REVIEW PAPER

UROLOGICAL ONCOLOGY

Adrenergic crisis due to pheochromocytoma – practical aspects. A short review

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Introduction The definitive therapy in case of pheochromocytoma is complete surgical resection. Improper preoperative assessment and medical management generally places the patient at risk for complications, resulting from an adrenergic crisis. Therefore, it is crucial to adequately optimize these patients before surgery. Optimal preoperative medical management significantly decreases morbidity and mortality during the tumor resection.

Material and methods This review addresses current knowledge in pre– and intraoperative assessment of a patient with pheochromocytoma.

Results Before surgery the patient is conventionally prepared with α–adrenergic blockade (over 10–14 days) and subsequently, additional β–adrenergic blockade is required to treat any associated tachyarrhythmias. In preoperative assessment, it is obligatory to monitor arterial blood pressure, heart rate, and arrhythmias and to restore the blood volume to normal.

Conclusions In conclusion, due to the pathophysiological complexity of a pheochromocytoma, the strict cooperation between the cardiologist, endocrinologist, surgeon and the anaesthesiologist for an uneventful outcome should be achieved in patients qualified for the surgical removal of such a tumor.

Key Words: adrenergic crisis ‹› pheochromocytoma ‹› surgery

Adrenergic crisis is not a rare phenomenon associated with pheochromocytoma. The factors triggering an adrenergic storm are attributed to excessive release of catecholamines from the pheochromocytoma tumor secondary to anxiety of the patient, or secondary to the induction of anesthesia and intubation. Moreover, these hormones released may be induced by drugs due to dopamine receptor blockade (e.g. droperidol), histamine release (e.g. morphine, atracurium), sympathetic stimulation (e.g. pancuronium), anticholinergic drugs (e.g. atropine), or catecholamine–sensitizing anesthetics (e.g. halothane, desflurane). Additionally, squeezing of the tumor during straining, positioning of the patient, by scrubbing, by intraperitoneal carbon dioxide insufflations during laparoscopy, or by direct manipulation of the tumor may induce adrenergic storm. Previously, the pheochromocytoma crisis was also associated with contrast media. In pregnancy excessive uterine contractions, fetal movements, normal vaginal delivery or Cesarean section may precipitate the adrenergic crisis [1]. The perioperative pheochromocytoma crisis may mimic other conditions such as a thyroid storm [2] or a malignant hyperthermia [3].

Pheochromocytomas are rare, catecholamine–secreting (predominantly norepinephrine) tumors arising from chromaffin cells of the adrenal medulla. Additionally, other substances are released by such a tumor, such as: dopamine, VIP, adrenocorticotropic hormones, and β–endorphins. Once the pheochromocytoma has been diagnosed, the mainstay of definitive therapy is complete surgical resection. Surgery

is not routinely advocated for the treatment of acute hyperadrenergic crisis. Prior to surgery, the effects of excess release of catecholamines must be minimized in order to avoid perioperative complications and improve outcomes [4, 5]. Surgical resection of the pheochromocytoma tumor is the only curative procedure. Laparoscopic adrenalectomy (LA) is a well–approved operative technique. The indications for LA include primary hyperaldosteronism, pheochromocytomas, and glucocorticoid secreting adrenal tumors. Szydelko et al. reported 16 pheochromocytomas among the group of 80 patients who had undergone LA [6].

Surgical resection of pheochromocytoma without preoperative medical preparation and intraoperative support places the patient at higher risk for complications from hemodynamic instability and hypertensive crises. Therefore, it is crucial to adequately optimize the patient with pheochromocytoma before surgery. Optimal preoperative medical management significantly decreases morbidity and mortality during the surgery [7]. Emerson et al. reported the decrement in mortality rate due to pheochromocytoma resection from 40–60% to 0–6% over the last 50 years [8]. In preoperative assessment it is obligatory to monitor arterial blood pressure, heart rate and arrhythmias and to restore the blood volume to normal. Additionally, anesthesiologists are obliged to assess the severity of hypertension and look for any end–organ damage, especially catecholamine induced cardiomyopathy [9, 10].

