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Original research

Laparoscopic adrenalectomy, a safe procedure for pheochromocytoma. A retrospective review of clinical series

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ABSTRACT

Background: Minimally invasive adrenalectomy for pheochromocytoma (PCC) is a complex surgical procedure especially because of the haemodynamic instability due to the excessive secretion of catecolamines, which may result in a considerable risk of conversion and complications.
Aim: By a multicentric retrospective study, the authors reported the results of laparoscopic adrenalectomies in patients operated for adrenal pheochromocytomas with the aim of investigating the role of the laparoscopic approach in managing adrenal disease.
Methods: Sixty patients, preoperatively treated with a selective alpha1-blocker, underwent 61 laparoscopic adrenalectomies for PCC smaller or larger than 6 cm – group A (≤6 cm), group B (>6 cm). We compared the two groups of patients analyzing haemodynamic instability, operative time, conversion rate, incidence of complications, length of hospital stay and medium and long-term outcomes.
Results: In 23 cases tumor was >6 cm in diameter. Average operative time was 165 min, with a 5% conversion rate. There was no mortality and morbidity rate was 8.3%. Intraoperative hypertensive crises were registered in 15% of patients, whereas 5/60 patients had hypotensive crises. After comparing the two groups of patients, no statistically significant differences in terms of haemodynamic instability, operative time, conversion rate, morbidity and length of hospital stay were observed.
Conclusions: As a surgical treatment of pheochromocytomas, laparoscopic adrenalectomy is an effective and safe approach, in selected cases even for PCCs >6 cm in diameter, although patients with such large tumors may have a higher conversion rate and more intraoperative hypertensive crises. Preoperative selective adrenergic blockade does not prevent intraoperative hypertensive crises, but by facilitating the pharmacological management of the perioperative haemodynamic instability, may avoid the onset of major adverse cardiovascular complications.

1. Introduction

Pheochromocytoma (PCC) is a rare neuroendocrine tumor, with a prevalence ranging between 0.1% and 0.6% in patients suffering from arterial hypertension.[1] Minimally invasive adrenalectomy (MA), which is associated with less pain, a lower morbidity rate, a shorter hospital stay, a more rapid recovery and a better cosmetic result than "open" surgery, is the gold standard for the treatment of adrenal tumors ≤6 cm in diameter and weighing <100 g.[2] An analysis of the published studies on PCC surgery, which only rarely involve case series of more than 50 patients, shows that the minimally invasive approach has significant advantages.[3] However, the role of laparoscopy in treating PCC >6 cm in diameter is still controversial for the presumed higher risk of malignancy and of local recurrence rate, and moreover it may be associated with longer operative times, a greater blood loss, a higher conversion rate, and several complications as well. Preoperative blood pressure

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control, a reduced manipulation of the adrenal gland and sparing of the adrenal capsule are the treatment guidelines. Provided that there is no evidence of local invasion or of supposed malignancy, laparoscopic adrenalectomy (LA) is successfully carried out even for patients with PCC >6 cm in diameter, but this indication is at present matter of debate.

We report the results of a multicentric retrospective study of 60 patients with PCC smaller or larger than 6 cm – group A (≤6 cm), group B (>6 cm), who underwent LA after preoperative selective adrenergic blockade with doxazosin. The purpose of the study was to compare haemodynamic instability, operative time, conversion rate, incidence of complications, length of hospital stay and medium and long-term results in both of the groups of patients.

2. Materials and methods

This study was accomplished by four surgical centers with a wide experience in adrenal surgery (two academic centers and two endocrine-surgery centers). A retrospective analysis was obtained from questionnaires in which patients data were collected, with details of the preoperative laboratory tests and diagnostic procedures for PCC, tumor size, perioperative complications, operative time, length of hospital stay, along with clinical, laboratory, and instrumental examinations after a five years follow-up. The sixty patients included in the study, suffering from either preoperative stable or paroxysmal hypertension associated with other signs or symptoms of cathecolamine excess, underwent laparoscopic adrenalectomy and were grouped according to the tumor size (group A ≤6 cm; group B >6 cm) (Table 1). Whenever malignancy was assumed, for local invasion or distant metastases, a minimally invasive approach was contraindicated. According to Zhu et al.,[4] until blood pressure (BP) and heart rate (HR) stabilization was achieved, (BP <160/90 mmHg for at least 24 h before surgery and HR <100 bpm), in absence of electrocardiographic ST-T changes for at least 1 week, every patient started a preoperative drug therapy, consisting of an alpha1-blocker – doxazosin, at least 15 days before surgery, with a mean daily dose of 4.54 ± 1.65 mg and a mean length of therapy of 21.15 ± 5.91 days. A beta-blocker (atenolol, 50 mg daily) was added in 6 cases with tachycardia (10%). A calcium antagonist (amlodipine besylate, 5 mg daily) in 3 cases (5%), an angiotensin receptor blocker (valsartan, 160 mg daily) in 2 cases (3.3%), and an angiotensin-converting enzyme inhibitor (ramipril, 10 mg daily) in 2 cases (3.3%) represented the associated preoperative drug therapy. Every patient underwent perioperative venous thromboembolism prevention. According to J. Varon,[5] systolic blood pressure (SBP) levels ≥180 mmHg or diastolic blood pressure (DBP) levels ≥120 mmHg were considered hypertensive crises, and levels <90 mmHg were considered hypotensive crises. For each case anesthesia chart and pathologic report were obtained. In 10/60 patients (16.6%), by means of blood samples and sometimes specimen samples, a genetic study looking for mutations of the RET protoncogene was performed. Diagnostic work-up included ultrasonography, CT scanning with contrast agent, Magnetic Resonance Imaging (MRI), whole body metaiodobenzylguanidine (MIBG) scintigraphy in order to confirm PCC diagnosis, and echocardiography. Patients were discharged if they had no cardiovascular complains or pain and had begun oral feeding. Follow-up consisted of 6-monthly, then yearly testing of urinary metanephrine levels and abdominopelvic CT scans with contrast agent.

