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PHEOCHROMOCYTOMA

A Atrash

Moderator: K Govender

UNIVERSITY OF
KWAZULU-NATAL

INYUVESI
YAKWAZULU-NATALI

School of Clinical Medicine

Discipline of Anaesthesiology and Critical Care

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INTRODUCTION

Pheochromocytomas (PHEOs) are neuroendocrine tumors which originate from chromaffin cells of the adrenal glands.[32] Paragangliomas (PGLs) are the extra-adrenal tumors which originate from chromaffin cells in other parts of the body.[32]

During embryonic development, the chromaffin cells present mostly near the sympathetic ganglia, paraganglia, vagus nerve and carotid arteries, and some chromaffin tissue may be present in the prostate, the bladder wall, gonads, rectum, renal and hepatic hili.[25] Therefore pheochromocytomas can develop at any of these places.[25]

The name, Pheochromocytomas, originated from the colour that fresh tissue changes to when oxidized by certain fixatives, i.e. catecholamine content is stained a dark grey-brown colour ("pheos" in Greek).[16] In 1912, the name meaning 'dusky-coloured tumour' was first mentioned by Pick, although the tumour was recognized by von Frankel years before.[30]

The first surgeries for excision of PHEOs were done by Roux (1926) and Mayo (1927).[30]

Although these tumors have been identified since the early 20th century, much of the recent information about PHEO/PGL has changed our understanding of these tumors which has led to appropriate diagnostic evaluation, better specific treatment options and improved outcomes for the patient.[32] However, wetheres is still no cure for these kinds of tumors and no successful long-term treatment for patients with metastatic disease.[32]

INCIDENCE OF PHEO/PGL

PHEO/PGLs are uncommon tumors which affect about 1 in 2500-6500 people, with an average of 500-1600 cases diagnosed each year in the United States.[32] However, the true incidence may be higher due to the delay in diagnosis until after death.[32] In Australia, a review of autopsy cases found that up to 0.05% had undiagnosed PHEO/PGLs.[32]

They are a rare cause of secondary hypertension.[32] In 2014 The Endocrine Society Clinical Practice Guidelines found that the prevalence of PHEO/PGL is 0.2-0.6% in patients with hypertension.[2] Also, the prevalence of extra adrenal and familial tumors in patients with germ-line mutations may be as high as 50%.[32]

The mean age of diagnosis is 43 years.[32] Around 10-20% of these tumors are identified in children, this is commonly associated with underlying genetic conditions.[32]

PATHOPHYSIOLOGY

Chromaffin cells are neuroectodermal in origin which produce catecholamines in different amounts related to the concentration of biosynthetic enzymes therein.[8,32]

Many adrenal tumors secrete either EPI or NE and a few rarely produce predominantly EPI.[8] Most of the extra adrenal pheochromocytomas secrete mainly NE.[8]

Catecholamine concentrations in pheochromocytoma are very high, which can at any time precipitate a hypertensive crisis.[8] Significant amounts of catecholamines secreted during an eruption produce a catecholamine storm called attacks.[8] Also, continuous and small eruptions create various signs and symptoms which are related to the constant stimulation of adreno-receptors by catecholamines.[8]

Observations done by G. Eisenhofer, which are unpublished, found that patients with pheochromocytomas that secrete NE had an average content of NE of about 1,760,000 pg/g tissue with about 53% of its secretion each day.[8] And in pheochromocytomas that secrete EPI had an average content of EPI of about 3,801,000 pg/g tissue with about 5% of its secretion each day.[8]

At these levels, any stimulation directed to the tumor may cause abrupt and significant amounts of catecholamine release which could exceed normal plasma levels by about 1000 times or more.[8] These variations in content of catecholamin explain different symptoms and signs which needs individualized treatment for each patient.[8]

CATECHOLAMINES AND ADRENOCEPTORS

To understand the pathophysiology of pheochromocytomas, we need to understand the biochemistry and function of catecholamines better.[32]

The adrenoceptors are the sites where catecholamines work.[8] These are found in excess in most patients with pheochromocytoma.[8] Both EPI and NE work on α- and β-adrenoceptors at different organs and systems but they have some overlapping with different effects.[8]

Norepinephrine is a more potent β_1-adrenoceptor agonist than EPI where EPI has a more potent effect on β_2-adrenoceptors than NE.[8] EPI is also a more potent α-adrenoceptor agonist than NE.[8] However, the concentration of NE and EPI at effector sites, and the proximity of sites of NE and EPI release to adrenoceptors are significant determinants of the response of these receptors to these catecholamines.[8]

