Role of Preoperative **Adrenergic Blockade** with Doxazosin on Hemodynamic Control during the Surgical Treatment of Pheochromocytoma: A Retrospective Study of 48 Cases

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HEADNOTE

Authors evaluated the effects of selective adrenergic blockade by means of doxazosin on blood pressure in 48 patients operated on for pheochromocytoma by a multicenter retrospective study. Age, tumor size, surgical approach, and operative time were analyzed as predictive factors of intraoperative hypertensive crises. Forty-eight patients underwent adrenalectomy-four open surgery and 44 laparoscopic surgery—for pheochromocytoma of adrenal glands from 1998 to 2008 after preoperative administration of doxazosin. Perioperative cardiovascular status modifications and surgical medium- and long-term outcomes were analyzed. There was no mortality, conversion rate was 4.5 per cent, and morbidity rate was 8.3 per cent. Intraoperative hypertensive crises (180/90 mmHg or higher) were observed in 14.5 per cent (seven of 48) of patients and were treated pharmacologically with no aftermath. None of the examined variables influenced the occurrence of intraoperative hypertensive episodes. Postoperative hypotension (lower than 90/60 mmHg) was observed in four of 48 patients (8.3%) and was treated by crystalloids and hydrocortisone. In the surgical treatment of pheochromocytoma, the preoperative adrenergic blockade by doxazosin does not prevent intraoperative hypertensive crises. Nevertheless, in our series, they were of short duration and were not associated with major cardiovascular complications. Perioperative hemodynamic instability was managed by preoperative pharmacological treatment, allowing low morbidity.
PHEOCHROMOCYTOMA (PCC) is a rare neuroendocrine tumor with prevalence ranging between 0.1 and 0.6 per cent in individuals with hypertension.1 Although most PCCs are thought to be sporadic, over one-third are associated with 10 known susceptibility genes.2, 3 The first successful resection of a pheochromocytoma was described by Roux in 1926.4 Progress in the fields of anesthesiology and surgery, a better understanding of the disease pathophysiology,5 and a preoperative appropriate blood pressure control allowed the decrease of mortality rates associated with PCC surgery as well as the morbidity resulting from intra- and postoperative cardiovascular hemodynamic disorders.6-8

However, in pheochromocytoma surgery, there is a high risk of hypertensive events because of the excessive catecholamine secretion, especially during tumor manipulation, and so appropriate drug therapy is recommended, but an "ideal" protocol is still the subject of controversy.

Selective a1 blockers-prazosin, doxazosin, terazosin- have been introduced to avoid the main side effects such as tachycardia, orthostatic hypotension, sedation, and any delayed therapeutic effect of phenoxybenzamine, which first had been considered the drug of choice for treating paroxysmal hypertension for a long time.

The aim of our study was to evaluate the role of the adrenergic blockade by doxazosin in managing perioperative pressure in 48 patients undergoing adrenalectomy for PCC. The influence of age, tumor size, surgical approach, and operative time on the intraoperative hypertensive crises was also evaluated.

Materials and Methods

The study was multicentric and retrospective. We performed a review of all the recorded clinical data of the patients who underwent adrenalectomy for pheochromocytoma between January 1998 and January 2008. Data were obtained by a questionnaire sent to four specialized centers in the Campania region (Italy) with a large experience in adrenal surgery and by surgeon recalls. Three of the centers are endocrine surgery units, and two are university centers. In most cases, patients were referred to surgery by regional endocrinological centers.

The questionnaire contained items about patients, pathology, surgery, and intraoperative blood pressure (BP) levels.

Diagnostic imaging consisted of ultrasonography, computed tomography (CT), magnetic resonance, metaiodobenzylguanidine scintigraphy, and echocardiography in each case.

Influence of age, tumor size, surgical approach, and operative time in case of intraoperative hypertensive episodes was also evaluated. According to Varon,9 systolic blood pressure (SBP) levels 180 mmHg or higher or diastolic blood pressure (DBP) levels 120 mmHg or higher were considered hypertensive crises, and levels lower than 90 mmHg were considered hypotensive crises.

