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Perioperative management of pheochromocytoma/paraganglioma: a comprehensive review

Manejo perioperatorio del feocromocitoma/paraganglioma: una revisión exhaustiva

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Abstract

Pheochromocytomas are rare neuroendocrine neoplasms that require adequate preoperative evaluation in order to prevent and lessen the serious complications of catecholamine hypersecretion. Preoperative management contributes to reducing morbidity and mortality rates in patients who have not been diagnosed with this condition and undergo any surgery. However, current mortality seems to be lower, a fact attributed to preoperative management with alpha blockers.

Keywords

Pheochromocytoma; preoperative care; intraoperative care; drug therapy; postoperative care.

Resumen

Los feocromocitomas son neoplasias neuroendocrinas poco frecuentes que requieren una evaluación preoperatoria adecuada, con el fin de prevenir y disminuir las complicaciones graves de la hipersecreción de catecolaminas. El manejo preoperatorio contribuye a disminuir las tasas de morbimortalidad en los pacientes que no han sido diagnosticados con esta entidad y son sometidos a cualquier cirugía. Sin embargo, la mortalidad actual parece ser más baja, hecho atribuido a un manejo preoperatorio con α -bloqueadores.

Palabras clave

Feocromocitoma; periodo preoperatorio; periodo intraoperatorio; tratamiento farmacológico; cuidados postoperatorios.

INTRODUCTION

Pheochromocytomas are rare neuroendocrine neoplasms arising from chromaffin cells of the adrenal medulla derived from the neural crest (1,2). They are characteristically catecholamine producers (3) and can be functional or non-functional (2); with an important hereditary component, they are considered the neoplasms with the highest genetic burden. Associated genetic syndromes include neurofibromatosis type 1 (NF1), multiple endocrine neoplasia (MEN 1 and 2), von Hippel-Lindau disease (VHL) and familial pheochromocytoma paraganglioma (4). Although this condition is usually benign, it has been associated with high morbidity and mortality secondary to catecholamine hypersecretion, and a risk of metastasis ranging between 10 and 20% (5-7).

They are more frequent between the fourth and fifth decades of life, with equal distribution in males and females (3). The incidence of pheochromocytoma/paraganglioma is 1 to 3 cases in 100,000 (7) and these neoplasms are an infrequent cause of secondary hypertension, with a prevalence ranging between 0.1 and 0.6% (4). However, incidence is underestimated considering that 50% of these neoplasms are found on autopsy (8).

Of patients with pheochromocytoma, 30-40% (6) present with the classic triad consisting of headache, diaphoresis and palpitations (9). They are less frequently associated with other non-specific symptoms such as nausea, vomiting, pallor, diarrhea, tremors, dyspnea, polyuria, polydipsia, anxiety and panic attacks (3,5,6) and other less common symptoms such as constipation (10) and ileus. Hypertension is usually the initial presentation (8), and it must be suspected if it meets the characteristics described in Chart 1 (11). Other manifestations associated with ectopic hormone secretion have been described, as shown in Table 1 (2,4).

Biochemical diagnosis is made based on fractionated metanephrines in plasma (sensitivity 97-100% sensitivity and 85-93% specificity) or in 24-hour urine (up to 97% sensitivity and up to 91% specificity) (4,9,14).

CHART 1. Criteria to suspect hypertension secondary to pheochromocytoma.

| |
|--|
| 1. Paroxysmal hypertension, resistant or early onset hypertension (< 20 years) |
| 2. Paradoxical blood pressure response (especially during β -blocker treatment). |
| 3. New onset hypertension or worsening of hypertension with the use of tricyclic antidepressants and other drugs. |
| 4. Severe symptomatic hypertension with the initiation of α -blocker therapy. |
| 5. Severe hypertension or hypertensive crisis after any procedure (e.g., anesthesia, endoscopy, surgery or angiography). |
| 6. In pregnant patients with hypertension that is not typical of pregnancy-induced hypertension. |

SOURCE: Adapted by the authors from Gunawardane and Grossman (11).

