

Perioperative management of pheochromocytoma

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Abstract : Pheochromocytoma is a rare catecholamine producing tumour, feared for its life threatening cardiovascular disturbances during anaesthesia. Improved medical and anesthetic management resulted in reduction of perioperative pheochromocytoma resection mortality from about 50% in the pioneer period to near 0% nowadays. Cardiomyopathy is usually reversible if managed properly. Stress related or (inverted) Tako Tsubo cardiomyopathy is a recent finding, deserving our attention. Preoperative alpha blockade should be performed to achieve cardiovascular stability and decrease uncontrolled intraoperative surges in blood pressure. During anaesthesia, additional antihypertensive (also mainly alpha blocking) agents are essential to prevent and overcome hypertensive crises. Magnesium sulphate is a safe and promising agent in improving cardiovascular stability and should have a place in standard therapy. A careful selection of anaesthetic drugs and techniques that cause the least hypertension is most important. Preoperative and intraoperative β -blockade can only be used as adjuvant therapy, mainly to control tachycardia and other rhythm disturbances. Postoperatively, the patient is transferred to the intensive care unit where adequate management of haemodynamic and metabolic complications takes place.

Key words : Anaesthesia ; pheochromocytoma ; adrenal gland neoplasms ; preoperative care ; intraoperative care ; postoperative care ; pregnancy ; catecholamine ; Tako Tsubo cardiomyopathy ; stress related cardiomyopathy ; magnesium sulphate ; alpha blockade.

INTRODUCTION

Epidemiology

Pheochromocytomas are rare catecholamine producing neuroendocrine tumours and an infrequent cause of arterial hypertension (0.1-0.6%) (1). Some tumours produce only norepinephrine, while others are able to transform norepinephrine into epinephrine by N-methylation. Tumours that contain epinephrine producing cells are therefore presumed to synthesize both amines. Nonadrenal tumours almost never produce epinephrine (2).

Advances in diagnosis and genetics have proven that the traditional rule of 10 for pheochro-

mocytomas (10% bilateral, 10% extra-adrenal, 10% familial and 10% malignant) is now obsolete. Prevalence of extra-adrenal tumours (often then referred as paragangliomas) is higher than 10% in some familial pheochromocytomas such as multiple endocrine neoplasia type 2 and Von Hippel-Lindau syndrome. Prevalence of extra-adrenal tumours can reach 20% and up to a quarter or more are hereditary. Metastases may be rare for adrenal pheochromocytomas (up to 5%), but may mount to 33% for extra-adrenal pheochromocytomas and peak even higher in patients with very specific mutations (1).

We recently diagnosed some cases of pheochromocytoma in our hospital. Laparoscopic pheochromocytoma resection took place after appropriate cardiovascular stabilisation.

An adequate anaesthetic management during pheochromocytoma surgery is of the utmost importance. Without proper treatment the perioperative mortality of (undiagnosed) pheochromocytoma can be as high as 85% (3).

In 1977 Engelman stated that successful surgery for pheochromocytoma depends more on the activities cephalad to surgical drapes than to those in the immediate operative field (4). Mayo and Roux were the first to report a successful surgical resection of pheochromocytoma in 1926 (5). Pioneers were confronted with mortality rates as high as 50%. In spite of improvements in medical and surgical treatment, morbidity rates of 40% and perioperative mortality rates of 2-4% were encountered during decades (6). Nowadays, several series show minimal morbidity and no mortality (6, 7), indicating a dramatically improved treatment.

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Genetics

Germ line mutations (1) in five genes have been identified to be responsible for familial pheochromocytoma. They cause the Von Hippel-Lindau syndrome (VHL gene), multiple endocrine neoplasia type 2 (RET gene), neurofibromatosis type 1 (NF1 gene), familial paragangliomas and pheochromocytomas (SDHB and SDHD gene). Pheochromocytomas associated with the Von Hippel-Lindau syndrome only produce norepinephrine. Familial paragangliomas and pheochromocytomas predominantly produce norepinephrine. Multiple endocrine neoplasia type 2 and neurofibromatosis type 1 produce both epinephrine and norepinephrine (1).

Symptoms

Pheochromocytoma is a very rare cause of high blood pressure only occurring in about 0.1% of hypertensive patients. However 85% of patients first present with this symptom, linked with marked increased urinary norepinephrine secretion and metabolites. Headache secondary to hypertension is the most common symptom. When the headaches are intermittent but regular, severe and associated with nausea and vomiting or with slow palpitations (baroreceptor-induced bradycardia) the possibility of pheochromocytoma should be considered. Patients present only in about 10-17% with paroxysmal symptoms such as paroxysmal tachycardia (sensed as palpitations), trembling, sweating, blanching associated with feelings of panic caused by the excessive secretion of epinephrine and dopamine (8). Occasionally, patients with predominantly epinephrine-secreting tumours present with hypotension and even shock (9).

Some patients also present with unexplained orthostatic hypotension on a background of hypertension (1).

Factors contributing to hypotension and shock include intravascular volume depletion, abrupt cessation of catecholamine secretion due to tumour necrosis, desensitisation of adrenergic receptors or hypocalcaemia. Shock can also be caused by a cardiovascular complication such as myocardial infarction, cardiac arrhythmias or a dissecting aortic aneurysm (1).

