

Perioperative hypertension in phaeochromocytoma patients undergoing adrenalectomy

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Abstract: This study was designed to compare perioperative blood pressure (BP) management in hypertensive patients with phaeochromocytoma undergoing preoperative α -blockade and in patients with other suprarenal gland tumors. Perioperative hemodynamic data and immediate postoperative outcome in two groups undergoing adrenalectomy were compared. 483 medical charts from urologic patients with tumors were analyzed. In the hypertensive ($n = 168$) group, 20 patients with suprarenal gland tumors were identified (phaeochromocytoma $n = 11$, other tumors $n = 9$). Demographic data, intraoperative consumption of fentanyl and phentolamine, preoperative hospital stay and postoperative ICU stay were compared. Mean arterial pressure (MAP) was registered on the day before surgery, before anesthetic induction, during surgery, and upon admission in the intensive care unit (ICU). Although BP values did not differ significantly on the day before anesthesia, before induction and during operation, significantly more antihypertensive drugs were used for BP regulation in phaeochromocytoma patients versus the other tumor group. The phaeochromocytoma group required significantly more fentanyl during surgery (370 ± 87 vs. 242 ± 35 μg ; $p = 0.04$). MAP upon ICU admission was significantly lower (85.1 vs. 97.4 , $p = 0.02$) after adrenalectomy in phaeochromocytoma patients versus the other tumor group. The postoperative MAP decreased significantly in the phaeochromocytoma group (21.51 mmHg, $p = 0.005$), whereas significant differences according to preoperative values were not observed in the other tumor group (5.5 mmHg, $p = 0.416$). Prolonged preoperative hospital stay (24.6 vs. 10.0 days, $p = 0.005$) and ICU stay were registered in the phaeochromocytoma group. Pheochromocytoma patients had more pronounced perioperative BP oscillations, needed more antihypertensive drugs, analgesics and required prolonged hospital stay than patients with other adrenal tumors. Prolonged α -blockade may have contributed to these effects.

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1 Introduction

Phaeochromocytoma is usually a benign, well-encapsulated, tumor of chromaffin tissue of the adrenal medulla or sympathetic paraganglia. The prominent symptom is persistent or intermittent hypertension, reflecting the increased secretion of catecholamines epinephrine and norepinephrine. Increased blood pressure variability, the absence of the night-time BP decrease and inverted circadian BP rhythm are more common in phaeochromocytoma patients compared to essential hypertension [1]. Phaeochromocytoma is the underlying cause of hypertension in 0.1% of hypertensive patients [2].

The anesthetic management of any surgical patient with pheochromocytoma is a challenge even to the most experienced anesthesiologist. Although the incidence of phaeochromocytoma is very low (0.2 – 2 per 100,000 adults per year) [2, 3], complications may be severe, especially in unrecognized tumors [4]. Common complications of intraoperative hypertension are myocardial ischemia, infarction or failure, pulmonary edema, intraoperative hemorrhage, cerebral encephalopathy, and acute renal failure. In patients with phaeochromocytoma those may arise during anesthetic induction, during the tumor resection or in the perioperative phase [4]. Intraoperative hypertension and tachycardia is a major problem in the anesthetic management of these patients. The incidence of severe intraoperative hypertensive episodes was reported between 5% and 13%, postoperative morbidity between 10.4% – 21.3% and postoperative death at 2.8% [5, 6].

Preoperative antihypertensive therapy contributed to the favorable outcome and reduced remarkably the perioperative mortality [7]. The traditional antihypertensive preoperative medical preparation uses the non-selective α -adrenoceptor blocker phenoxybenzamine and a β -adrenoceptor blocker, propranolol [8]. Other agents, including selective α -adrenoceptor blockers, doxazosin and prazosin, and calcium channel antagonists have been used effectively [1]. Since the number of patients in the studies is often low, there are some controversies as to the best regimen [9]. The duration of preoperative preparation is still not defined and is a matter of a debate, too.

This study was aimed to observe differences between two groups of patients undergoing adrenalectomy. The patients were allocated by the tumor type and preoperative medication. Since both groups in this study were hypertensive, a perioperative blood pressure management was compared in the susceptible phaeochromocytoma patients receiving preoperative α -blockade and in the patients suffering from other, non-catecholamine secreting tumors.