TABLE 1. Possible hormonal secretion by the pheochromocytoma.

| Hormone | Clinical manifestation |
|---|--|
| Adrenocorticotropin (ACTH) | Hypercortisolemia and Cushing syndrome |
| Parathyroid hormone-related peptide (PTHrP) | Hypercalcemia |
| Vasopressin | Syndrome of inappropriate antidiuretic hormone secretion |
| Vasoactive intestinal peptide (VIP) | Watery diarrhea |
| Growth hormone releasing hormone | Acromegaly |

SOURCE: Adapted by the authors from Turchini et al. (2); Tsirlin et al. (4); Zhou and Ding (12) and Edafe et al. (13).

Mean delay in diagnosing this condition is approximately 3 years (15). It is estimated that 1.5-14.0% of incidental findings of adrenal masses on computed tomography (CT) or magnetic resonance (MRI) imaging studies are pheochromocytomas (6). This review article provides an overview of the preoperative, intra-operative and postoperative management of patients with pheochromocytoma.

PREOPERATIVE MANAGEMENT

Minimally invasive laparoscopic surgery performed through a retroperitoneal approach is the treatment of choice for

pheochromocytoma resection (15,16). An adequate preoperative assessment is crucial before the surgical procedure in order to prevent or reduce severe complications from catecholamine secretion (15,17), even in asymptomatic and normotensive patients (15). This assessment includes the administration of antihypertensive drugs for blood pressure and heart rate control and to prevent the onset of arrhythmias (18,19); clinical history, laboratory tests and cardiovascular assessment (18). Moreover, diminished blood volume from chronic vasoconstriction must be restored (19) using saline solution and allowing salt consumption.

TABLE 2. Preoperative pharmacological management.

| Non-selective α -adrenergic receptor antagonists | | | | |
|---|--|--|---|--|
| | Half-life | Dose | Administration | Side-effects |
| Phenoxybenzamine | Half-life 24 hours (14,23) | Daily dose 1 mg/kg, titrated every 4 days | Administer 7 to 21 days before the intervention (4,14,16). Discontinue 24-48 hours before surgery (23). | Could produce refractory postoperative hypotension and reflex tachycardia (14,24). |
| Selective α -1 receptor antagonists | | | | |
| | Half-life | Dose | Administration | |
| Prazosin | Half-life 2-3 hours (25) | Initial dose 0.5 - 1 mg every 4-6 hours titrated to a maximum dose of 20-24 mg/day (9,20) | When the last dose is given the night before the surgery, blood concentration drops to ineffective levels (20). | |
| Doxazosin | Half-life 16-30 hours (24,25) | Initial dose 1 - 2 mg/day titrated to control blood pressure up to a maximum dose of 16 mg/day (9). | Does not cause tachycardia or sedation (23,25) due to low ability to cross the blood-brain barrier (14) | |
| Terazosin | Short action (26) | Initial dose 1 mg/day which can be increased to 20 mg/day depending on blood pressure control target (9) | | |
| Tyrosine hydroxylase inhibitor | | | | |
| | Dose | Administration | Use | Side-effects |
| Metyrosine | Initial dose 250 mg every 6 hours, gradually increased to a maximum dose to 4 g/day (9,24) | Administer 2-3 days before the intervention (4) | Used when blood pressure control is not achieved with α and β -blockers or in cases of refractory hypertension (4,14,24). Useful in patients with metastatic tumors (25-27), unresectable tumors (9) or biochemically active tumors (27) | In monotherapy causes incomplete depletion of catecholamine stores (27) |
| β -blockers | | | | |
| Propranolol | Initial dose 10-40 mg every 6-8 hours (4) | Start 3-4 days after α -blockade initiation (16) | | |
| Atenolol | Dose 100 mg/day (20) | Start 3-4 days after α -blockade initiation (16) | Used to minimize undesirable bronchial and peripheral vascular side-effects (20) | |
| Metoprolol | Dose 50-200 mg/day (20) | | | |
| Calcium channel antagonists | | | | |
| Amlodipine | Dose 5 - 20 mg (9,23,27) | | | |
| Nicardipine | Dose 60 to 90 mg/day (9,23,27) | Nicardipine infusion is started at a rate of 5 mg/hour, increasing by 2.5 mg/hour every 5 minutes up to a maximum of 15 mg/hour (16) | Used in normotensive or mildly hypertensive patients given that they lack the limitations of α -blockers (15) | |
| Nifedipine | Dose of 30 - 90 mg (9,20,27) | | | |
| Verapamil | Dose of 180 to 540 mg per day (17,27) | | | |
| Diltiazem | Dose of 90-240 mg/day (9) | Used in normotensive or mildly hypertensive patients given that they lack the limitations of α -blockers (9) | | |

SOURCE: Authors.