2.1. Anesthesiological management

In each case, in order to expand plasma volume, intravenous volume loading was carried out in the preoperative holding area. Patients received general anesthesia, with no epidural anesthesia. All operations were undertaken by orotracheal intubation, without anesthetizing upper airway. Invasive arterial pressure monitoring was routinely performed. A central venous catheter was placed before every intervention. No pulmonary artery catheters (Swan-Ganz catheters) were used. Haemodynamic data were recorded. Heart rate, systolic and diastolic blood pressure were recorded before inducting anesthesia, after CO_2 inflation, before and after adrenalectomy. After inducing anesthesia with remifentanil (0.25 mcg/kg/min) and propofol (2 mg/kg), cisatracurium besylate (0.2 mg/kg), which was also used as muscle relaxant during surgery, was administered. Anesthesia was maintained with inhalation of sevoflurane and nitrous oxide 50% in oxygen, supplemented with remifentanil infusion. Intraoperative muscle relaxation was maintained with intermittent boluses. Blood loss and fluid volume loading during surgery were also recorded. Intraoperative treatment of hypertensive crises consisted of intravenous administration of nitroprusside (initial dose: 0.2 mcg/kg/min, administered by continuous intravenous infusion; maintenance dose was titrated up to a maximum of 10 mcg/kg/min), esmolol (1 mg/kg bolus dose over 30 s, followed by a 150 mcg/kg/min infusion, whenever necessary, adjusting the infusion rate as required up to 300 mcg/kg/min to maintain the desired HR and/or BP), urapidil (starting dose: 0.25–0.4 mg/kg or 25 mg; maintenance dose: 9 mg/h of continuous intravenous infusion), clonidine (single bolus: 75–150 μg in 5 min, or by continuous infusion: 0.4–5 μg/min).

Table 1
Patients data and pheochromocytoma size.

	Group A ≤6 cm 37 patients (61.6%)	Group B >6 cm 23 patients (38.3%)	*p*-value
Mean age (years)	44.16	39.56	0.03
Male patients	8 (21.6%)	13 (56.5%)	0.01
Site			
right	20 (54%)	11 (47.8%)	0.7
left	18 (48.6%)	12 (52.1%)	
Mean size (cm)	3.9	8.3	0.001
ASA score			
1–2	23 (62.1%)	15 (65.2%)	1.0
3–4	14 (37.8%)	8 (34.7%)	
Mean 24 h urinary catecholamines (pg/dl)	585.62 (120–1800)	751.17 (147–3490)	0.1

2.2. Surgery

Every adrenalectomy was performed using transperitoneal laparoscopy, with the patient positioned in the lateral decubitus. Four trocars were inserted in the case of a right PCC and three in the case of a left one, while one supplementary trocar was used in 11/60 cases (18.3%). In one case of bilateral adrenalectomy, after removing the first gland, the patient was repositioned on the table for the second, separate procedure. Carbon dioxide pneumoperitoneum was kept at 12–14 mmHg. According to "vein first" technique, at the beginning of the operation, the main adrenal vein was identified and divided between clips. In the cases of right PCC >6 cm, procedure began with superior and lateral mobilization of the adrenal gland to facilitate identification of vena cava and right renal vein, followed by the section of the main adrenal vein. In most patients adrenal gland dissection was carried out by ultrasonic or bipolar shears. Surgical specimens were always extracted through a mini-laparotomy at the site of a trocar, using a specimen extraction bag. A drainage tube, usually preferred by the surgeons participating to this study, was routinely placed and then removed after 1–2 days. Postoperatively, patients were not routinely referred to the Intensive Care Unit. No patient received epidural analgesia.

3. Statistical analysis

Data were expressed as mean ± SEM, unless otherwise specified. Statistical analysis was performed with SPSS version 11.5 (SPSS©, Chicago, IL, USA). Significance was assigned with a *p*-value <0.05.

4. Results

4.1. Patient demographics

Our series consisted of 60 patients, 39 women and 21 men, with a mean age of 42.4 ± 14.38 years, who underwent a total of 61 LAs, between January 1998 and December 2011. No cases of preoperative stroke were reported. Associated diseases of interest included insulin-dependent diabetes mellitus in 13 cases (21.6%) and dilated cardiomyopathy in 4 cases (6.6%). There was one case (1.66%) of a genetically determined polyendocrine syndrome: multiple endocrine neoplasia (MEN) 2A with a triple RET mutation (634, 640, 700).[6] Urinary catecholamines were elevated in 58/60 patients. Preoperative 24-h mean concentration was 649.08 ± 548.885 pg/dl (n.v. = 0–115 pg/dl), respectively 585.62 ± 395.44 in group A and 751.17 ± 740.28 in group B. Thirty cases of PCC in the right adrenal gland, 29 in the left adrenal gland and 1 bilateral tumor were reported with an average diameter of 5.6 cm (3.9 cm group A–8.3 cm group B) (range 2.4–11 cm). In 23/60 patients (38.3%) the tumor was larger than 6 cm, in 37/60 (61.6%) the PCC was equal to or smaller than 6 cm (Table 1). Preoperative treatment with doxazosin was well tolerated without important side effects, allowing an efficacious BP and HR control.