2 Statistical methods and Experimental Procedures

In the group of 483 consecutive urologic patients scheduled for tumor surgery between January 2005 and March 2006 in a single clinical institution, 168 patients were hypertensive. Twenty-four patients in this group had adrenal tumors and underwent elective unilateral adrenalectomy. Four incomplete medical records were excluded. The medical charts of 11 patients with pheochromocytoma (53.2 ± 12.4 years) and 9 patients with other

suprarenal gland tumors (54.2 ± 12.0 years) were analyzed in the retrospective manner. The preoperative estimation of 24-h or overnight urine collection for metanephrine or normetanephrine levels and tumor localization estimated by computed tomography were used for preoperative diagnostics. In all 11 phaeochromocytoma patients in this study, postoperative pathologic examination confirmed the preoperative diagnosis. The type of tumor confirmed in the other tumor group was: metastatic renal cancer ($n=3$), other metastases ($n=2$), ganglioneuroma ($n=2$), one nonfunctional adenoma and one adrenal cyst.

The demographic data, drugs used in the blood pressure or heart rate control, perioperative mean arterial pressure (MAP), and postoperative outcome were registered.

Nine out of eleven patients in the phaeochromocytoma group underwent extensive preoperative medical preparation with phenoxybenzamine (α -adrenergic antagonist with long duration of action) and β -blockers over three weeks in average.

Adrenalectomies were performed under general endotracheal anesthesia. All patients were given midazolam $0.03 \text{ mg}\cdot\text{kg}^{-1}$ as sedative premedication. The induction agent was propofol $2 \text{ mg}\cdot\text{kg}^{-1}$, whereas fentanyl in bolus doses $100 - 200 \mu\text{g}$, and inhalation anesthetic sevoflurane up to 2.2% (1.5 MAC) in $\text{O}_2:\text{N}_2\text{O}$ 35 : 65 vol% as required by clinical criteria was used for the maintenance of anesthesia. Vecuronium $0.1 \text{ mg}\cdot\text{kg}^{-1}$ was used to facilitate artificial ventilation of the lungs. A pulse oxymetry, electrocardiography and invasive arterial blood pressure monitoring were used in all patients. A central venous catheter was placed through the internal jugular vein after induction in general anesthesia.

Blood pressure values were registered in five-minute intervals. Anesthetic balancing was the principal method of blood pressure regulation. In patients who did not respond to anesthetics, blood pressure was maintained by phentolamine injections. Tachycardia ($>110 \text{ beats min}^{-1}$) unresponsive to opioids was treated by propranolol injections. Hypotensive episodes were defined as systolic blood pressure $<90 \text{ mmHg}$. Intraoperative hemodynamic instability was assessed by the need for specific therapeutic intervention. Therefore, the use of vasoactive and cardioactive drugs, total intraoperative dose of fentanyl and the duration of operation and anesthesia were recorded. Preoperative hospital stay, perioperative complications and ICU stay were compared.

2.1 Statistical analysis

Data are expressed as mean $\pm$ standard deviation (SD). The comparisons between two groups were performed using Mann-Whitney and chi-square test. Comparisons within groups were made using Friedman's test. A $p < 0.05$ was considered statistically significant.

3 Results

Patients in both groups had similar characteristics regarding age, sex and body mass index (Table 1).

Table 1 Preoperative characteristics of two groups of hypertensive patients undergoing adrenalectomy in a single clinical institution.

Patients groups	Pheochromocytoma (<i>n</i> = 11)	Other suprarenal gland tumors (<i>n</i> = 9)	
Characteristics	Mean ± SD	Mean ± SD	<i>p</i>
Age (years)	53.2 ± 12.4	54.2 ± 12.0	0.42
Male/female	5/6	5/4	> 0.1
BMI	24.7	23.9	0.3
Preoperative hospital stay (days)	24.6	10	< 0.01*
Preoperative medication (number of all drugs per patient)	2.63	1.64	0.01*

* Statistically significant differences between groups (Mann-Whitney test, $p < 0.05$)

Patients in the phaeochromocytoma group had a longer hospital stay and received significantly more antihypertensive drugs than the patients with other suprarenal gland tumors. The overall preoperative hospital stay was 24.6 days in phaeochromocytoma patients and 10 days in patients with other tumors ($p < 0.01$). Patients in the phaeochromocytoma group received an average of 2.63 antihypertensive drugs daily. Nine patients were given α -adrenergic blockers, 9 β -adrenergic blockers, 6 calcium channel antagonists and 6 patients used other drugs in the preoperative course. Patients scheduled for operation of other suprarenal tumors used significantly less antihypertensive drugs per patient in the preoperative course ($p < 0.05$). Four used β -adrenergic blockers, 3 calcium channel antagonists, 5 used combination of other drugs and 2 patients took no drugs.