Both NE and EPI in patients with pheochromocytoma act as hormones as they are released into circulation.[8] EPI causes vasodilation which results in hypotension by acting potently on β_2-adrenergic receptors of the skeletal muscle.[8] On the other hand, NE cause vasoconstriction resulting in hypertension due to α_1-adrenoceptor affect within vasculture.[8] Both catecholamines with NE to a higher degree cause increased heart rate by stimulation of β_1-adrenoceptors.[8]

In addition, EPI is important as a metabolic hormone.[8] Specifically, EPI stimulates thermogenesis, ketogenesis, lipolysis and glycolysis, and also stimulates glycogenolysis and gluconeogenesis to raise plasma glucose.[8] EPI also has potent effects on β_2-adrenoceptor of the lung causing dilation of airways.[8]

Therefore, patients with pheochromocytomas that secrete EPI more frequently have episodic symptoms and signs with light-headedness or syncope, palpitations, anxiety, and hyperglycemia than patients with NE secreting pheochromocytoma, who more often have continuous symptoms and signs including headache, hypertension and sweating.[8]

These different specific effects of catecholamines on adrenoceptors explain the various clinical presentations and give an idea about which appropriate preoperative adrenergic blockade is needed.[8]

Some patients need higher amounts of adrenoceptor blockers than other patients in spite of high level of catecholamine concentration, which is often seen in metastatic phaeochromocytoma.[8] This is explained by desensitization which happens by two mechanism: (1) reduction in the number of receptors on the cell, or (2) decrease in the binding affinity to the receptors.[8] This mechanism partially protects the patient from the harmful effects of high levels of catecholamines and also favours administration of lower doses of catecholamine synthesis inhibitors and adrenoceptor blockers to decrease side effects of these drugs.[8]

CLINICAL PRESENTATION

The pheochromocytoma is termed “Tumor of Tens”:[13]

10% are extra-adrenal,
10% are malignant,
10% are bilateral,
10% are found in asymptomatic patients, and
10% are hereditary.

Mutations of the Succinate Dehydrogenase gene (*SDH*), which is recently described, has explained a much stronger hereditary component than what was known before.[13] Currently, up to 24% of pheochromocytomas may have a genetic basis.[13]

Pheochromocytoma presentation has a classic triad which includes: (1) episodic headache, (2) sweating, and (3) palpitations.[13,32] Constant hypertension is frequently considered part of the clinical presentation.[13]

In a retrospective study, they found 51% of pheochromocytoma cases were associated with blood pressure abnormalities, while 24% of patients had headaches and palpitations.[13] While 0.5% of these cases of pheochromocytoma had persistent hypertension. [13]

Pheochromocytoma patients frequently presented with various sets of symptoms which may include anxiety, visual blurring, chest and abdominal pain, nausea and vomiting, papilledema, transitory electrocardiographic changes, orthostatic hypotension, and psychiatric disorders.[13]

Sometimes, patients have normotensive, or “asymptomatic,” pheochromocytomas which are discovered accidentally.[13] The prevalence of an asymptomatic pheochromocytoma is about 21%.[13] Retrospective studies have shown no difference in radiographic, demographic and pathologic characteristics in these tumors.[13]

The reasons for the results in these studies are unknown, but some have mentioned that the cardiovascular system appears to be desensitized to catecholamines.[13] Patients with a genetically related tend to have smaller tumors, or are younger in age and more expected to be normotensive.[13]

Familial Pheochromocytoma:

Familial pheochromocytoma has been associated with germline mutations in six genes.[13] Their names are the von Hippel-Lindau gene (*VHL*) that leads to von Hippel-Lindau (VHL) syndrome, the *RET* gene which causes multiple endocrine neoplasia type 2 (MEN-2), the neurofibromatosis type 1 gene (*NF1*) which leads to neurofibromatosis type 1 (NF1) disease and mitochondrial succinate dehydrogenase (*SDHB, SDHD*, and *SDHC*) mutations.[13]

Von Hippel-Lindau:

Mutations in *VHL* gene cause Von Hippel-Lindau syndrome.[32,13] The VHL protein controls cellular processes such as angiogenesis and also controls the activity of hypoxia-inducible factor alpha (HIFα).[32] Like MEN2, VHL is associated with multiple tumor types and can be divided into three types based on the risk of PHEO/PGL.[32]

VHL type 1, is characterized by the development of central nervous system hemangioblastomas, retinal angiomas, and islet cell tumors of the pancreas, renal carcinomas, endolymphatic sac tumors, or cysts and cystadenomas of the kidney, pancreas, epididymis, or broad ligament.[32] This type doesn't develop PHEO/PGL.[32,13]