Preoperative management lowers morbidity and mortality rates in patients diagnosed with this condition who undergo any type of surgery (16,17,19). Mortality rate in uncontrolled patients ranges between 30-45% (9). This is due to the high risk of hypertensive crisis, malignant arrhythmias and intra-operative multiple organ failure (16,17). However, current mortality appears to be lower due to preoperative management with α -blockers.

The use of α -blockers is the suggested first choice for premedication (9,16,20) over a period of 10 to 14 días (19-21). In general, the use of β -blockers as adjunct therapy is required (19). Regardless of the pharmacological regimen used, the sitting blood pressure goal is <130/80 mm Hg, and standing systolic blood pressure <90 mm Hg must be avoided (15,16,20). The recommended sitting and standing heart rate values are 60-70 bpm and 70-80 bpm, respectively (16,20).

Pharmacological management includes α -blockers, β -blockers, channel calcium blockers and tyrosine hydroxylase inhibitors (9,17,18), as described in Table 2.

Non-selective α -blockers: Phenoxylbenzamine

Phenoxylbenzamine is used to reduce vasoconstriction and intraoperative hypertensive crises, (18) and to achieve normal hemodynamic parameters (20). Its limitation is low availability in most countries.

Selective α -1-receptor antagonists

They reduce the risk of postoperative hypotension (3). Prazosin, doxazosin and terazosin potentially induce severe postural hypotension immediately after the first dose (22). Monitoring is required due to the risk of orthostatic hypotension. Fluid intake (4,14,20) and increased salt consumption are required (9,19) in order to counteract

intraoperative hemodynamic instability (20). Risk factors for hemodynamic instability are described in Chart 2.

β -blockers

Their use is recommended following successful α blockade because of worsened hypertensive episodes when used as monotherapy (22). Propranolol is the most widely used agent (4).

Non-selective blockers are contraindicated in patients with bronchospastic airway disease and with congestive heart failure. In those cases, cardioselective β -blockers

CHART 2. Risk factors for hemodynamic instability.

| |
|---|
| 1. Large tumors > 3 to 4 cm |
| 2. Higher catecholamine levels |
| 3. Uncontrolled blood pressure |
| 4. Preoperative orthostatic hypotension |

SOURCE: Adapted by the authors from Fishbein et al. (17).

are preferred (4). These medications can be given 1 to 3 times a day, with dose adjustments to achieve a heart rate between 60-80 bpm (18). Pulmonary edema can occur in patients with cardiomyopathy because of β stimulus removal, and β blockade can produce severe hypotension, bradycardia and asystole in these patients (19).

Labetalol has been used for preoperative blockade but should not be the first choice and its use is not recommended (4,22) because it can precipitate the onset of hypertensive crises (20,28) or paradoxical hypertension as a result of weaker α -antagonist and stronger β -antagonist action (20). In most patients, adequate blood pressure control is not achieved because of its lower

α -blocking ability (28). Its use has also been associated with reduced ¹³¹I-MIBG uptake and must be discontinued 2 weeks before the ¹³¹I-MIBG scan in order to avoid false negative results (22). In practical terms, labetalol is considered a pure β -blocker in pheochromocytoma preoperative management.

Calcium channel antagonists

They are used as adjuncts to the treatment with α -blockers in cases of uncontrolled blood pressure (4,14,15,22). They are also used as second-line medications in patients with mild hypertension or severe α -blocker-induced orthostatic hypotension, in normotensive patients, and in patients with paroxysmal hypertension with no baseline arterial pressure elevation (25). Moreover, they are effective in the management of intraoperative hemodynamic fluctuations, particularly in small tumors. (27)

Controversies regarding preoperative management

Mortality associated with pheochromocytoma resection has dropped over time. A historical cohort comparison showed a reduction in cardiovascular events and mortality in patients who received α -blockers when compared to those that did not, making α blockade the standard of care in the preoperative setting. However, there is not evidence from randomized studies. Four retrospective studies suggest that mortality, cardiovascular complications and blood pressure are no different in patients with and without α blockade. This has led to a world-wide controversy regarding the routine use of α -blockers, pointing to the need of conducting controlled randomized studies to answer the question of whether or not the routine use of α -blockers is beneficial in pheochromocytoma patients (26,29-32).