Anesthesia chart and pathology reports of each patient were obtained.
Forty-eight patients, with either preoperative stable or paroxysmal hypertension, who underwent adrenalectomy, were included in the study (Table 1).

According to Zhu,6 until BP and heart rate (HR) stabilization is achieved (BP lower than 160/90 mmHg for at least 24 hours before surgery and HR lower than 100 beats/min), in absence of electrocardiographic ST-T changes for at least 1 week, every patient started a preoperative drug therapy consisting of an a1 blocker, doxazosin, at least 15 days before surgery with an average daily dose of 4.66 ± 2.39 mg and an average length of therapy of 22.6 ± 4.66 days. A b-blocker (atenolol, 50 mg daily) was added in five cases with tachycardia (10.4%). A calcium antagonist (amlodipine besylate, 5 mg daily) in two cases (4.16%), an angiotensin receptor blocker (valsartan, 160 mg daily) in one case (2.1%), and an angiotensin-converting enzyme inhibitor (ramipril, 10 mg daily) in one case (2.1%) represented the associated preoperative drug therapy. In each case, plasma volume was preoperatively expanded by crystalloid solutions. Postoperative hypotensive crises were treated by hydrocortisone and crystalloids.

Postoperatively, patients were not routinely referred to the intensive care unit. No patient received epidural analgesia.

Patients were discharged if they had no cardiovascular complains or pain and had begun oral feeding.

Follow-up consisted of 6 months then yearly testing of urinary metanephrine levels and contrast-enhanced abdominopelvic CT scans.

Anesthesia

Patients received general anesthesia without epidural anesthesia. All operations were undertaken by orotracheal intubation without anesthetizing the upper airway. Invasive arterial pressure monitoring was routinely performed. A central venous catheter was placed before every intervention. No pulmonary artery catheters (Swan-Ganz catheter) were used. Hemodynamic data were recorded. Heart rate, SBP, and DBP were recorded before inducting anesthesia, after CO2 inflation, before and after adrenalectomy. After induction of anesthesia, with remifentanil (0.25 mg/kg/min) and propofol (2 mg/kg), cisatracurium besylate (0.2 mg/kg), which was also used as a muscle relaxant during surgery, was administered. Anesthesia was maintained with inhalation of sevoflurane and nitrous oxide 50 per cent 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 mg/kg/min, administered by continuous intravenous infusion; maintenance dose was titrated up to a maximum of 10 mg/kg/min), esmolol (1-mg/kg bolus dose over 30 seconds followed by a 150-mg/kg/min infusion, whenever necessary, or a loading dosage infusion of 500 mg/kg/min for 1 minute followed by a 4-minute maintenance infusion of 50 mg/kg/min, adjusting the infusion rate as required up to 300 mg/kg/min to maintain the desired HR and/or BP), urapidil (starting dose: 0.25 to 0.4 mg/kg or 25 mg; maintenance dose: 9 mg/hour of continuous intravenous infusion), or clonidine (single bolus: 75 to 150 mg in 5 minutes, or by continuous infusion: 0.4 to 5 mg/min).

Surgery

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Surgery

Data were analyzed by using SPSS Version 14.0 (SPSS Inc., Chicago, IL). Yates-corrected x2 test was used to evaluate differences in categorical variables, and an independent sample test was used for continuous variables. A P value < 0.05 defined statistical significance.

Results

Patients Demographics

Thirty-two women and 16 men, with a mean age of 44.35 ± 15.43 years, were enrolled. Twenty-three cases of PCC in the right adrenal gland, 24 in the left adrenal gland, and one bilateral tumor were reported. Associated diseases included insulin-dependent diabetes in nine patients (18.7%) and dilated cardiomyopathy in two patients (4.16%). Only eight of 48 cases (16.6%) were investigated for mutations of the RET protooncogene. There were two cases of genetically determined polyendocrine syndromes: a multiple endocrine neoplasia (MEN) type 2A as a result of a triple mutation of the RET proto-oncogene (634,640,700)10, 11 and a neurofibromatosis 1.