VHL type 2, are at risk of PHEO/PGL.[32,13] It is further sub-classified into three types: type 2A (without renal carcinomas and infrequent type 1 tumors), type 2B (with renal cell carcinoma or any type 1 tumors), and type 2C (only PHEO/PGL and without any type 1 tumors).[32,13]

VHL patients are usually associated with a high rate of bilateral tumors and usually develop norepinephrine/normetanephrine-secreting adrenal PHEOs.[32]

The age of onset of PHEO/PGL associated with VHL is about 30 years.[32] However, some younger patients, as young as 5 years have been reported.[32]

Patients with VHL have infrequent metastases and there is a chance of recurrent and multiple primary tumors developing.[32]

Multiple Endocrine Neoplasia (Type 2):

Multiple endocrine neoplasia type 2 (MEN2) is associated with mutations (*RET*) gene.[32,13] The RET protein is a receptor tyrosine kinase that controls cellular apoptosis and cellular proliferation.[32,13]

Patients who have MEN2 are usually associated with medullary thyroid cancer (MTC) which is the most common association in these patients.[32] MEN2 is further divided into three types: MEN2A, MEN2B, and familial MTC.[32]

MEN2A is the most common type and has 95% chance of developing medullary thyroid cancer, 50% chance of PHEO, and 15-30% chance of hyperparathyroidism.[32,13]

Patients with MEN2B typically present with mucosal ganglioneuromas and marphanoid body habitus.[32] This type has 100% chance of developing with medullary thyroid cancer and 50% chance of PHEO.[32] Patients with familial MTC do not have a risk of developing PHEO.[32]

Patients with MEN2 who develop PHEOs are usually associated with epinephrine/ metanephrine-secreting tumors in the adrenal gland and about half of them presented with bilateral tumors.[32]

The rate of malignancy is rare in this group of patients although it is higher in patients who have more aggressive MEN2B.[32]

The age of onset for PHEO in this group of patients is usually between 30 and 40 years.[32] The majority of cases have a strong family history which helps identify the carriers early in life.[32]

Therefore, regular and early screening usually identifies tumors while they are still small.[32] This helps to keep the rate of metastasis low in patients with MEN2.[32]

Neurofibromatosis Type 1:

Neurofibromatosis type 1 (NF1) is associated with various manifestations which can include PHEO/PGL, MTC, parathyroid tumors, carcinoid tumors, chronic myeloid leukemia and peripheral nerve sheath tumors.[13,32] The rate of PHEO/PGL found in NF1 is much lower than in VHL or MEN2.[32]

Germline mutations in the *NF1* gene cause NF1.[32] This gene encodes a GTPase activating protein which is important to cellular growth and differentiation.[32] Genetic testing can rarely be performed because of the large size of the gene.[32]

Therefore, diagnosis is usually related to clinical criteria.[32,13] Diagnosis can usually be made at a young age because of the frequent presence of café au lait spots from birth.[32,13]

Screening for PHEO/PGL is not usually performed regularly because it is relatively infrequent in NF1 patients.[32,13]

PHEO/PGL tumors in patients with NF1 usually appear at a mean age of 42 years.[32]

Epinephrine/metanephrine-secreting in adrenal PHEOs are more common than PGLs.[32] Bilateral adrenal tumors are infrequent and the metastatic rate for NF1 tumors is about 12% which is higher than MEN2 or VHL.[32]

Recently, somatic mutations in NF1 gene have been related to the pathogenesis of sporadic PHEO/PGL.[32] A study was done on 53 sporadic tumors, they found that 41% of tumors had inactivating somatic *NF1* mutations.[32] These results suggest that these kind of mutations are a relatively common cause of PHEO.[32]

Succinate dehydrogenase mutations:

For many years, new familial syndromes associated with PHEO/PGL development were known clinically, but the mechanism of inheritance was unclear.[32] It was only in 2000, the identification of succinate dehydrogenase subunit D (*SDHD*) mutations in families with familial PGL began to be explained.[32]

Further studies done in later years identified other sub-units, *SDHB* and *SDHC*, *SDHA* as heritability genes for PHEO/PGL.[32]

Mutations in a complex assembly factor, SDH assembly factor 2 (*SDHAF2* which in yeast known as *SDH5*), were also related to familial PHEO/PGL.[32]

Because succinate dehydrogenase has a role as mitochondrial complex II in both the electron transport chain and the Krebs cycle, *SDH* mutations affect cellular metabolism.[32]