INTRAOPERATIVE MANAGEMENT OF PHEOCHROMOCYTOMA

The intraoperative course in patients with pheochromocytoma depends on many factors associated with the tumor itself, patient baseline status and comorbidities, adequate α blockade alone or combined with β blockade before the surgery, and expected or unexpected intraoperative events (such as the timing of tumor devascularization). Consequently, it is very important for the surgical team to be prepared for major surgery, creating checklists that include the required supplies, medications that should not be used or used with care, the critical intraoperative and postoperative steps, and emphasizing assertive, closed-loop communication to avoid any mistakes. Constant handling of high-risk medications could lead to fatal outcomes.

Patient assessment on admission to surgery

On the day of surgery, patient assessment should focus on determining adequate α -blockade, which significantly changes intraoperative and postoperative morbidity and mortality. In 1982, Roizen et al. described the most widely used way to make this determination (Chart 3) (33). In another study 5 years later, (34) the same author reported a drop in mortality greater than 50% when those criteria were met. However, some authors suggest that these parameters should be revisited because better blood pressure control is likely to be required, avoiding the induction of orthostatic hypotension (21). This general assessment needs to consider factors such as stress, pain, tremors, hypoxia, hyperventilation and hypothermia and ensure that they are under control before starting the surgery because they could trigger a catecholaminergic crisis requiring the postponement of the procedure. A pheochromocytoma-induced crisis is more a medical rather than surgical emergency,

(35) although there are case reports of surgical management in crises that do not respond to medical management. (18) In most cases, it is advisable to use an anxiolytic medication such as a benzodiazepine (36) or non-pharmacological measures to reduce stress preoperative, including the presence of family members, music of the patient's liking and permanent accompaniment to answer any questions and provide explanations regarding the anesthetic plan. Adequate pre-warming, monitoring and temperature control before and during the surgical procedure are also recommended.

Another important consideration is to assess volume status on admission to the operating theater. These patients are known to be relatively hypovolemic, secondary to chronic vasoconstriction due to prolonged catecholaminergic influx. Hence the need to provide clear recommendations during the preanesthetic assessment regarding fluid intake, avoiding fasting times of more than 8 hours and drinking water up to two hours before the surgery; moreover, early intravenous fluid replacement must be initiated at the time of preparation for surgery in order to maintain normal volume (21). However, several authors are against fluid loading before surgery, creating a controversy, as discussed below.

CHART 3. Roizen criteria for determining adequate α -adrenergic blockade.

1. No blood pressure reading $> 160/90$ mm Hg during the 24 hours leading up to the surgery.
2. Orthostatic hypotension must be present, with readings $> 80/45$ mm Hg.
3. No ST-T changes on the electrocardiogram during at least 1 week before the surgery.
4. No more than 1 premature ventricular contraction every 5 minutes.

SOURCE: Adapted by the authors from Roizen et al. (34).

In 2018, Jiang et al. published a study of 134 patients in which they mention three risk factors for intraoperative hemodynamic instability: tumor diameter ≥ 5 cm (OR: 2.5), systolic blood pressure fluctuation greater than 50 mmHg (OR: 3.1), and preoperative diabetes (OR: 2.2), with an incidence of instability of up to 60% when 3 factors are present (37). Other risk factors described include high norepinephrine levels, profound orthostatic hypotension following the initiation of α -blockade, and mean arterial pressure greater than 100 mmHg before induction (38). Moreover, perioperative complications of normotensive pheochromocytomas are usually underestimated, but it has been found that they are associated with an equal number of intraoperative instability episodes as those associated with hypertension before surgery (39).

A preoperative electrocardiogram is recommended as part of the assessment on the day of surgery to identify any arrhythmias, signs of ischemia, branch block or established left ventricular hypertrophy. (40).