An unusual and life-threatening presentation is a pheochromocytoma multisystem crisis that consists of multiple organ system failure, temperature often near 40° C, encephalopathy, and hypertension or hypotension which demands immediate,

medical stabilisation. Emergent tumour removal is necessary if the patient's condition continues to deteriorate (10).

Metabolic effects of pheochromocytoma include hyperglycaemia, lactic acidosis and weight loss (11).

Differential diagnosis

Pheochromocytoma is a great mimic. Patients with essential hypertension can have associated hyper adrenergic features such as tachycardia, sweating and increased cardiac output. Patients with anxiety attacks can have associated blood pressure elevations. Differential diagnosis is usually decisive after 24 hour urine collection (metanephrines). Repeated collections during attacks may be necessary. Vasopressor crisis after clonidine withdrawal and the use of cocaine or monoamine oxidase inhibitors may also mimic pheochromocytoma paroxysms. Factitious crisis by self-administration of sympathomimetic amines can occur in mentally disturbed patients. Posterior fossa tumours or subarachnoid haemorrhage may cause increased excretion of catecholamines or catecholamine metabolites. These conditions are mostly obvious regarding the neurologic conditions. The possibility of subarachnoid haemorrhage secondary to pheochromocytoma should always be considered. Diencephalic or autonomic epilepsy may be associated with paroxysmal spells, hypertension and increased plasma catecholamine levels. An abnormal encephalogram and beneficial response to anti-convulsant therapy form often the clue to differentiate this rare entity from pheochromocytoma (12).

Catecholamine-secreting metastatic carcinoid tumours and even more infrequent other amine-precursor-uptake decarboxylation (APUD) tumours may present very similar as pheochromocytoma (13).

PREOPERATIVE MANAGEMENT

Cardiac evaluation

After careful anamnesis and cardiologic examination, diagnostic tests should be done. Electrocardiography detects rhythm disturbances and signs of cardiomyopathy. Echocardiography further evaluates cardiac function and determines the type of cardiomyopathy.

Hypertrophic cardiomyopathy as a result of chronic norepinephrine-induced hypertension is

found relative frequently and is mostly symmetric and concentric (10). Hypertrophic cardiomyopathy can rarely induce changes simulating hypertrophic obstructive cardiomyopathy (HOCM) with asymmetric septal hypertrophy, systolic anterior motion of the mitral valve, mitral regurgitation and dynamic left ventricular outflow obstruction (14, 15).

Dilated cardiomyopathy has also been reported and can be reversible after tumour removal (16, 17). Other variants of dilated cardiomyopathy like global hypokinesia, marked antero-apical involvement and predominant anterior and posterior wall involvement are also described in phaeochromocytomas (18).

A recent and probably under-diagnosed finding in phaeochromocytoma is the stress-related or (inverted) Tako Tsubo cardiomyopathy. Tako Tsubo cardiomyopathy, also called left ventricular apical ballooning syndrome or broken heart syndrome, was first described in Japan in the early 1990s. Patients with Tako Tsubo cardiomyopathy were usually postmenopausal women affected by heart failure after severe (emotional) stress (19). A typical left ventricular dysfunction pattern (Tako Tsubo) associated with typical ECG changes is observed. In contrast to myocardial infarction coronary arteries are normal and myocardial dysfunction is transient. The pathophysiology of stress-induced cardiomyopathy and phaeochromocytoma-induced cardiomyopathy, are believed to be similar and mediated by catecholamines. Catecholamines probably cause heart failure by myocardial stunning (20). In phaeochromocytoma it seems that most case reports (20, 21, 22, 23) have a Tako Tsubo-like pattern also called inverted Tako Tsubo, with inverted echocardiographic findings. A typical Tako Tsubo pattern has also been described (24, 25).

Tako Tsubo cardiomyopathy may result in marked decreased ejection fraction that typically undergoes spontaneous recovery, as long as the patient receives appropriate haemodynamic support. Use of extracorporeal life support is sometimes necessary in case of severe cardiogenic shock (25).

Pulmonary oedema in phaeochromocytoma patients is rare and may be rapidly fatal. In most patients, pulmonary oedema is cardiogenic, but non cardiogenic mechanisms have also been speculated. Some theories of the latter are: catecholamine-induced post capillary venoconstriction resulting in a rise in pulmonary-capillary hydrostatic pressure, increased alveolo-capillary permeability due to catecholamines and the catecholamine-induced neutrophil accumulation in the lung (26).

Pathologic findings on electrocardiograms are common in patients with phaeochromocytoma.

Pathologic findings include signs of myocardial hypertrophy (high QRS amplitudes, abnormal R-wave, ST-segment changes and T-wave changes) and prolongation of the Q-Tc interval. Tako Tsubo cardiomyopathy usually shows deep T-wave inversion following ST segment elevation in widespread leads. In phaeochromocytoma, an inverted electrocardiographic pattern has also been described with tall upright T-waves following ST segment depression. Inverted Tako Tsubo is thus another cause of tall upright T-waves beneath the hyper acute phase of myocardial infarction, hyperkalaemia and some cerebrovascular accidents (23).