Before surgery, the patient is conventionally prepared with α–adrenergic blockade (over 10–14 days) and subsequently, additional β–adrenergic blockade is required to treat any associated tachyarrhythmias [9, 11]. A non–competitive, non–selective α–adrenergic blocker (phenoxybenzamine) is commonly used for α–receptor blocking. The treatment is typically started 7–21 days prior to surgery at 10 mg once or twice daily and increased by 10–20 mg every 2–3 days for optimal blood pressure and symptom control. If the side effects of phenoxybenzamine (e.g. orthostatic hypotension, fatigue, nasal congestion, nausea, etc.) become intolerable, alternative drugs may be considered (e.g. doxazosin, terazosin, etc.) [4]. In addition, selective competitive α1–adrenergic antagonists are preferably used in some cases because such drugs do not induce reflex tachycardia and can be adjusted rapidly before surgery due to a shorter duration of action [12]. Kinney et al. [13] observed significant increases in arterial blood pressure especially during tumor manipulation, despite preoperative α–adrenergic blockade. Thus, α– and β–blockade should be continued until the day of the pheochromocytoma resection except for phenoxybenzamine, which may be stopped the day before surgery as it has a long half life and can cause postoperative hypotension [14]. The tachycardia induced by α–receptor blockade can be suppressed by carefully introducing β–adrenergic blockers (e.g. atenolol: 100 mg, bisoprolol: 10–20 mg). Moreover, β–receptor blockade should never be instituted until α–receptor blockade is fully established as unopposed α–stimulation may lead to severe hypertension [12]. Also, a calcium channel blocker (nifedipine: 30–90 mg) has been employed in the hemodynamic control [14]. Many data suggest a growing evidence about the effectiveness of these blockers as first line agents. Walz et al. [15] routinely used high–dosage alpha–blockade with phenoxybenzamine in 126 patients, with pheochromocytoma and retroperitoneal paragangliomas, who qualified for surgery. Moreover, it is worth to note that randomized clinical trials showed that in the case of 73 patients without an α–receptor blockade before the resections of a catecholamine–producing tumor, there were no significant differences in the maximum systolic blood pressure or in the incidence of hypertensive episodes during surgery [16]. Preoperative sedation and anxiolysis using benzodiazepines provides the reduction of anxiety and prevents significant hemodynamic fluctuation during the induction of anesthesia [9]. Close communication between the surgeon and the anesthesiologist is absolutely crucial to the success of intraoperative management of patients undergoing resection of a pheochromocytoma [17]. In general a mid to low thoracic epidural anesthesia combined with adequate general anesthesia and selective adrenergic antagonists is sufficient for proper control of hemodynamic surges in response to tumor manipulation and catecholamine release [18]. It should be taken into careful consideration during surgery that a sudden decrease in the circulating catecholamines may occur after the adrenal vessels ligation, leading to hypotension. Thus, the vasodilatatory agents should be discontinued and a modest fluid bolus should be given. Also, an infusion of a vasoconstrictor agents (e.g. norepinephrine, phenylephrine) may be required temporarily [17]. Several factors associated with increased risk of intraoperative hemodynamic instability were described, as follows: 1) higher norepinephrine plasma level, 2) tumor size larger than 4 cm, 3) postural hypotension following blockade of α–receptors [19]. Thus, strict intraoperative monitoring is crucial due to the higher risk of complications associated with the resection of catecholamine secreting tumors. Severe arterial hypertension should be treated with intravenous administration of sodium nitroprusside (SM) and phentolamine (short acting α–blocker). SM is preferred due to the rapid vasodilatory properties

and shorter duration of action. It should be started at 0.5–5.0 mcg/kg of body weight per minute and titrated for optimal blood pressure response. In case of arrhythmia development, the use of esmolol or lidocaine should be considered [4]. Moreover, the most common postoperative complications after adrenalectomy are hypoglycemia and arterial hypotension. Hypoglycemia accounts for 10–15% of patients after pheochromocytoma resection. In such cases insulin is no longer suppressed by excess catecholamines, which are removed from circulation after adrenalectomy. On the other hand, hypotension resistant to conservative therapy (e.g. intravenous fluid replacement), especially in the setting of bilateral adrenal manipulation, should raise suspicion for adrenal insufficiency and be treated with stress doses of glucocorticoids and intravenous pressors to maintain adequate arterial blood pressure [20].

In conclusion, due to the pathophysiological complexity of pheochromocytoma, the strict cooperation between the cardiologist, endocrinologist, surgeon and the anaesthesiologist for an uneventful outcome should be achieved in patients qualified for the surgical removal of such a tumor.

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