Surgical technique

In the majority of sites world-wide, laparoscopy is currently the gold standard for the resection of masses under 6 cm and less than 100 grams (41,42), because of the association of this technique with lower catecholamine release, less postoperative pain, earlier ambulation, lower incidence of pulmonary thromboembolic complications and shorter length of stay when compared to the open technique (43,44). The type of approach (transperitoneal vs. retroperitoneal) must be selected based on center and surgeon expertise as well as on the need for bilateral resection or the type of associated endocrine neoplasm (45,46). From the standpoint of anesthesia, it is important to consider that the transabdominal approach is performed on supine or lateral recumbency, while the retroperitoneal approach requires prone or lateral recumbency (47).

Total adrenalectomy is currently recommended in unilateral functional tumors, while partial adrenal resection is only considered when there is certainty of full removal of the functionally active tissue (45) and in cases of hereditary pheochromocytoma in which the patient has already undergone adrenalectomy of the contralateral side (40).

Intraoperative monitoring

Recommended monitoring varies among sites; however, there are general guidelines regarding the use of two peripheral venous accesses, preferably 18G or less, arterial catheter (40) - ideally inserted in the awake patient for adequate monitoring of pressure values during induction and intubation, being careful to infiltrate the puncture site to avoid intense pain - and one central venous access for vasoactive drugs (48), placed under general anesthesia.

As for the ideal intraoperative measurement of blood volume and cardiac output, there are different recommendations in major surgery. It is generally agreed that the use of static measurements such as central venous pressure (CVP) does not have a place in this surgery because of a poor relationship with left ventricular filling pressure and little use in guiding intraoperative resuscitation. On the other hand, before falling out of use, some authors tried to determine adequate intraoperative volume infusion using the pulmonary artery catheter, with very promising results (49). However, the Swan-Ganz catheter is currently known to have significant limitations (50) with its use being reserved probably for some cases of severe pulmonary hypertension. Consequently, other less invasive methods have been proposed. In late 2019, the preliminary results of an interesting prospective study that assessed the use of intravenous fluids in patients undergoing laparoscopic pheochromocytoma and non-hormonally active adrenal tumor resection under esophageal Doppler guidance were

published (51). The authors found that adequate cardiac indices could be achieved with the restrictive use of intravenous fluids and reported the presence of vasoplegia but no hypovolemia following tumor resection, showing the need for intraoperative and even postoperative monitoring of cardiac output. This shows the importance of using some form of dynamic measurement of cardiac output to guide volume infusion requirements and the use of vasoactive drugs during surgery. There is a wide range of devices, some already endorsed in major surgery, that use cardiac output measurement strategies, some more invasive than others, but with a lower number of reported adverse events than pulmonary artery catheterization. They use variables such as pulse wave contour, systolic volume variability, CO₂ reinhalation, bioimpedance, bioreactance and even transpulmonary thermodilution. They seek to provide more accurate and safer guidance than conventional clinical methods (urinary output, capillary filling, vital signs, etc.) or the Swan-Ganz catheter. However, they are not free from complications or limitations (arrhythmias, need for constant calibration, vascular accesses and more studies to validate their use in this type of surgery). More and more, this has opened the way for transesophageal echocardiography to guide intraoperative resuscitation (52), mainly in patients with severe underlying heart disease or very active tumors (53). This method offers great advantages over those already mentioned. Apart from providing almost all the variables of hemodynamic concern in real time, it shows anatomical and local contractility derangements suggestive of infarction or structural alterations that could change intraoperative management; moreover, in head-to-head comparisons with pulmonary artery wedge pressure (PWP), it has been shown that many PWP values considered acceptable are associated with inadequate left ventricular filling (54). Its great limitation at present is the unavailability of equipment and trained staff for intraoperative performance.

Another important consideration is intraoperative blood glucose monitoring, which needs to be adequately addressed as will be explained later, particularly after an episode of catecholamine release or following ligation of the venous drainage of the lesion (40). Additionally, monitoring of temperature changes is also important, ideally with a central or peripheral thermometer, with the aim of maintaining normal temperature and as tight a gap as possible, with special emphasis on avoiding hyperthermia.