Decreased QRS voltage due to phenoxybenzamine therapy has been found in patients with sustained hypertension. Surgical resection of a phaeochromocytoma results in normalization of QRS amplitudes and Q-Tc intervals in most patients (10).

Echocardiography is valuable in detecting dysfunction, evaluating improvement with α -adrenergic blockade, and determining the optimal timing of surgery. An echocardiogram should be done regardless of blood pressure levels to evaluate for the presence of hypertrophic cardiomyopathy, dilated cardiomyopathy and certainly for inverted Tako Tsubo cardiomyopathy. In contrast to Tako Tsubo cardiomyopathy, where the left ventricular apex (apical ballooning) is dyskinetic or akinetic and the basal portion is hyperkinetic, the inverted pattern (thus akinesis in basal and mid-segments and hyperkinesis of the apical segment) is observed in "inverted Tako Tsubo" (25, 26).

Echocardiography is also the main diagnostic tool in detecting the very rare presence of cardiac phaeochromocytoma (10).

Successful tumour removal is reported to relieve symptoms and to normalize clinical features. QRS amplitudes and Q-Tc intervals normalize in most patients (10). In HOCM several authors reported only a partial regression of abnormal thickness of the posterior wall and interventricular septa (after 2 years). Even if there may be some persistent structural changes in the myocardium, it is clear that phaeochromocytoma induced HOCM has a more favourable prognosis than classic HOCM, which is a life-long disease (15).

Preoperative medical treatment

Without preoperative medical treatment, induction of anaesthesia, manipulation of the tumour or other stimulation can cause massive catecholamine release resulting in hypertensive crisis, stroke,

arrhythmias, pulmonary oedema or myocardial infarction (9).

BOUTROS *et al.* (27) indicated that preoperative α -adrenergic blockade is not absolutely necessary and had excellent results in a small series of patients without α blockade. 63 patients were enrolled in their series, 6 patients received phenoxybenzamine, 28 prazosin and the remaining 29 received neither drug.

Intravenous sodium nitroprusside and nitroglycerin were used to control intraoperative hypertensive episodes, alone or in combination in all but 10 patients. BOUTROS *et al.* concluded that omitting α -adrenergic blockade was safe because almost all patients (one died due to another cause) were discharged without stroke or myocardial infarction. Stroke and myocardial infarction are two extreme complications and can not be used as an argument for omitting appropriate blood pressure control. Considering the present standard of care, their conclusion may be inadequate and dispose the patients to unnecessary morbidity (and mortality) as a result of extreme hypertension.

STEINSAPIR *et al.* (28) had disastrous results (2 out of 7 patients died) when omitting α -blockade. They conducted a retrospective analysis of patients who received alpha-methyl-para-tyrosine (AMPT) and prazosin ($n = 6$), AMPT and phenoxybenzamine alone ($n = 14$), phenoxybenzamine alone ($n = 6$), or no medication ($n = 7$) during 3 weeks before tumour removal. Patients without preoperative α -blockade had significant higher intraoperative peak systolic pressures and need for intraoperative α -blockade (phentolamine).

There are no large randomised prospective studies that establish the most effective drug regimen before surgery, but we will review some drugs that have shown to be useful.

Phenoxybenzamine has been the standard preoperative α -blockade therapy in the United States since the 1950s (8). It produces a non-competitive blockade by covalent binding of the drug to the receptor. Because of its long duration of action and oral availability it is very suited for outpatient use (29). The initial dose of phenoxybenzamine is 10 mg twice a day. The dose is increased every 2-3 days by 10-20 mg to a total daily dose of 1 mg kg⁻¹, which is mostly sufficient (1).

Phenoxybenzamine has several disadvantages. First, the expansion of intravascular volume takes 2-3 weeks (30). Second, being a non-selective α -adrenoceptor antagonist, it blocks α_2 -adrenoceptors, especially those on the pre-synaptic membrane

of adrenergic neurone terminals which are part of a negative feedback loop regulating release of norepinephrine. Consequently, the release of norepinephrine at cardiac sympathetic nerve endings is uninhibited and what would otherwise be normal sympathetic nerve activity causes undesirable chronotropic and inotropic effects. This can be controlled by adjuvant β -adrenoreceptor antagonists. Third, the block of the α -receptor is irreversible and may be prolonged, depending on the rate of re-synthesis of the receptors. Patients are often very somnolent in the first 48 h after surgery due to persistent central α_2 adrenergic blockade. Even when administration was stopped 24-48 hours before surgery, prolonged α -blockade postoperatively can not completely be prevented (8). They often experience peripheral oedema because of exaggerated correction of hypotension (8).

Considering its variable absorption and slow peak effect (three to four hours after absorption) (3), phenoxybenzamine should also be avoided for immediate management in hypertensive crises. There are case reports of carcinoma in humans after long-term treatment with phenoxybenzamine and repeated intraperitoneal administration of phenoxybenzamine in rats and mice resulted in peritoneal sarcomas (31).

Prazosin is an antihypertensive agent that causes a decrease in total vascular resistance. The exact mechanism is unknown, but recent animal studies suggested the blockade of postsynaptic α -adrenoreceptors. Unlike conventional α -blockers the antihypertensive action of prazosin is usually not accompanied by a reflex tachycardia. There is also no clinical significant change in cardiac output, heart rate, renal blood flow and glomerular filtration rate (31).