Clinical presentations can vary greatly although mutations in the *SDH* genes all affect the same complex.[32] *T*umors that relate to SDH mutations are mostly extra-adrenal, although some tumors has been reported in adrenal.[32]

Tumors which have these kind of mutations usually have noradrenergic or dopaminergic phenotypes.[32] However, biochemically silent tumors have also been reported and are associated frequently with *SDH*-related PGLs.[32]

DIAGNOSIS:

Biochemical Evaluation:

Biochemical testing should be performed: if the patient is symptomatic, if the patient has adrenal incidentaloma or if the patient has a hereditary risk for developing a pheochromocytoma or paraganglioma.[4]

Historically, most institutions depend upon 24 hour measurements of total urinary metanephrines and catecholamines.[13] Studies done at the Mayo Clinic, found that urinary measurements of total catecholamines and metanephrines had a sensitivity of 98% and specificity of 98%.[13]

Also, measurements of urinary epinephrine or norepinephrine were found to have a sensitivity and specificity of 100% and 97% respectively.[13] Unfortunately, the collection of urine in 24 hours can be a burden on the patients.[13]

The levels of catecholamine release fluctuate in many tumors which can cause false-negatives during times of low catecholamine release.[32] On the other hand, measurement of urine or plasma metanephrines are the most accurate test available.[32] Its sensitivity is about 99%, and its specificity has been recorded within the range of 85% - 89%.[13]

False positive results can be due to many causes such as phenoxybenzamine, tricyclic antidepressants, radiographic contrast dye, major depression, congestive heart failure, and panic disorder.[13,32]

The test which can be used to differentiate false-positive results from true-positive results is called the clonidine suppression test.[13.32] The centrally acting α-2 agonist is unable to suppress the release of epinephrine and norepinephrine in pheochromocytoma.[13] This test has a diagnostic accuracy of 92%.[13]

PHEO/PGL is suspected when the centrally acting α-2 agonist fails to suppress the levels of plasma normetanephrine below the upper reference limit or by 40% of the initial value, and further workup should be done.[32]

Recent studies have found the usefulness of plasma methoxytyramine which is metabolite of dopamine in diagnosing PHEO/PGL.[32] Measurements of methoxytyramine can be helpful in detecting dopamine-secreting tumors which can easily be missed by classical measurements of metanephrines.[32]

Chromogranin A (CgA) is a polypeptide that is released by chromaffine cells with catecholamines and its measurement is frequently used to help diagnose patients with PHEO/PGL.[32] It has been reported that elevated CgA levels found in 91% of patients with PHEO/PGL.[32] It can be used as a marker to monitor the disease because of its non-specificity.[32] However, the sensitivity for diagnosing PHEO/PGL can be close to 100% when it is used with catecholamine measurements.[32]

The use of appropriate reference ranges for specific ages is critical and can affect results.[32] A recent study found that when reference ranges based on patient age were

used, they showed an increase in the sensitivity of plasma normetanephrine and metanephrine from 88.3% to 96.0%.[32]

Imaging:

The next step after diagnosis of PHEO has been confirmed by biochemical studies is localization of the tumor.[13,32] It should be done by combining at least two imaging techniques.[34,32,13] Anatomical imaging studies include computed tomography (CT) and magnetic resonance imaging (MRI), which should be done with functional imaging studies to locate adrenal, extra adrenal, recurrent, or metastatic PHEOs.[32]

Most tumors (about 95%) happen within the abdomen. And, the most common sites occurring outside the adrenal are the superior and inferior para-aortic areas (75%), the thorax (10%), the bladder (10%), and the head, neck, and pelvis (5%).[32]

The percentage of adrenal masses in the general population is about 5–9%.[34] And, the percentage of benign incidental masses in patients without known primary cancers is about 90%.[34] Nonfunctional adrenal masses in patients without clinical evidence of adrenal hyperfunction is about 85%.[34] In spite of that, evaluation should be done on every adrenal mass to rule out hypersecretion, malignancy, or metastasis to the adrenal gland.[34]

Anatomical Imaging:

Sensitivity of both CT and MRI for adrenal pheochromocytomas is 98%–100%.[13] MRI is more sensitive for extra-adrenal pheochromocytomas.[13]

CT can detect the size of adrenal PHEOs of 0.5–1.0 cm or larger and extra adrenal PHEOs at least 1.0–2.0 cm in size.[34] Small PHEOs, 1–2 cm in diameter usually appear homogeneous and show uniform enhancement when contrasted with soft tissue density.[32] Larger PHEOs can be inhomogeneous due to the hemorrhage and can be seen with areas of low density due to tumor necrosis.[32] CT of the chest and neck should be performed when CT of the abdomen and pelvis is negative.[32]