Type of anesthesia and anesthetic drugs

The main intraoperative goal from the anesthetic point of view is to maintain hemodynamic stability throughout the procedure. This requires paying close attention (some suggest the use of a checklist) to critical moments such as laryngoscopy, patient positioning, surgical incision, pneumoperitoneum initiation, manipulation of the lesion, and ligation of venous drainage of the tumor. This is achieved by means of appropriate anesthetic depth and the use of the right drugs at each critical step of the surgery. For example, the use of videolaryngoscopy could be considered for intubation because, as has been shown in other types of surgeries (55), sympathetic response can be diminished, when used by trained hands. On the other hand, filling pressure and CO₂ injection rate must be controlled slowly and progressively during pneumoperitoneum insufflation in order to avoid inappropriate stimuli that could trigger a sympathetic response.

Given the paucity of comparative studies of the different inhaled agents, strong recommendations are lacking. However, it is clear that halothane increases complications (56), while desflurane causes sympathetic stimulation (57). Although there are a few reports dating back to the 1980s on the successful use of enflurane and isoflurane (58), referral centers prefer the use of sevoflurane over the other agents

because of its hemodynamic stability (59), wide availability and safety (57).

As for intravenous anesthetics, there are no large studies in patients undergoing pheochromocytoma resection. There are some reports in the literature of the use of all available induction drugs in our setting, with special emphasis on propofol because of its pharmacodynamics and cardiovascular effects. Even for intraoperative maintenance, propofol has been used in combination with a potent opioid in total intravenous anesthesia (TIVA) (60) as a target controlled infusion (TCI). It is always important to highlight the need for monitoring the depth of anesthesia using bispectral index (BIS) or entropy to achieve adequate control. Etomidate is also recommended for induction because of its great hemodynamic stability; however 11 β -hydroxylase inhibition must be borne in mind because of the potential to cause relative adrenal failure, requiring the use of steroids for its resolution. Good outcomes have been documented over the past decade with the intraoperative use of dexmedetomidine (61) infusion, always bearing in mind that it may give rise to profound bradycardia. Also, other induction agents such as ketamine must be used with caution because of the theoretical possibility of increasing catecholamine release, as is also the case with all potential histamine release inducers.

The neuromuscular relaxants most widely used in our setting (cisatracurium, rocuronium and vecuronium) have been found to trigger less histamine release when compared to most other muscle relaxants (62), making them ideal for use in this context. Atracurium (63) and pancuronium (64) are associated with increased sympathetic activity and potential arrhythmias in this population, hence the recommendation by some authors to cisatracurium over other relaxants (33). On the other hand, succinylcholine must be used with caution, considering that autonomic stimulation and fasciculations could trigger a mechanical stimulus of the tumor, inducing catecholamine release

(65). That is why the use of rocuronium is emphasized in situations requiring rapid sequence intubation, at the indicated dose for this use (1.2 mg/kg), making sure sugammadex is available for reversal should the need arise.

In patients with difficult airway predictors or a history of a difficult airway in whom awake intubation is decided, special care must be taken to avoid a hypertensive crisis during induction. The recommendation in such cases is to follow the recently updated awake intubation guidelines proposed by the Difficult Airway Society (66), consisting of four steps, emphasizing steps 2 and 4, namely, adequate topicalization (using 20 to 30 sprays with 10% lidocaine spray, making sure adequate anesthesia is achieved and boosting the region if needed), and sedation with the suggested use of remifentanyl-TCI 1 to 3 ng/mL.

On the other hand, although the implementation of opioid-free anesthesia has been gaining traction in the world, the use of opioids is critical in this type of surgery in order to achieve tight pain control during the procedure and avoid peaks of adrenergic bursts. The use of any opioid anesthetic is accepted as good clinical practice, but there is a growing number of reports on remifentanyl because of its pharmacological profile that favors easy and rapid titration when compared to the others (67). The use of TCI and BIS is advisable in order to achieve adequate control of the situation. Moreover, morphine and meperidine must be used with caution, given the potential to elicit histamine release or potential sympathetic stimulation, respectively.