Prazosin has a high first pass-metabolism, high clearance and a short elimination half-life (2-3 h). Prazosin was probably underdosed by many physicians (first-pass mechanism). Due to a short half life, ineffective levels were reached at the time of surgery. This explains why it was not widely used. A starting dose of 1 mg every 8 h, gradually increased up to 12 mg (20 mg (31)) daily is now recommended (8).

Doxazosin is a competitive and selective α_1 -adrenoreceptor antagonist with long duration of action (elimination half life of 22 hours (31)), allowing once-a-day dosing (1 mg increasing up to 16 mg) (8). As presynaptic α_2 adrenoreceptors are not blocked, tachycardia doesn't occur, omitting the

need of β -blockade unless the patient has a predominantly epinephrine secreting tumour. PRYS-ROBERTS *et al.* (32) showed in a small group of 27 patients that doxazosin was as effective as phenoxybenzamine in controlling arterial pressure and heart rate before and during surgery with fewer undesirable side effects before and after surgery. PAN *et al.* (33) demonstrated however in a group of 38 patients that doxazosin does not expand volume as well as phenoxybenzamine but also has fewer side effects. They argued that doxazosin is only suited for phaeochromocytomas with mild or moderate hypertension (33).

Renal impairment doesn't affect the plasma levels of doxazosin significantly. Doxazosin is extensively metabolized in the liver and should therefore be used with caution in patients with liver dysfunction (31).

Terazosin is also a competitive and selective α_1 adrenergic blocker. Terazosin decreases blood pressure within 15 minutes following oral administration. Terazosin is completely absorbed following oral administration and has minimal hepatic first pass metabolism. Impaired renal function has no significant effect on elimination. Plasma levels peak about one hour after dosing and decline with a half life of approximately 12 hours (31).

Despite its less favourable elimination half life one could use terazosin in patients with liver dysfunction.

Labetalol is a selective α_1 and non selective β -adrenergic blocker with predominantly β -adrenoreceptor blocking activity. Both oral and intravenous administrations are available (31). Labetalol has been used in phaeochromocytoma surgery since 1976 (34), but several disadvantages have limited its extensive use. First it has potential hypotensive effects after tumour resection due to its plasma half life of 6 to 8 hours (31, 34). Second, the predominant β -blocking effect may provoke a paradoxical rise in blood pressure, particularly if the tumour is predominantly secreting epinephrine (31, 35). Labetalol should be used with caution in patients with phaeochromocytoma and may have no advantage over conventional regime of α -blockade followed by additional β blockade.

As mentioned before, β -blockade is not the cornerstone in phaeochromocytoma management. Its use is restricted to limit tachycardia, arrhythmias caused by epinephrine circulation or as adjuvant to phenoxybenzamine. Propranolol should never be started before adequate arteriolar dilatation by α -

blockade because of the risk of precipitating acute pulmonary oedema. The underlying mechanism is a propranolol-induced β_1 - and β_2 -blockade that leads to unopposed α effects and sudden elevation of afterload (36).

Beta 1 selective adrenoreceptor antagonists such as atenolol (100 mg.day⁻¹) or bisoprolol (10-20 mg.day⁻¹) minimize undesirable side effects in the bronchi or peripheral vasculature (8).

Alpha-methyl-para-tyrosine competitively inhibits tyrosine hydroxylase, the rate limiting step in catecholamine biosynthesis (31). It decreases the deleterious effects of catecholamine release by reduction of catecholamine stores and can be taken by mouth in a dose of 0.5 g.day⁻¹ to 4 g.day⁻¹. Two retrospective studies indicated that the use of AMPT as an adjunct to phenoxybenzamine resulted in less additional antihypertensive drug treatment than phenoxybenzamine alone. This finding has not been verified by any prospective study (10).

Magnesium sulphate has been shown useful and effective in case of failure to achieve haemodynamic stability by conventional agents. A usual dose starts with an initial intravenous bolus of 4 g magnesium sulphate, followed by an infusion starting at 1 g.h⁻¹. Magnesium sulphate decreases catecholamine release, is a highly effective α -adrenergic antagonist and antiarrhythmic when large doses of epinephrine infusions are being given and is predominantly an arteriolar dilator (3).

Prazosin, terazosin, labetalol hydrochloride, atenolol, bisoprolol, urapidil and magnesium sulphate are commercially available in Belgium (37). Phenoxybenzamine is not available in Belgium.

Risk of excessive orthostatic hypotension can be avoided by increasing salt and fluid intake. In addition, this reduces the risk of postoperative hypotension (1).

WITTELES *et al.* (29) demonstrated that preoperative outpatient management is acceptable for almost all phaeochromocytoma patients. Outpatient management not only reduces costs (50% reduction in total days of hospitalisation) but also allowed patients to prepare for surgery more comfortable and in many cases to continue working until the operation (29).