When PHEO tumor is localized by CT, there is no need to do MRI, but functional imaging is still needed to confirm the diagnosis and to rule out metastasis.[32] However, if patient has proven biochemically to have PHEO and the CT is negative, an MRI should be done.[32] MRI has the highest sensitivity between the current available imaging techniques.[32]

MRI should be performed instead CT in pregnant women, children and in situations where exposure to radiation should be decreased.[34]

Unfortunately, CT and MRI have a specificity of about 70% because the incidence of adrenal incidentalomas is high.[13]

Functional imaging:

Functional imaging is an important part in the evaluation of PHEO/PG.[32] Functional imaging can help to diagnose primary or metastatic tumors that might have been missed with CT/MRI. Also, it can help determine metabolic activity of the tumours.[32]

Functional imaging has been performed with ^{123}I- or ^{131}I metaiodobenzylguanidine (MIBG) scintigraphy.[32] MIBG can enter cells through norepinephrine transporters because it has a structure which is like norepinephrine.[32]

The test of choice for functional imaging is [123I] MIBG scintigraphy.[32,34] It has a sensitivity of 83–100% and specificity of 95–100%.[34] When it is not available, [131I] MIBG scintigraphy should be performed and it has a sensitivity of 77–90% and specificity of 95–100%.[34] Because [123I] MIBG can be given in higher doses, detection rate is better, and time between injection and getting the image is shorter.[32]

In recent years, some important limitations to MIBG scintigraphy have also been discovered.[32] False-negative results can occur with succinate dehydrogenase subunit B (SDHB) mutations, relayed tumors and with extra-adrenal tumors.[32] Also, MIBG scintigraphy may unsuccessful in detecting metastatic disease.[32] Some medications such as tricyclic antidepressants, opioids and antihypertensives such as labetalol, can affect the uptake of MIBG and lead to less intense which cause false-negative results.[32]

Also, the PET scan has recently become more widely used in the diagnosis of PHEO/PGL due to shorter acquisition time, higher sensitivity and better image resolution.[32] Multiple tracers have been used and studied in patients with PHEO/PGL.[32] The most commonly available one is ^{18}F fluorodeoxyglucose (FDG) which is an analog of glucose that can be taken up through a glucose transporter.[32] FDG PET scanning can be a useful especially for patients with metastatic disease or SDHB mutations.[32] However, FDG is not specific to PHEO/PGL because other tumors can also be detected by this method.[32]

There are other more specific tracers which can be used, but these are less widely available.[32] The first one is ^{18}F-fluorodopa (FDOPA) and the second one is ^{18}F-fluorodopamine.[32] Both are catecholamines precursors and amino acids analog that can be taken up by the amino acid transporter.[32] An increase in the availability of these two tracers in the future will significantly help to improve the diagnosis.[32]

Another more functional imaging technique which can be used in diagnosis of PHEO/PGL is Octreoscan scintigraphy.[32,13,34] This technique works by introducing radioactively labeled octreotide to bind to somatostatin receptors which are often expressed on the cell membranes of PHEO/PGL.[23] However, the expression of these receptors between patients with PHEO/PG are various which affect the sensitivity of this method.[23]

PHEOs are better identified with octreoscan when compared with [123I]MIBG (87 vs 57%) because [123I]MIBG as well as [18F]DA sometimes give negative results in patients with malignant PHEOs.[34] This is possibly because of decreased expression NE transporter on the cell membrane of less well-differentiated cells.[34]

PREOPERATIVE ASSESSMENT

The only curative procedure is surgical resection of the tumour.[25] Before surgery it is important to control arterial blood pressure, heart rate and any arrhythmias and to return the blood volume to normal.[25] Pheochromocytomas management represent significant challenges to the anesthesiologist.[2]

The anesthesiologist should get relevant history from the patient and examine the patient for any end-organ damage which includes specifically cardiac failure and catecholamine induced cardiomyopathy which is associated with a high mortality.[25] Also, assessment of the severity of hypertension should be included when evaluating the patient.[25]

Assessment should include the following:[25]

ECG: which may show any type of arrhythmias, hypertrophy, cardiomyopathy, infarction or ischaemia.[25]

Chest X-ray: which may show pulmonary oedema or cardiomegaly

Echocardiography: needs to be used to evaluate left ventricular dysfunction, assess the response after alpha adrenergic blockade, and determine the right time for the surgery.[25]

Haematocrit and a baseline full blood count: can be used with serial monitoring to assess the adequacy of volume expansion after starting alpha adrenergic blockade.[25]

