

Pheochromocytoma, the Challenge to Anesthesiologists

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Abstract

Once the diagnosis of pheochromocytoma is made, the tumor must be localized and pre-treated before surgical resection. The operation is usually delayed until hypertension is controlled. A good preoperative preparation including also hormonal evaluation, careful and smooth induction of anaesthesia, good collaboration between the surgeon and anaesthesiologist, and finally taking care in the postoperative period, are the most important steps of the treatment. These are also the focus data, mentioned by several authors in their papers regarding the successful treatment of pheochromocytoma, considered as a challenge to the anaesthesiologist.

Keywords: Adrenal gland; Pheochromocytoma; α -blocking agents

Introduction

Pheochromocytoma is a neuroendocrine tumor arising from chromaffin cells in the adrenal medulla causing less than 0.1% of all cases of hypertension [1-3]. Usually, tumors are benign but in 10% of the cases it may be malignant. These tumors may secrete the catecholamines (dopamine, norepinephrine, and epinephrine) which explain all the clinical manifestations of the tumors. In rare cases there are neuroendocrine chromaffin tumors that arise outside of the adrenal medulla referred as paragangliomas.

This tumor is occasionally familiar or part of the multiple endocrine adenoma type IIa or type IIb. Type IIa con-

sists in medullary carcinoma of the thyroid, parathyroid adenoma or hyperplasia, and pheochromocytoma. Type IIb is pheochromocytoma in association with phakomatoses such as von Recklinghausen's neurofibromatosis and von Hippel-Lindau disease [2].

The clinical manifestations of a pheochromocytoma depend on the profile of catecholamine secretion: If the tumor secretes norepinephrine, clinical picture is associated with hypertension. If epinephrine is the major secreted catecholamine, tachycardia, tachydysrhythmias and hypotension often result.

Pheochromocytoma presents a great challenge to the anesthesiologist, referring to differential diagnosis and the clinical features as hypertension, tachycardia and dysrhythmias, cardiac ischemia or myocardial dysfunction, hyperglycemia, intravascular volume depletion, and lactic acidosis. Twenty-five percent to 50% of hospital deaths in patients with pheochromocytoma occur during induction of anaesthesia or during operative procedures for other causes [2, 4].

Diagnosis

Diagnosis is based on clinical manifestations (excessive sweating; headache; hypertension; orthostatic hypotension; previous hypertensive or arrhythmic response to induction of anaesthesia or to abdominal examination; paroxysmal attacks of sweating, headache, tachycardia, and hypertension; glucose intolerance; polycythemia; weight loss; and psychological abnormalities), on MRI, CT, and finally in laboratory examinations [5] (Table 1).

Preoperative Preparation and Evaluation

A patient with a known pheochromocytoma scheduled for tumor resection undergoes intensive preoperative medical pretreatment. The main problems are as follows [1-3, 5-8]:

1. Medical control of blood pressure;
2. Correction of intravascular volume;
3. Assessment of end-organ consequences of the disease

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Table 1. Characteristics of Tests for Pheochromocytoma [2]

Test/Symptoms	Sensitivity (%)	Specificity (%)	Likelihood Ratio	
			Positive Result	Negative Result
Vanillylmandelic acid excretion	81	97	27.0	0.20
Catecholamine excretion	82	95	16.4	0.19
Metanephrine excretion	83	95	16.6	0.18
Abdominal computed tomography	92	80	4.6	0.10
Concurrent paroxysmal hypertension, headache, sweating, and tachycardia	90	95	18.0	0.10

(e.g., cardiomyopathy);

4. Normalization of glucose and electrolyte levels;
5. Hormonally evaluation of the patient.

The aims of preoperative preparation are to prevent an acute hypertensive crisis in the operating room and then to minimize catecholamine induced hemodynamic changes during anesthesia and surgery. The preoperative evaluation (Table 2) and adequate preparation is defined when systemic blood pressure is below 160/90 mmHg, no orthostatic hypotension, no ventricular premature beats and changes in ST morphology.