The following criteria for optimal preoperative condition have been recommended (38) and cited until recently (1, 10): blood pressure should be reduced below 160/90 mmHg for at least 24 hours before surgery; orthostatic hypotension should be present, but blood pressure in the upright position

should not fall below 80/45 mmHg ; the electrocardiogram should be free of ST-T changes for at least 1 week and there should be no more than 1 premature ventricular contraction every 5 minutes. The need for those criteria is doubtful. First, the necessity of orthostatic hypotension should be questioned strongly ; expansion of the already reduced plasma volume is essential to avoid shock after sudden diffuse vasodilatation at the time of tumour removal (39). Second, ST or T changes can be related to (inverted) Tako Tsubo cardiomyopathy which is completely different from myocardial ischemia or infarction.

Preoperative sedation and assurance by the anaesthetist may decrease anxiety and prevent marked haemodynamic fluctuations in the immediate preoperative period. No preoperative anxiolytics have proven to be superior to others (10).

Pregnancy

Phaeochromocytoma occurs in about 1 out of 54000 pregnancies (40). During pregnancy, hypertension from a phaeochromocytoma can mimic toxemia (8) or pre-eclampsia (1). Before 1969, maternal and foetal mortality were 48% and 55% respectively. Thanks to ante partum diagnosis and the use of α -blocking agents, foetal mortality has decreased to as low as 14% and maternal mortality has decreased to zero (40).

When tumour resection is necessary, pre-treatment to achieve medical stabilization is preferred (41) to reduce (high) foetal and maternal mortality during surgery. The safety of α -adrenergic blocking agents during pregnancy has not been established (pregnancy category C), but these agents probably improve foetal survival in pregnant patients with phaeochromocytoma if titrated carefully (42).

Little or no catecholamines cross the placental barrier and most of the remaining are metabolized by placental catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO). Phenoxybenzamine does cross the placental barrier. Alpha blockade by maternal phenoxybenzamine can cause hypotension in neonates. Glucocorticoids regulate the expression of cardiovascular adrenergic receptors and may help to counteract the down regulation of adrenergic receptors and thus prevent hypotension. There are no data on the transmission of phenoxybenzamine via breast feeding or its effects on the breast fed. Neonates born to mothers receiving phenoxybenzamine should be monitored closely in an intensive care unit, with particular

observation for hypotension and respiratory distress.

Circulating catecholamine concentrations increase exponentially at birth to support adaptation to extra uterine life. Any blockade of catecholamines may impair the neonate's ability to cope with hypoxia or other stressors. Failure of catecholamine activation has been associated with neonatal hypoglycaemia and idiopathic apnoea of prematurity.

The secretion of surfactant and secretion of lung fluid is mediated by β_2 adrenergic receptors. Rats given β_2 antagonists in the immediate neonatal period cannot survive hypoxia. Labetalol should therefore be used with caution in pregnant patients (pregnancy category C) (33). Specific β_1 antagonists do not cause an increase in hypoxia induced mortality. Animal research shows that intact α receptors may be important in the maintenance of cardiac function in the first week of life (40).

Timing of surgery is controversial. If the diagnosis is made in the first trimester, the consensus is to remove the phaeochromocytoma. If the diagnosis is made in the third trimester, medical treatment is preferred, followed by resection at the time of caesarean section or shortly after vaginal delivery. The second trimester is the optimal time for surgical intervention because the risk of spontaneous abortion is minimal. If there is a legitimate concern that the lesion is malignant, resection should be undertaken as soon as possible (41).

INTRAOPERATIVE MANAGEMENT

Monitoring

An intra-arterial catheter should be placed under local anaesthesia before induction of anaesthesia, in order to respond quickly to haemodynamic changes. A central venous catheter is also recommended (7, 8) to administer vasoactive agents and to monitor central venous pressure. Monitoring should include patient glycaemia, temperature and diuresis (43).

A pulmonary catheter for measurement of pulmonary capillary wedge pressure and cardiac output may be helpful because of discrepancy between right-sided and left-sided filling pressures, particularly during tumour manipulation or during rapid infusion of fluids, even without apparent pre-existent cardiac dysfunction. However, the routine use of pulmonary catheter remains controversial (10).

Transoesophageal echocardiography (44) is an additional tool to optimise intravenous fluid administration and assess perioperative changes in ventricular function.

Surgery

Very gentle positioning of the patient is most important and palpation of the abdomen has to be avoided, as this can result in catecholamine release from the tumour (45).

Development of laparoscopic surgical techniques has provided an alternative to open surgical procedures. Laparoscopic surgery is associated with less postoperative pain, shortened hospital stay, shortened convalescent period and improved cosmetic result. Laparotomy and laparoscopy result in similar blood loss and complications (39). A recent retrospective cohort study by HUMPREY *et al.* compared laparoscopic adrenalectomy (n = 30) to open procedure. No significant differences in postoperative complications, intraoperative hypertensive episodes or hypotensive episodes, nor need for antihypertensive or vasopressive agents were found. The length of postoperative stay was shorter and tumour size was smaller in the laparoscopic group (46).

High flow insufflation and excessive high intraabdominal pressures should be avoided.

Anaesthetic technique

General anaesthesia is the technique of choice. Some clinicians prefer to add a regional technique such as a low thoracic epidural catheter, but the risk of hypertension during placement must be considered (8). Antihypertensive as well as vasopressor medication should be available.