Renal function test: such as urea, creatinine and electrolytes should be included in the preoperative evaluation.[25]

Insulin therapy might need when there is hyperglycaemia. And, calcium level should be assessed to rule out the presence of MEN type 2.[25]

Preoperative assessment of these types of patients is essential in successful perioperative management.[2] In 1982, Roizen *et al* suggest a group of criteria which is now called the **Roizen criteria**, to show the efficacy of adequate preoperative alpha blockade.[2] These criteria include:[2]

1. No BP more than160/90 mmHg in hospital for 24 hours before the surgery.[2]
2. No orthostatic hypotension with BP less than 80/45 mmHg.[2]
3. No ECG changes (ST or T wave) during one week before the surgery.[2]
4. No > 5 premature ventricular contractions in one minute.[2]

Through many years, these criteria have stayed consistently reliable.[2] Data has been found in the literature showing poorer outcomes when these criteria are not followed with patients before tumor resection.[2]

As reported by Roizen *et al* his group has shown a decreased mortality from a pheochromocytoma resection from 13% - 45% before alpha blockade to 0-3% after alpha blocker has been used.[2] Most of the centers now use some or all of these criteria during the preoperative assessment for PCC resection for an appropriate pharmacologic preparation before PCC resection

PREOPERATIVE MANAGEMENT

Adrenergic crisis can lead to an uncontrollable situation which may happen at the time of induction, intubation or during tumour handling.[25] There should be close communication between the endocrinologist, cardiologist, anesthesiologist, and the surgeon in order to get a better outcome.[25]

Alpha blockade is the main drug that can be used during preoperative preparation for pheochromocytoma patients and it has been recorded as safe for over 60 years.[2] Multiple techniques have been suggested for pharmacologic preparation in patients with PCC, however, to date there is no randomized trial that has compared the efficacy of these different approaches and there is no universally accepted method of preoperative BP control.[2]

Most of the centers routinely use alpha-adrenergic and beta-adrenergic blockade in combination with calcium channel blockers.[2]

The alpha-adrenergic blockade is typically started 10-14 days before the operation to normalize blood pressure and to expand the contracted intravascular volume. This can be helpful especially in the higher risk pheochromocytoma patients.[2,25] Successful alpha blockade can be estimated by normalizing BP, mild orthostasis with nasal stuffiness .[2,25]

In the United States, phenoxybenzamine is the drug that is most commonly used for alpha blockade particularly in hypertensive crises.[2] In hospitalized patients, the doses for this drug range between 10 mg IV two times per day as starting dose to 1 mg/kg as total dose per day.[2] For outpatients, they can take an oral dose of 10 mg two times per day for at least 10-14 days before the operation.[2]

Other competitive and short-acting alpha-1 antagonists include prazosin, doxazosin and terazosin.[2,25] Prys- Roberts used doxazosin before the operation in twenty patients who had PCC or PGL, with doses of 2 to 8mg per day, and found that blood pressure was controlled in the same way as with phenoxybenzamine.[25]

The availability and cost effectiveness of the drugs affect the choice of the drug not only the preference of the physician.[25] Whatever drug is used, it should be started by carefully administering small doses and then the dose slowly increased until orthostatic hypotension occurs which indicates adequate alpha blockade.[25]

Tachycardia and arrhythmias can happen during alpha receptor blockade due to unopposed beta receptor activity.[25] These can be managed carefully by giving beta adrenergic blockers.[25,2] Beta blockade should never be introduced before making sure that alpha adrenergic blockade effect is established, because unopposed alpha stimulation can cause severe hypertension.[25]

The calcium channel blockers (dihydropyridines) are still useful in perioperative management and due to a less likely cause of orthostatic hypotension they are relatively easier to titrate.[2] IV nicardipine is most widely used in the perioperative setting as it has been well studied .[2]

SURGICAL APPROACH

Anesthetic management is largely affected by surgical approach which can make the management complicated.[2] Most of the centers use a laparoscopic method as preferred for most pheochromocytoma resections. This was supported by data across many years and it has been well documented as a better method. [2] The advantages of laparoscopic surgery in general include the following:[2]

- Less painful[2]

-Earlier mobilization and recovery[2]

-Reduced pulmonary and thromboembolic complication post-operative[2]

Shorter hospital stays[2-]

-Cost effectiveness.[2]

Open procedures are typically reserved for larger masses and extra-adrenal tumors with limited access.[2]