Other medications must also be avoided, including metoclopramide because of reported hypertensive crises in patients with pheochromocytoma. Some authors suggest flagging patients who are allergic to this medication, if they have been documented to have catecholamine-producing pheochromocytoma (68), or at least including this drug to the checklist as a preemptive measure.

Although there are no studies comparing the neuroaxial technique alone versus general anesthesia, the latter has been the standard of care for pheochromocytoma resection. Intraoperative hemodynamic instability requiring mild corrections (including hypertensive crisis as well as hypotension) during ligation of tumor venous drainage is more difficult to manage when the patient is under spinal anesthesia. A total sympathetic block with spinal anesthesia is not advisable either because of difficult hemodynamic control during surgery. Consequently, most reports of satisfactory use of neuroaxial techniques involve the use of epidural analgesia combined with general anesthesia (69), mainly in the obstetric population (70).

Intraoperative hemodynamic changes

Painful stimuli and tumor manipulation are the main causes of intraoperative hypertensive responses. The former can be managed with analgesia and adequate anesthetic depth, while the latter must be addressed with the use of rapid vasodilator infusions, requiring the availability in the operating room of a potent vasoactive agent already prepared. In our setting, the most frequently used agents are nitric oxide modulators (nitroprusside or nitroglycerine) (71). However, other options include β -blockers like labetalol or esmolol (preferred in adrenalin-secreting tumors) (72), calcium channel blockers like nicardipine (always remembering its long half-life), or even magnesium sulphate which inhibits catecholamine release because of its direct action on the catecholamine receptor and plays an important role particularly in cases of concomitant arrhythmias, at a dose of 50 mg/kg followed by infusion of 1 to 2 g/h (73). Sometimes, the combined use of two or more antihypertensive drugs is required, with the most commonly described being nitroprusside plus esmolol or labetalol, with or without magnesium sulphate (74). Likewise, very large increases in

catecholamines, particularly adrenaline, could trigger ischemic events. Although they initially manifest as hypertensive crises, they could lead to severe instability episodes resulting from cardiogenic shock or ischemic origin, or secondary to stress cardiomyopathy. These cases require prompt correction of the crisis in an attempt at maintaining adequate cardiac output. In the event inotropes are required, the use of milrinone is preferred over dobutamine and levosimendan, because of its mechanism of action and ease of titration. Typical hemodynamic crises in this context depend on the type of catecholamine secreted by the tumor, and may manifest in the form of bradycardia with severe hypertension, or tachyarrhythmia with or without cardiac output compromise (75).

It has traditionally been considered that these patients come to surgery in a relatively hypovolemic state due chronic vasoconstriction secondary to permanent tumor catecholamine stimuli. For this reason, when the massive influx of catecholamines is interrupted, vasoconstriction diminishes, leading to arterial hypotension; on occasions, this is aggravated by the residual effect of preoperative α and β blockade, and can result in refractory shock (76). This is why the recommendation is to ensure normal volemia or mild hypervolemia (preferably guided by dynamic monitoring) at the time of ligating the venous drainage of the lesion, as well as the availability of a vasopressor with a rapid onset of action and easy to titrate, such as norepinephrine. It is important to highlight that usual doses may be ineffectual due to α and β -receptor downregulation caused by prolonged endogenous catecholamine stimulation. Therefore, some authors recommend the concomitant use of vasopressin based on its mechanism of action on V1 receptors. The concept of relative hypovolemia in these patients is currently under discussion and the advice is to use some form of dynamic cardiac output monitoring to guide fluid replacement, and to consider an earlier initiation of vasopressors at the time of clipping venous drainage to the tumor.

Intraoperative blood glucose derangements

Hyperglycemia may be present upon arrival in 10 to 15% of patients due to excess circulating catecholamines that result in phenomena such as α -1 receptor-mediated glycogenolysis, insulin release inhibition (α -2), lipolysis (β -1), and increased glucagon release. Regular intraoperative monitoring is recommended, mainly at the start of the procedure, after a catecholamine release crisis, or following tumor devascularization because of the strong risk of hypoglycemia once the catecholamine rush is interrupted. However, given the high incidence of blood glucose abnormalities, serial intraoperative monitoring is recommended, starting even during the preoperative period. Although recommendations for intraoperative glycemic management are derived from studies conducted mainly in the field of cardiovascular surgery or intensive care (77), it is advisable to correct hyperglycemia only when values are higher than 180 mg/dL (78) and hypoglycemia when values drop below 70 mg/dL.