Regarding the elevated blood pressure several regimens have been reported in the preoperative period. Phenoxybenzamine, a nonselective, noncompetitive, long acting α -adrenergic blocker for many years has been a mainstay of therapy [1-11]. Because some patients may be very sensitive to the effects of phenoxybenzamine, it should be given initially in doses of 20 to 30 mg/70 kg orally once or twice a day. Most patients usually require 60 to 250 mg/day. The efficacy of therapy should be judged by the reduction of symptoms (especially sweating) and stabilization of BP. The optimal duration of α -blockade therapy may last

from 3 days to 2 weeks. Because of its prolonged effect on α -receptors, it has been recommended to discontinue it 24 to 48 hours before surgery, in order to avoid refractory or severe hypotension after the adrenal gland has been removed. Short-acting, selective, competitive α 1-adrenergic receptors blockers (e.g., doxazosin 2 - 6 mg daily) have been used to prepare patients for surgery [2, 5, 8, 10-12]. A potential advantage of competitive, selective α 1-blockade is that, once the tumor has been resected and excess catecholamine release eliminated, α -adrenergic receptors return quickly to normal function, leading to less hypotension. In our institution, during the period 2006 - 2009 we have performed 19 open adrenalectomy catecholamine secreting hormones. We preferred always Doxazosin for preoperative treatment. Tachycardia as a consequence of elevated catecholamine levels must be treated with β -blockers. The β -blockade must not be instituted before initiation of α -blockade so that α -adrenergic activation would be unopposed in the vasculature. Propranolol, a non selective $\beta_{1,2}$ -blocker with a half-life greater than 4 hours, is most frequently used. Most patients require 80 to 120 mg/day. Some patients with epinephrine-secreting pheochromocytomas, may need doses up to 480

Table 2. Preoperative Evaluation of Patients With Pheochromocytoma

	Definition
Cardiovascular	Palpitations, tachycardia, diaphoresis, pallor, angina, history of myocardial infarction, dyspnea, orthopnea, hypertension, heart rate, congestive heart failure (S ₃ or S ₄ gallop, jugular venous distention, pulmonary crackles), intravascular volume depletion (orthostatic hypotension, dry mucous membranes, poor skin turgor)
Neurologic	Headache, diaphoresis, feelings of apprehension
Gastrointestinal	Abdominal pain, nausea, malnutrition, gastrointestinal bleeding, diarrhea, palpation may precipitate a crisis

mg/day. Other drugs, including prazosin, calcium channel blocking drugs [13], magnesium [14-16], clonidine and dexmedetomidine [17], have also been used to achieve suitable degrees of α -adrenergic blockade before surgery. The combination of Doxazosin with a calcium channel blocker (verapamil 120 - 240 mg every day or nifedipine 30 - 90 mg every day) is an effective combination for resistant cases.

Intraoperative Management

Laparoscopy remains gold standard, having some advantages to open surgery, except paragangliomas resection [5, 9, 18].

Invasive monitoring and central vein access is crucial. The use of all the drugs that increase sympathetic tone, like ketamine, ephedrine, pancuronium, desflurane, must be avoided.

Anesthesia induction and tracheal intubation must be smooth in order to avoid hypertension and tachycardia. Several drugs or techniques are proposed to blunt sympathetic response such as: opioids, esmolol, nicardipine, nitropruside, nitroglycerin, magnesium sulfate, fenoldopam, urapidil [11].

During the surgical manipulations, brisk hemodynamic changes may happen. The hypertension control is often attained by nitropruside, nicardipine, propofol, nitroglycerine, magnesium and/or by deepening the anesthesia. Tachyarrhythmias are often controlled by β -adrenergic blocking agents like esmolol, metoprolol.

Volume depletion correction is important and it is performed by infusion of crystalloids or colloids.

After the adrenal gland has been removed, the hypotension may be severe and it can be controlled by epinephrine, norepinephrine, dopamine or vasopressin [19], especially in the patients receiving phenoxybenzamine.

Postoperative Considerations

Postoperative care remains crucial and is focused on metabolic changes like hyperglycaemia and decreased cortisol level, pain treatment and residual postoperative hypertension [8, 13, 19]. The differential diagnosis for persistent hypertension includes a missed pheochromocytoma, surgical complications with subsequent renal ischemia, and underlying essential hypertension.

In addition to the reduction in plasma catecholamines and third-space fluid losses, the residual effects of phenoxybenzamine and α -methylparatyrosine, secondary to long half-lives, are present for up to 36 hours. Thus the hypotension may be present. Vasopressor therapy may be necessary if hypotension occur. Steroid supplementation is necessary for patients who had bilateral adrenalectomies or if hypoad-

renalism is suspected.

The need for controlled ventilation is dictated by the extent of surgery, the site of surgery, and the patient's medical condition.

Aggressive postoperative acute pain treatment is essential. Pain relieving reduce pulmonary and thromboembolic events, the likelihood of residual hypertension, and enhance the quality of life in the early postoperative period.

After the patient discharged, he must be referred to an endocrinologist for further follow-up.

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