The duration of adrenalectomy and anesthesia was similar in the two groups (Table 2). Patients in the phaeochromocytoma group needed significantly more opioids (370 μ g vs. 242 μ g), which resulted in prolonged anesthesia. ICU stay was longer in the phaeochromocytoma group versus the other tumor group.

Table 2 Duration of adrenalectomy, anesthesia, intraoperative drug requirement and ICU stay in two groups of patients undergoing adrenalectomy.

Group	Pheochromocytoma (<i>n</i> = 11)	Other suprarenal gland tumors (<i>n</i> = 9)	
Characteristics	Mean ± SD	Mean ± SD	<i>p</i>
Duration of surgery (min)	169.1 ± 43.1	156.7 ± 54.4	0.412
Duration of anesthesia (min)	216.4 ± 44.2	178.7 ± 49.7	0.131
Intraoperative opioid (Fentanyl, μ g)	370 ± 87	242 ± 35	0.007*
Intraoperative α -blocker (phentolamine, number of patients)	3	0	> 0.1
ICU stay (days)	4.5 ± 1.9	3.3 ± 2.3	0.237

* Statistically significant differences between groups confirmed by Mann-Whitney test ($p < 0.05$).

The mean arterial pressure (MAP) recorded on the day before surgery (MAP1), before anesthesia induction (MAP2) and 10 minutes after surgical incision (MAP3) were not significantly different in patients with pheochromocytoma from patients with other suprarenal tumors (Figure 1). Immediately upon admission into the ICU (MAP4) the pheochromocytoma group had a significantly lower MAP (85.1 vs. 97.4 mmHg, $p=0.024$) and diastolic blood pressure than the other tumor group (68.2 vs. 88.2 mmHg).

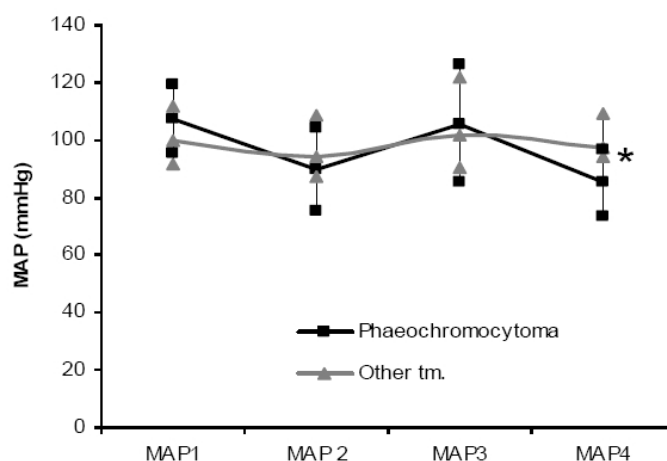


Fig. 1 MAP values (mean $\pm$ standard deviation) in pheochromocytoma patients (closed squares) and in the group of patients with other tumors (grey triangles) undergoing adrenalectomy. Mean arterial pressure on the day before surgery (MAP1), before anesthesia induction (MAP2), and 10 minutes after surgical incision (MAP3) did not differ significantly between the groups. MAP4 registered immediately upon the admission in the ICU was significantly lower in the pheochromocytoma group, represented with the asterisk * ($p = 0.024$).

The principal method of blood pressure regulation was anesthetic balancing. It was efficient in all nine patients in the other tumor group. Patients in the pheochromocytoma group required more fentanyl, which was supplemented with phentolamine in three patients. A satisfactory blood pressure control was achieved in 10 patients. One patient had severe hypertensive episode with blood pressure 200/130 mmHg and intraoperative tachycardia with pulse up to 140 beats per minute. Blood pressure was efficiently controlled by anesthetics. Heartbeat was decreased below 100 minute⁻¹ after propranolol injection.