Preoperative mean 24-hour urinary catecholamine concentration was 620.5 ± 577.27 pg/dL (normal value, 0 to 115 pg/dL) and PCC mean size was 6.12 ± 2.75 cm. Preoperative treatment with doxazosin was well tolerated without important side effects, allowing efficacious BP and HR control.

Surgical Outcomes

With regard to the operative approach and PCC size-seven of 48 PCCs greater than 8 cm-LA was performed in four patients with PCC larger than 8 cm, whereas in the last three cases, OA was preferred. A more accurate comparison between OA and LA was not performed because of the small number of OA (four of 48 patients [8.33%]). The overall mean operative time was 159.9 ± 60.60 minutes (Table 1), 182.5 ± 13.22
Both in open and laparoscopic adrenalectomy, mean blood loss was 120 ± 61.48 mL also if PCC was larger than 6 cm (respectively, 4 of 4 open and 13 of 44 laparoscopic). Blood transfusion was required in one case of PCC smaller than 6 cm in diameter for an adrenal capsular hemorrhage during laparoscopic adrenalectomy. There was no mortality. Morbidity rate was 8.3 per cent (4 of 48 patients) and consisted of one case of abdominal wall hematoma (laparoscopic), one case of delayed wound healing (in a diabetic patient, laparoscopic), one serosanguineous fluid collection in the adrenal region associated with high fever (40°C; open), treated by percutaneous ultrasound-guided drainage, and a case of pneumothorax (laparoscopic), which resolved after pleural drainage. No patient had hypoglycemic crises. Conversion to open surgery was necessary in two of 44 patients (4.54%), in one case as a result of suspected infiltration of renal vessels, not confirmed by pathology, which found a desmoplastic reaction, and in the other case because of adhesions between the gallbladder and right colon.

There was no relationship between preoperative doxazosin dose and intraoperative hypertensive crises, which occurred at induction of anesthesia and during handling of adrenal glands in seven of 48 patients (14.5%) (2 of 4 patients open, 5 of 44 patients laparoscopic) (Table 1). At induction, two of 48 patients (4.1%) had paroxysmal hypertension with peaks of 180/90 and 180/120 mmHg with HR of 85 and 90 beats/min resolved after drug therapy. Further episodes of hypertension, with a median BP of 260/160 mmHg (range, 230/160 to 320/150 mmHg) and a mean HR of 94 ± 13.87 beats/min, were observed during manipulation of adrenal glands in four of 48 patients (10.4%) and ceased after adrenalectomy. Hypertensive crises were not associated with any significant complication such as cerebral vascular accident, pulmonary edema, myocardial infarction or ischemia, cardiac arrhythmia, or multiorgan failure, and no postoperative mechanical ventilation was required.

Concerning the relationship between hypertensive crises and PCC size, five patients with PCC ranging between 6 and 16 cm in diameter, two of whom underwent open surgery and three laparoscopic surgery, had the highest BP levels (230/130 to 320/150 mmHg) (Fig. 1). In these cases, the highest BP levels were observed during adrenal gland manipulation in a patient who underwent open surgery to remove a PCC 7 cm in diameter (290/110 mmHg) and in a patient who underwent laparoscopic adrenalectomy to remove a PCC 8 cm in diameter (320/150 mmHg) (Table 1), and the 24-hour preoperative urinary catecholamine concentration was, respectively, 725.5 pg/dL and 655 pg/dL (normal value, 0 to 115 pg/dL).

There was no statistical influence for anyone of the examined variable-age, size, surgical approach, and operative time-on the occurrence of intraoperative hypertensive crises (Table 2). No intraoperative hypotensive episodes were observed.

Postoperative Outcomes

After awakening from anesthesia, two of 48 patients (4.16%) (laparoscopic) were hypotensive (70/40 mmHg, 80/65 mmHg) and were treated by crystalloids and hydrocortisone. On postoperative Day 1, two of 48 patients (4.16%) (laparoscopic) had hypotension (80/60 mmHg, 80/50mmHg), which was successfully treated by hydrocortisone and crystalloids. No relationship was observed between operative time and PCC size (Table 1). Mean hospital stay was 3.72 ± 1.86 days, respectively, 8.25 ± 3.59 days after open surgery and 3.32 ± 1.52 days after laparoscopic adrenalectomy. One male patient, after laparoscopic resection of a PCC less than 6 cm in diameter, was openly reoperated on through a posterior approach as a result of disease.
persistence associated with adrenal retrocaval remnants. Surgical pathology did not report any malignancy. After a 5-year follow-up (3 to 13 years), no complication and/or disease recurrence were observed.