An adequate depth of anaesthesia before intubation and during the surgical procedure is necessary, in order to prevent a hypertensive crisis. Some authors already start intravenous antihypertensive drugs before induction of the patient (47). Laryngotracheal topical application of lidocaine at least 2 minutes before intubation attenuates the cardiovascular response of endotracheal intubation (48). It also improves cardiovascular stability on emergence by reducing the incidence of coughing after tracheal extubation (49).

Sevoflurane is the inhalation agent of choice (7) and should be preferred over desflurane which causes significant sympathetic stimula-

tion (10). Nitrous oxide can be used safely. A target controlled infusion with propofol can be used to maintain anaesthesia. Propofol blunts, in contrast to etomidate, the hypertensive response caused by intubation (50). In poorly prepared patients, induction can result in catecholamine resistant hypotension due to severe volume depletion.

Ketamine and ephedrine cause indirect increase in catecholamine levels and should be avoided. Naloxone also provokes release of catecholamines (51).

Pethidine causes sympathetic stimulation and droperidol has been associated with extreme hypertension and should therefore both be avoided (10).

Opioids are known to suppress catecholamine secretion, probably via a stabilizing effect on actin filaments (52). Morphine however can trigger a phaeochromocytoma crisis via histamine release (10).

An adequate amount of opioids should be given and plasma levels should be maintained during the operation. On theoretical grounds this could be an argument for the continuous administration of opioids, in order to avoid surges in catecholamine secretion due to opioid withdrawal. As we mentioned earlier, a similar reaction is observed when naloxone is administered.

Both sufentanil (47) and fentanyl (8) have been used frequently, but remifentanil is probably a better choice because it is easy to titrate, fast acting and exerts a dose dependent decrease in arterial blood pressure and heart rate (53). When using remifentanil it is obvious that adequate postoperative pain relief is mandatory. Remifentanil has been used in doses up to 3 mcg.kg⁻¹ min⁻¹ to control haemodynamic changes (54, 55). BRESLIN *et al.* (56) used remifentanil alone to control intraoperative blood pressure in patients pre-treated with alpha- and beta-adrenergic receptor blocking agents. They noted significant hypotension, bradycardia and failure to prevent the increases in blood pressure and plasma catecholamine levels associated with tumour manipulation in two cases. They concluded that remifentanil alone is not sufficient to provide cardiovascular stability and specific antihypertensive drugs should be used.

The muscle relaxants vecuronium, rocuronium and cisatracurium provide good cardiovascular stability (10, 31). Succinylcholine should be avoided because of fasciculations and transient rise in abdominal pressure (10). Atracurium should also be avoided because of increased incidence of histamine release (10, 31, 57).

Surgical influences

The anaesthetist must be aware that the creation of a pneumoperitoneum in a phaeochromocytoma patient may cause a much greater increase in catecholamines (58) than in other laparoscopic surgery (59). The stimulus may be either a direct tumour compression or a change in tumour perfusion. In addition, a pneumoperitoneum with CO₂ may lead to hypercapnia and acidosis, which in turn are known stimuli of catecholamine secretion (47).

Tumour manipulation can also significantly increase catecholamine levels in plasma. Rise in catecholamine levels may occur even after early adrenal vein ligation, probably due to extensive tumour vascularisation (47).

After phaeochromocytoma removal, intravascular volume depletion should be anticipated, especially when sufficient preoperative volume expansion by alpha blockade could not have been established.

Control of hypertensive crises

Acute hypertensive crises are usually controlled by nitroprusside or phentolamine and in case of tachydysrhythmia a β -blocking agent is administered (57). Betablockers should be used carefully, as they can result in deleterious unopposed alpha effect. The α_1 blocker urapidil and the calcium antagonist nicardipine hydrochloride may be good alternatives, but clinical experience is still limited. Fenoldopam mesylate may only be beneficial in patients with renal impairment. Labetalol can improve cardiovascular stability when administered just before surgical incision bearing in mind its long half life. Magnesium sulphate can improve intraoperative cardiovascular instability when other drugs failed. Esmolol hydrochloride quickly controls tachycardia.

Phentolamine, urapidil, nicardipine hydrochloride, labetalol, esmolol hydrochloride and magnesium sulphate are available in Belgium (37).

Sodium nitroprussiate decreases preload and afterload, has an immediate onset and a fast recovery (1-2 min) (10). It has to be titrated by continuous infusion starting with 0.5-1.5 mcg.kg⁻¹ min⁻¹ increasing to 8 mcg.kg⁻¹ min⁻¹ (57). Sodium nitroprussiate is beneficial in patients with complicating acute myocardial infarction or congestive heart failure. At higher doses toxic substances such as thiocyanate and cyanide are produced (10). It is sensitive to toxic degradation if exposed to sunlight.

In case of high dose administration, MetHb and lactic acidosis should be followed.

Failure of sodium nitroprussiate to control haemodynamic disturbances has been reported (60, 61). Sodium nitroprussiate dilates both arterioles and venules. It could decrease the reflex vasoconstriction in an already significantly hypovolemic patient and thus increase baroreflex mediated catecholamine release (10).

Phentolamine is a competitive α_1 adrenergic and weak α_2 receptor antagonist with short duration of action (5 min) that may be given in intravenous boli or by continuous infusion (31). Tachycardia can be prevented by simultaneous β -blockade (10).

