracurium

have similarly been shown to be insignificant with their repeated and safe use by many anaesthesiologists [27,60–63]. Most of the present-day inhalational agents including desflurane have also been used safely during intraoperative anaesthesia maintenance [27,64]. The maximum stimuli to the release of catecholamines occur at the manipulation of the gland in both open and minimally invasive techniques. The size of the tumour may thus be an important factor influencing the haemodynamic stability intraoperatively (see above). Some hypertensive surges are expected despite adequate α -receptor blockade. The key to managing these crises is fast but short-acting intravenous vasodilating agents. In the present day, apart from the traditionally used sodium nitroprusside and nitroglycerine, anaesthesiologists have several choices depending on the local availability. Sodium nitroprusside and nitroglycerine, however, still remain the most commonly used drugs to curb intraoperative hypertensive surges in many centres (including ours). In addition to vasodilation, control of tachycardia is also important during hypertensive crises. The short-acting β -blocker, esmolol, is a good choice for this indication.

Once the tumour has been isolated, a variable degree of hypotension is usually expected in most of the patients. In almost 70% of cases, the hypotension is amenable to fluid therapy and the rest may require an infusion of one or more vasopressors for a short duration. After the surgery, almost all the patients are shifted either to intensive care or high-dependency units, mainly to manage the haemodynamic instability (if present). Hypoglycaemia is another complication that may be encountered frequently in the postoperative period and needs diligent monitoring and management.

Postoperative course

The postoperative follow-up in these patients is prolonged. Depending on the standard guidelines, patients may require yearly or even more frequent biochemical and imaging-based follow-up to detect recurrences [2–4]. Clinical symptoms, especially hypertension and adrenergic symptoms, are also an important part of follow-up [65]. Up to 25% of patients, with or without recurrence, may be hypertensive (persistent or newly developed hypertension) at the end of 5 years [66].

Conclusion

Haemodynamic instability is the hallmark of the catecholamine-releasing PCC and PGL and the main indication for the removal of these tumours. Many non-modifiable factors such as tumour size, location of the tumour, association with genetic syndromes and secretory activity of the tumour influence the perioperative haemodynamics in these patients. However, many modifiable factors such as type of preoperative preparation including antihypertensive medications and fluid therapy and anaesthetic techniques have also been considered to

Table 3 Anaesthetic drugs that may be detrimental to haemodynamic stability in patients undergoing surgery for pheochromocytoma and paraganglioma removal

Drugs to be avoided ^a	Cause
Morphine Atracurium Cis-atracurium Pancuronium D-Tubocurarine Gallamine	Histamine release and/or anticholinergic
Ketamine Desflurane Pancuronium Succinylcholine	Sympathomimetic activity
	Physical compression of tumour by drug-induced fasciculations

^aSome or all of these drugs have been/are being used safely in patients.

influence the perioperative haemodynamic behaviour in these patients. knowledge of these factors is important for the perioperative physicians, especially anaesthesiologists, to anticipate and manage the associated haemodynamic disturbances effectively.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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