Discussion

In the surgical treatment of pheochromocytoma, because of the excessive release of catecholamines, there is a high risk of hemodynamic disorders and preoperative pharmacological management is recommended. In our practice, a preoperative selective adrenergic blockade with doxazosin did not prevent intraoperative hypertensive episodes, but major related cardiovascular complications—cerebral vascular accident, pulmonary edema, myocardial infarction or ischemia, cardiac arrhythmias, and multiorgan failure—were not observed, although in some patients, SBP rose up to 300 mmHg. A hypotension postoperative rate of 8.32 per cent was reported, and in each case, hypotensive crises were of short duration and were successfully treated by hydrocortisone and crystalloids. A similar incidence is reported in previous papers6, 12-14 after the preoperative administration of selective a blockers or calcium antagonists, whereas longer and more frequent crises are reported after phenoxybenzamine therapy, causing more profound a-blockade.12, 15, 16

We performed a literature review to compare our results.

Alpha Blockers

PCC is a rare tumor, most commonly found in women in their 40s and 50s, and with an annual incidence in the United States of 1.55 to 2.1 per 100,000 individuals.17

The hyperkinetic, vasoconstrictive, hypovolemic hypertension caused by PCC is paroxysmal in 48 per cent of patients and sustained in 29 per cent, whereas the remaining patients are normotensive.2

Before a blockers were introduced in the 1950s, perioperative mortality, currently limited to 0 to 6 per cent,8, 18-20 ranged between 24 and 50 per cent.21, 22

The first drug therapy suggested, after the 1950s, was a combination of b blockers and phenoxybenzamine, a nonselective a blocker, which for a long time had been considered the drug of choice for treating paroxysmal hypertension. It has delayed and unfavorable side effects such as tachycardia, orthostatic hypotension, postoperative hypotension and edema, drowsiness, sedation, hypoglycemia, nasal congestion, miosis, nausea, vomiting, and sexual dysfunction.

Kinney15 reported no mortality and a morbidity rate of 31.5 per cent in 143 patients treated with phenoxybenzamine. The most common complication was persistent hypertension (higher than 180 mmHg for more than 10 minutes).

To avoid the side effects of phenoxybenzamine, selective a1 blockers were used, first prazosin, proposed by Wallace and Gill in 1978, which was not very successful, then terazosin and doxazosin, which are currently widely used. Doxazosin, a competitive selective a1 antagonist, lipophilic with high bioavailability and relatively long-acting (half-life 16 to 30 hours), is administered once daily (1 to 16 mg/day),13, 15 and in our experience, a mean dose of 4.66 ± 2.39 mg daily was effective in preoperative BP control with no important
side effects. It does not cause tachycardia and has a low risk of postoperative hypotension that in our series was 8.32 per cent (four of 48 patients). Tauzin-Fin, in 18 patients treated with an a1 blocker and a b blocker for 15 days preoperatively, reported that an effective preoperative adrenergic blockade does not prevent perioperative hypertensive crises but neutralizes the effects of catecholamines. Pryz-Roberts reported better BP control with 2 to 8 mg/day of doxazosin than with phenoxybenzamine with no hypotension. Kocak, in a retrospective study of 49 patients with PCC, did not find any statistically significant difference between the hemodynamic responses of the patients treated with phenoxybenzamine and of those treated with selective a1 blockers. In our series, hypertensive crises occurred at induction of anesthesia in two of 48 cases (4.1%) and during adrenal gland manipulation in five of 48 patients (10.4%), confirming that "adrenal manipulation" may cause most hemodynamic changes. Alpha 1 blocker therapy, alone or in combination with b blockers, calcium antagonists, or plasma volume expansion, is therefore the most commonly used treatment protocol before PCC surgery.