INTRA-OP MANAGEMENT

As mentioned previously, a pheochromocytoma operation is one of the most anesthetic challenging even in the best qualified centers in the world.[2,25] The essential goal is to give an anesthetic that provides stable hemodynamic condition to face catecholamine surges especially during laryngoscopy, peritoneal insufflation, tumor handling and surgical stimulation.[2] The anesthetic should also provide stable hemodynamic condition after tumor ligation, which has an opposite scenario.[2]

Close communication with the surgical team, in addition to accurate technique and careful planning are essential.[2]

Pre-induction

Pre-operative sedation and anxiolysis in the pre-operative period in order to prevent marked haemodynamic fluctuation is preferably achieved with a benzodiazepine.[25] Also, a small dose of IV midazolam before transfer patient to the operating suite can make the patient more calm and provide less risk of hypertensive crises at induction.[2]

Short-acting alpha 1 antagonists can be given on the morning of the operation but phenoxybenzamine and doxazosin should be stopped 12-24 hours before the operation because they are long-acting agents.[2]

The patient should be transferred to the operating room carefully to avoid any strenuous stimulus which may lead to catecholamine release.[25]

A large-bore peripheral IV lines should be inserted routinely before the induction after connecting ECG, pulse oximeter and non-invasive BP monitor.[2,25]

Arterial and central line catheters should be inserted under local anesthesia before the induction for monitoring the haemodynamic condition and for rapid pharmacological intervention when needed it.[2,25]

A pulmonary artery catheter is not mandatory and should only be inserted for patients with preoperative cardiovascular compromise and for patients who have severe left ventricular dysfunction.[25]

Routine monitors should include: capnography, inspired oxygen concentration (FiO2), pulse oximetry, ECG, temperature, neuromuscular blockade, and urine output.[25]

Careful attention should be focused when organizing vasoactive infusions which will be used intraoperatively.[2] Common vasodilators include sodium nitroprusside, nitroglycerin, nicardipine, diltiazem as indicated, magnesium sulfate, esmolol infusion and vasoconstrictors such as vasopressin and norepinephrine.[2] Patients with catecholamine cardiomyopathy should add inotropes such as epinephrine, and dobutamine with milrinone in the case of right ventricular dysfunction.[2]

Plasma expanders, colloids and blood products as indicated should be used to provide rapid volume expansion.[2]

Anesthetic Induction

Different anesthetic techniques have been used for the resection of pheochromocytoma.[25] Regional anesthesia with or without general anesthesia has been used for this operation.[25] Based on many years of experience in this kind of operation, Prys-Roberts has suggested a technique of anesthesia which includes adequate general anesthesia combined with mid to low thoracic epidural and he has suggested selective adrenergic antagonists to manage hemodynamic change during tumor manipulation.[25]

Various drugs have been proposed to control haemodynamic surges during the operation, but the selection of drugs to be used depends on the availability, particularly in developing countries and on the requirement of the patient.[25]

The drugs predominantly used are propofol and etomidate.[2] Propofol has been documented as a safe agent for these patients; etomidate can be useful especially in patients with volume depleted because of its cardiovascular stability.[2] All agents that cause histamine release should be avoided.[2] Thiopentone can cause histamine release but it has been used widely without side efects.[25] Ketamine, because of its sympathomimetic effects, is usually avoided.[2]

Blunting the intubation response is a crucial step during anesthetic induction in this operation and it can be achieved by using opioids, IV lidocaine, or infusions of nitroglycerin, sodium nitroprusside and nicardipine.[2]

The choice of neuromuscular blocker before intubation is very important in this kind of operation.[2] The depolarizing agent, succinylcholine can cause catecholamine release due to compression of the tumor as a result of muscle fasciculation and due to stimulation of the autonomic ganglia.[2] Nondepolarizing agents, Pancuronium has a vagolytic effect which can exert a pressor response.[2] Atracurium and mivacurium can cause histamine release.[2] However, Atracurium has been used by Prys-Roberts regularly for this operation since 1984 without any adverse effects.[25] Vecuronium, cisatracurium and rocuronium cause least histamine release with cardiovascular stability and have shown to be suitable for use.[25] Vecuronium is the most commonly used agent in this operation at the Mayo Clinic.[2].