Urapidil, a competitive and selective short acting α_1 blocker is also a central serotonergic receptor agonist (31). It has a fast onset and a high bioavailability, high clearance and short elimination half-life (2-4.8 h). TAUZIN-FIN *et al.* (62) successfully used urapidil in 18 patients. They first stabilized them 15 days before surgery with prazosin (5 mg.day⁻¹) and bisoprolol (10-20 mg.day⁻¹). Afterwards they switched to an intravenous infusion (10-15 mg.h⁻¹) of urapidil 3 days before surgery and continued it intraoperatively. STEIB *et al.* (63) used urapidil with good result in a small series of seven patients.

Nicardipine hydrochloride, a calcium channel blocker is a potent peripheral and coronary vasodilator. It has a rapid onset (1-5 min), short duration of action (3-6 h) and low incidence of side effects (31). A starting dose at 1 mcg.kg⁻¹ min⁻¹, 15 min before anaesthesia is a common practice. Some authors prefer it to nitroprussiate because it causes no reduction of preload, induces less tachycardia; it has less potential for overshoot hypotension and no cyanide toxicity (10). It should also be able to control blood pressure more rapidly with fewer dose adjustments. Although it has been shown to inhibit catecholamine release in vitro, this has not been shown in vivo (10).

Fenoldopam mesylate is a peripheral vasodilator with fast onset and short duration, acting via selective stimulation of dopamine 1 receptors. It also binds with moderate activity to α_2 receptors (31). Fenoldopam has several adverse effects (flushing, hypotension, dizziness, headache, tachycardia, increase in intraocular pressure and hypokalaemia) but the most undesired effect is the increase in renal blood flow and rise in diuresis and natriuresis which worsens postoperative hypo-

volaemia. On the other hand, this may be beneficial in patients with renal dysfunction (64). It should also be noted that fenoldopam can cause oliguria occasionally (31).

Labetalol is a selective α_1 and non selective β adrenergic blocker that is not very suited for administration during surgery due to its long half life and induction of hypotension after tumour resection (10, 31). Labetalol may also provoke elevated vascular resistance and paradoxical hypertension. The pathophysiology is an insufficient α_1 blockade along with a blocked β_2 mediated vasodilatation (65).

When administered only at initiation of anaesthesia and respecting a maximal dose of 1.2 mg.kg^{-1} it can reduce intraoperative blood pressure instability without aggravation of postoperative hypotension (34).

Magnesium sulphate has also proven its benefit in the intraoperative setting (66, 67). JAMES (68) already demonstrated in 1989 that MgSO_4 , used as the principle anti-adrenergic agent (in 15 of 17 anaesthetics), was able to control cardiovascular changes at induction, tracheal intubation and in most patients even during intraoperative tumour manipulation. In 4 of these patients additional sodium nitroprussiate was required to control the arterial pressure during handling of the tumour. In five patients catecholamine release was studied and MgSO_4 was found to reduce catecholamine concentrations from the time of induction until tumour handling.

DROLET *et al.* also used MgSO_4 as the main agent to control arterial pressure during phaeochromocytoma resection in 2 patients. Magnesium sulphate showed to control hypertension, even in highly metabolic active tumours. They recommend an initial intravenous dose of $40\text{-}60 \text{ mg.kg}^{-1}$ followed by a continuous infusion of 2 g.h^{-1} . At time of intubation or tumour manipulation an additional dose of 1-3 g seems adequate. Plasma concentrations of MgSO_4 were 1.5 and 1.9 mmol.l^{-1} which is comparable with those measured by James M.F. (average values of 1.9 mmol.l^{-1} and maximal values of 1.9 mmol.l^{-1}). Care should be taken in case of renal dysfunction. Theoretically MgSO_4 prolongs the effect of non-depolarizing (and maybe also depolarizing) muscle relaxants. Vecuronium block was reversed easily with neostigmine and the influence of MgSO_4 in the concentrations used is probably clinically not important. Calciumgluconate could be used as antidote to reverse prolonged muscle relaxation caused by excessive MgSO_4 plasma levels (69).

One case report has also shown successful combined use of MgSO_4 and epidural anaesthesia in a patient with severe coronary artery disease (70).

A paediatric case report showed that MgSO_4 provided good cardiovascular stability in a child with the Von Hippel Lindau disease that underwent laparoscopic right adrenalectomy. In this case, a MgSO_4 bolus injection of 40 mg.kg^{-1} was followed by a continuous infusion of $15 \text{ mg.kg}^{-1}.\text{h}^{-1}$. After creation of a pneumoperitoneum, blood pressure rose to 180/110 mmHg along with a tachycardia of 120 bpm, which was relieved with a MgSO_4 bolus injection of 40 mg.kg^{-1} and a higher continuous infusion of $30 \text{ mg.kg}^{-1}.\text{h}^{-1}$. Small doses of nicardipine (0.4 and 0.5 mg) were used to attain preoperative systolic blood pressure values. MgSO_4 plasma concentrations varied between 2 and 4 mmol.l^{-1} intraoperatively (71).