Calcium Antagonists

Calcium antagonists act on vascular smooth muscle, inhibit calcium-dependent norepinephrine release, and can be combined with blockers. Proye reported good control of BP and peripheral vascular resistance with intraoperative nicardipine. Lebuffe reported mortality of 2.8 per cent (one death resulting from heart failure, one from intraoperative hemorrhage, and one from pulmonary embolism) and postoperative morbidity of 9.5 per cent in 105 PCCs. Systolic blood pressures higher than 220 mmHg, greater than 180 mmHg, and lower than 80 mmHg were recorded in 13, 2.8, and 12.3 per cent of patients, respectively. This author reported that although calcium antagonists cannot prevent all cardiovascular complications in patients with PCC, they reduce mortality and complications. In our analysis, mortality or major cardiovascular complications were not reported, with an incidence of intraoperative hypertensive crises similar to that reported by Lebuffe-14.5 versus 15.8 per cent-with the highest peak of 320/150 mmHg during laparoscopic treatment of an 8-cm PCC.

Preoperative Protocols

About current protocols, van der Horst-Schrivers found that in eight Dutch university hospitals, either phenoxybenzamine or doxazosin is administered for at least 7 days in combination with plasma volume expanders, often with b blockers and never with calcium antagonists. This treatment seems to guarantee the best results.

Reports regarding the effects of the preoperative drug therapy show contradictory data. Most of the cited studies are small, retrospective, containing heterogeneous cohorts of patients in which treatment is not standardized. Perry, in a study of 33 cases, reported a lower rate of hypotension in treated patients but did not observe any difference between mortality rates of treated and untreated patients. Different from our experience, Deoreo, in a study of 46 patients taking no drugs, and Boutros in 63 patients, did not report any benefit from a blocker therapy. Like in our series, Ulchaker, in 113 patients who underwent surgery at the Cleveland Clinic between 1977 and 1994, reported no mortality among patients treated preoperatively with a blockers but more severe cardiovascular complications: three cases of pulmonary edema, two cases of heart failure, and one case of stroke that, however, was never observed in our series. The author therefore concluded that preoperative adrenergic blockade is not essential, and calcium channel blockers are effective in patients with PCC. Newell observed that adrenergic blockade did not prevent intraoperative hypertensive crises, tachycardia, or ventricular arrhythmia. However, Steinsapir reports two deaths among
patients who underwent surgery without preoperative therapy. Zhu6 reported more stable perioperative hemodynamic changes in patients pretreated with doxazosin, irrespective of phenoxybenzamine, in a recent series of 67 cases. Also, Weingarten,16 analyzing the results from two large medical centers, concluded that nonselective a-blockade produces a better decrease of intraoperative hypertension, but it is followed by a longer hypotension requiring a greater use of vasopressors.

Conclusions

The absence of a control group of untreated or preoperatively differently treated patients was the main limit of our retrospective analysis. According to several authors,6, 13, 23, 31-35 we recommend treatment with doxazosin (2 to 10 mg daily) for at least 2 weeks preoperatively, even in normotensive patients.36 Concerning the preoperative management of pheochromocytoma, selective a1 blockers-doxazosin-are well tolerated without important side effects resulting in very effective BP control. Beta blockers may be also associated. In our experience, adrenergic blockade did not prevent intraoperative hypertensive episodes but allowed their optimal pharmacological control. In fact, hypertensive crises were of short duration and were effectively treated with nitroprusside, esmolol, urapidil, and clonidine. Significant cardiovascular complications were not observed, even in patients whose SBP rose up to 300 mmHg. None of the examined variables- age, tumor size, surgical approach (laparotomic/ laparoscopic), operative time-influenced the occurrence of intraoperative hypertensive episodes. So, at present, these events seem to be, singularly, independent complications in the adrenalectomy for PCC, and preoperative drug treatment, by improving the management of the perioperative hemodynamic instability, is associated with lower morbidity.

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REFERENCES


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---- INDEX REFERENCES ----

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