Enflurane and isoflurane have been widely used without adverse effects.[2] Halothane is arrhythmogenic and can sensitize the myocardium to circulating catecholamines, and is contraindicated in this operation.[2] It is recommended by many that Desflurane not be used because of its sympathetic stimulation.[2] Sevoflurane is commonly used for pheochromocytoma excision and its use depends upon economic issues and availability.[2]

Use of opiates can be varied depending on the type of the surgery (open vs. laparoscopic), opiate tolerance and hemodynamic state of the patient.[2] Morphine and hydromorphone are commonly used, although remifentanil has been used successfully in many institutions.[2]

MAINTENANCE AND SURGERY

Hypertension during the operation can happen during positioning of the patient, skin incision and intubation.[2] This hypertension response is due to excessive release of catecholamine from nerve endings and it is usually temporary and responds rapidly to the therapy.[2] On the other hand, manipulating the tumor during the operation usually causes a far more dramatic response which is due to significant increases in the level of norepinephrine and epinephrine in plasma.[2] These two conditions can cause severe hemodynamic unstable conditions which include significant cardiac output reduction and left ventricular systolic and diastolic dysfunction.[2] Immediate action should include two steps: first, increase depth of anesthesia and second, give direct arterial vasodilators.[2]

Sodium nitroprusside, prazosin, phentolamine, nitroglycerine and various other drugs such as magnesium sulphate, nicardipine, diltiazem and esmolol have been used to control intraoperative rises in BP.[25]

Sodium nitroprusside is the most commonly used agent because of its potent arterio-venodilator with fast and short action and can be used as an intravenous infusion in a dose around 0.5 mcg kg-1 min-1.[25] Intravenous nitroglycerine can also be used as it also has rapid onset and short duration with the main effect on capacitance vessels.[25]

Phentolamine can also be used in this situation as incremental doses of 1 to 2 mg or as an infusion because of its rapid action and short duration of action.

Beta adrenergic antagonists such as Esmolol can be used to control tachycardia, tachyarrhythmias and blood pressure during the operation because of its rapid effect and short duration.[25] Metoprolol in doses of 1-2 mg IV boluses has also been used during the operation with good results.[25]

Magnesium sulphate has different mechanisms which include inhibition catecholamine release from chromaffin cells, strong calcium antagonist and alters the adrenergic receptors response.[25] Prof. James has achieved hemodynamic control during the operation by using magnesium sulphate with a loading dose of 40 - 60 $mg.kg^{-1}$ followed by an infusion of 1-2 g/hr.[25] At the time of tumor manipulation, more doses were needed in all patients.[25]

Also, calcium channel blockers such as nicardipine and nifedipine have been used to control hemodynamic intraopratively.[25]

It's been difficult to choose the best drug to use during resection of pheochromocytoma to control the haemodynamic because of the difficulty in running well designed randomized trials due to the rarity of the situation.[25] It has been suggested to use the drug or method that the anesthetist is most familiar with.[25] The availability and cost effect are also issues which affect choosing the drugs in developing countries.[25]

After ligation of adrenal veins, hypotension can happen as a result of the sudden decrease in the level of catecholamines in circulation.[25] At this time, blockers and vasodilators should be stopped and fluid bolus should be given.[25] Vasopressor infusion such as phenylephrine or norepinephrine may be needed.[25] Vasopressin is mostly effective for hypotension that occurs after tumor resection because it does not depend on adrenergic receptors for its effect.[2]

POST OPERATIVE MANAGEMENT

At the end of the operation, the patient can be extubated or can be kept ventilated depending on the peri-operative state of the patient.[25] In both scenarios the patient should be kept in ICU or in the high care unit for at least 24 hours with close monitoring of his hemodynamic condition.[25]

Hypertension, hypotension and hypoglycaemia are the most important complications during post operative time.[25] Around half of the patients stay hypertensive for several days due to high level of catecolamines which can remain high for one week.[25] Therefore, patients may need to restart antihypertensive medications.[25] In the case of persistent hypertension, residual tumor should be considered.[25]

Also, persistent hypotension can happen which can be due to the residual effect of the adrenergic block use during the preoperative period, due to intra-abdominal bleeding, inadvertent ligation of the renal artery or due to inadequate fluid resuscitation .[25]

Hypoglycemia can occur due to the lack of suppression of pancreatic beta cell and insulin level increase.[25] Therefore, monitoring blood glucose levels should be considered during and after the operation.[25]

CONCLUSION

Although the mortality rate intra-operatively for patients with pheochromocytoma has reduced remarkably, anesthetic management is still a challenge to most expert anesthesiologist.[25] It is very important to control hypertension during the pre-operative phase with alpha adrenergic blocking agents followed by beta adrenergic blocking drugs where required and adequate volume expansion.[25]

Successful management of patients with pheochromocytoma required experienced team of endocrinologist, endocrine surgeon and anesthesiologists with good communication between them.[2,25] Various anesthetic techniques and medications have been used successfully and different combinations of vasodilating and antihypertensive drugs have been used intra-operatively during the resection of pheochromocytoma with good results.[25]

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