POSTOPERATIVE MANAGEMENT

Postoperative management is critical in order to ensure timely intervention in cases of tumor recurrence, incomplete resection, development of metastases, and complications such as hypertension (79), hypotension or hypoglycemia within the first 24 hours postoperatively (15), a drop in cortisol levels, and pain treatment (79). Postoperative monitoring these patients in special care units is recommended.

Fractionated metanephrines in 24-hour urine must be measured 1 to 2 weeks after the resection. High levels are associated with residual adrenal disease, metastasis or incomplete resection, and continuation of anti-adrenergic therapy is required in order to control symptoms (4). Routine diagnostic imaging is not recommended, except in cases of elevated metanephrines (8) or for follow-up in patients at risk of metastasis (16).

Annual fractionated metanephrine testing for life has been suggested (4,16), even in patients with normal levels (16), because these values do not rule out residual microscopic disease (80). This allows timely identification of metastatic disease, tumor recurrence and late-onset primary tumors (16). In patients with familial/hereditary disease (especially in patients with SDHB mutations), paragangliomas or neoplasms larger than 5 cm, clinical and biochemical follow-up is required 6 months after surgery and then every year for life, due to the high risk of recurrence (8).

In close to 50% of patients, persistent hypertension is present because catecholamine levels remain high during 7 to 10 days after the surgery due to residual neoplasm (81), autonomic instability, pain and volume overload (80). Abrupt discontinuation of the medication may give rise to severe rebound hypertension (4). Close to 25-50% of patients may persist with hypertension after surgery (75,80).

Hyponatremia and hypoglycemia must be ruled out in cases of drowsiness (75), which occurs in 4 to 17% of patients within the first 4 hours after surgery. It is advisable to measure blood glucose levels and administer dextrose-based fluids until oral intake is tolerated (8).

Postoperative hypotension is the result of a sharp drop in catecholamines after surgical resection, preoperative volume contraction, intraoperative blood loss (8,80), and administration of phenoxybenzamine and metyrosine (79). If it persists after volume resuscitation (8,80), inadequate fluid administration, bleeding or anesthesia-induced residual vasodilation must be ruled out (75).

Treatment of acute postoperative pain is essential. Besides reducing pulmonary and thromboembolic events, it improves residual hypertension and early postoperative quality of life (79). Postoperative pain management can be achieved through different approaches. Neuroaxial techniques have been used successfully for decades, particularly the epidural technique (69) that can help balance analgesia intraoperatively to a significant degree. However, some authors

advise against the use of these techniques because of their association with profound hypotension due to pharmacological sympathectomy which requires a higher use of intravenous fluids and vasopressors intraoperatively and during patient stay in high dependence units. This has led to a growing use of regional anesthesia in the context of both open as well as laparoscopic major abdominal surgery. Although there are no comparative studies in pheochromocytoma resection, it could be surmised that an erector spinae plane (ESP) block, ideally leaving a catheter in place on the side of the resection, could be of great help in reducing opioid use and accelerating the recovery process, mainly in the context of open surgery. Other blocks, such as the paravertebral and transversus abdominis plane blocks have a very small role to play in this arena, given that the former may lead to a sympathetic block with its well-known consequences especially in these patients, while the latter does not provide adequate control of visceral pain, although it could be effective in surgical wound pain management. These techniques always require adjunct oral or intravenous pain management as part of a multimodal approach. If no regional technique is possible, given the importance of postoperative pain control, a multimodal approach must include the use of patient controlled anesthesia (PCA) with a low histamine release and easy-to-titrate opioid such as hydromorphone, fentanyl or even remifentanyl.

It is worth remembering that local or metastatic recurrences have been found in 5% of patients on 5-year follow-up after complete tumor resection (8). The risk or recurrence is higher in young patients (< 20 yrs), and in patients with syndromic presentation, paragangliomas and larger neoplasms (15).

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ARG, HPZ, LFVJ: Design of the proposal, review of the literature, writing and approval of the manuscript.

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