Esmolol hydrochloride is a fast and short acting ($t_{1/2}$ 9 min) selective β_1 antagonist. It is the first choice β -blocking agent for the intraoperative treatment of tachycardia in phaeochromocytoma patients (72). The initial loading dose is 500 mcg.kg^{-1} during 1 minute, followed by a four minute maintenance infusion of 50 mcg.kg^{-1} and adjusted by clinical effect afterwards (57).

Steroid replacement

In case of bilateral adrenalectomy, steroid replacement is necessary to avoid an Addisonian crisis, but even with proper treatment, this can not always be avoided (73). The usual dose is 40 mg methylprednisolone three times a day on the day of operation, diminished to 20 mg and 10 mg three times a day on postoperative day 1 and 2 respectively (3). Afterwards, oral substitution takes place with prednisone 5 mg and fludrocortisone 0.1 mg each morning along with prednisone 2.5 mg each evening (10).

An alternative steroid replacement scheme is : 100 mg intravenous hydrocortisone given prior to operation, followed by 100 mg of intravenous hydrocortisone every 8 hours for 1 day or an equivalent daily dose of oral prednisolone, then a subsequent rapid 3 day taper to a maintenance dose of 25 mg twice daily of hydrocortisone or an equivalent dose of oral prednisolone (74).

POSTOPERATIVE MANAGEMENT

After surgery the patients need close monitoring at the intensive care unit. Hypotension and

hypertension are observed frequently. Hypotension is more pronounced when phenoxybenzamine is used because of the presence of α -adrenoreceptor blockade along with an abrupt fall of stimulating catecholamines. Postoperative bleeding is a common and serious complication. Approximately 50% of the patients experience hypertension during the first postoperative days, probably caused by elevated catecholamine stores in adrenal nerve endings that last about a week (10).

Hypoglycaemia due to rebound hyperinsulinism can occur when the inhibitory effect of norepinephrine on insulin producing cells is eliminated (α_2 receptor) (10).

Postoperative follow up includes evaluation of plasma metanephrine levels at approximately 6 weeks and 6 months after surgery. Yearly follow up is advised in familial pheochromocytoma because recurrence rate is higher (39).

A large Swedish retrospective study of patients who were surgically treated for pheochromocytoma demonstrated a mortality rate of twice that of the control group. The main causes were cardiovascular and tumour diseases. Life long follow up should be recommended (75).

CONCLUSION

Pheochromocytoma remains a challenging life threatening disease. Numerous drugs have been used to establish perioperative cardiovascular stability. A lack of placebo-controlled randomized trials makes it difficult to decide which treatment is superior. So far, we have to learn from small series of patients, case reports and think about ways to provide the best cardiovascular stability.

Preoperative medical stabilization is recommended in order to limit the deleterious effects of catecholamine release and to allow volume expansion. Traditional regimens include the (oral) administration of α -adrenoreceptors blockers such as phenoxybenzamine, prazosin, doxazosin and urapidil (1). Phenoxybenzamine was considered as the gold standard. It is the only non-competitive α -blocker and therefore has the most powerful and long lasting action but has shown to be carcinogenic after long term treatment. Since we now have several alternatives, it is unlikely that it would be approved in our country.

Doxazosin is the most suited alternative because its half life allows once a day dosing.

Terazosin and prazosin have a shorter half-life and are alternatives to doxazosin. Terazosin is a good alternative to doxazosin in patients with liver dysfunction. Only prazosin and terazosin are available in Belgium.

Selective β -blocking agents such as atenolol or bisoprolol limit reflex tachycardia caused by alpha blockade. AMPT, a drug that blocks catecholamine synthesis, may be useful as an adjunct to phenoxybenzamine. Magnesium sulphate is a promising agent that could be added to standard therapy.

STEINSAPIR *et al.* (28) showed that AMPT as an adjunct to alpha blockade results in better blood pressure control and less need for antihypertensive medication.

Unfortunately, only limited data are available and alpha-methyl-para-tyrosine is not available in Belgium.

Magnesium sulphate can be used easily and has shown to improve cardiovascular stability in a limited series of patients undergoing pheochromocytoma surgery. Considering its few adverse effects, this is probably a promising agent for hospitalized patients before surgery and can be continued intraoperatively to improve and manage hypertension.

Tachycardia is treated with selective β_1 antagonists such as atenolol or bisoprolol.

Induction takes place with propofol, a potent opioid (remifentanyl) and a muscle relaxant with good cardiovascular stability such as vecuronium, rocuronium or cisatracurium. Anaesthesia is maintained with sevoflurane (and nitrous oxide), an opioid (remifentanyl infusion) and a muscle relaxant in continuous infusion or bolus administration. Neuromuscular monitoring should be performed. Control of intraoperative hypertensive crises has traditionally been established with sodium nitroprusside or phentolamine. Both have several disadvantages and other agents have been explored. Nicardipine is a useful alternative for nitroprussiate. Urapidil has also been used in limited series. Labetalol is long acting and therefore less suitable but undesired postoperative effects can be minimized when given in limited dose at initiation of anaesthesia. Fenoldopam causes unwanted natriuresis and diuresis, but this can be a desired effect in patients with renal dysfunction. A β -blocking agent, preferably esmolol, can be added if needed to counteract tachycardia.

In the postoperative period proper treatment of hypotension, hypertension, postoperative bleeding and hypoglycaemia should take place in the intensive care unit. Patient follow up is recommended.

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