Two patients in the pheochromocytoma group were hypotensive before anesthesia induction (MAP2, 66 mmHg) and two on admission in the ICU. All these patients were treated preoperatively with phenoxybenzamine. A blood pressure manipulation up was achieved by volume loading. Comparison within groups using Wilcoxon's tests revealed significant differences between particular measurements in the pheochromocytoma group, suggesting blood pressure instability (MAP1 vs. MAP2 decrease by 17.6 mmHg, $p=0.026$; MAP3 vs. MAP4 20.6 mmHg, $p=0.005$). Particular MAP measurements in the other tumor group were not significantly different (Figure 1).

Six out of eleven patients in the phaeochromocytoma group and three out of nine patients in the other tumor group were operated using laparoscopic technique. After all 20 patients were analyzed separately, no differences were observed between the laparoscopic ($n=9$) and the open group ($n = 11$) in blood pressure, duration of surgery, anesthesia, anesthetic dose of fentanyl and entire hospital stay. The only significant difference between the two groups was regarding the postoperative ICU stay: 5 days in the open group versus 2.7 days in the laparoscopic adrenalectomy group ($p = 0.008$).

4 Discussion

This study revealed that hypertensive phaeochromocytoma patients given prolonged preoperative α -blockator phenoxybenzamine expressed more blood pressure oscillations than hypertensive patients with other suprarenal gland tumors. The results of the study emphasized some dilemmas related to prolonged multidrug preoperative preparation.

Hypertensive crisis is the most common and the most feared anesthetic complication during adrenalectomy for phaeochromocytoma, non-catecholamine secreting tumors surgery and during the manipulation with normal adrenal tissue [6, 10, 11]. It may result in severe postoperative morbidity and mortality [4]. A decrease in the postoperative morbidity correlates directly with the efficiency of hypertension control [5, 7].

The value of preoperative hypertension control in phaeochromocytoma patients was pointed out by many authors [3, 5]. In the absence of controlled studies of large groups of pheochromocytoma patients, the use of preoperative α -blockade has a mostly theoretical pharmacological basis. α -adrenergic blockers phenoxybenzamine, prazosin, and doxazosin were used in most of the preoperative preparation protocols with the same efficiency [3, 8, 12]. The duration of such treatment is still not defined and varies widely. Long preoperative treatment with α -blockers lasting for three weeks, was commonly used [2, 13], and may be combined with the β -blocker propranolol, as is the practice in our institution [5].

Contrary to this, there are attempts to decrease the duration of preoperative treatment and the average cost of the treatment [3]. Tauzin-Fin *et al.* have achieved a good α_1 receptor blockade as measured by catecholamine release after continuous IV infusion of urapidil $10 - 15 \text{ mg h}^{-1}$ for 3 days before surgery until the adrenal gland had been removed [14]. Boutros *et al.* reported no differences between groups of patients receiving phenoxybenzamine, prazosin or neither drug in the preoperative course. Based on these observations some authors suggest that patients can undergo successful surgery without preoperative profound and long-lasting α -adrenergic blockade [11, 15]. A rationale for this therapeutic approach may be short half-life of α -adrenoreceptors (approximately 23 – 33 hours) and fast receptor reappearance due to receptor synthesis after it was blocked by phenoxybenzamine [16]. From this perspective the treatment that is longer than two half-lives seems to be unjustified.

The hypotension is a common intraoperative and postoperative complication related to phaeochromocytoma surgery [17, 25]. Severe hypotension was observed in 12.3% of

phaeochromocytoma patients [6]. Preoperative α -blockade with long acting agents may pronounce hypotension and render blood pressure control more difficult [3, 4, 17]. In this situation either norepinephrine or phenylephrine and rarely epinephrine or dopamine can be used to treat hypotension [4]. The occurrence of hypotension may be minimized by the introduction of other antihypertensives more appropriate for rapid drug titration [14, 18]. Although postoperative MAP in phaeochromocytoma group was significantly lower than what was observed in the other tumor group, hypotension was efficiently managed in our study by anesthetic balancing or volume loading. Severe hypotension, major cardiovascular complications and cardiac arrest were reported in patients who received preoperative α -blockade. Based on the results of published articles, it is hard to conclude which is the particular influence of tumor removal or drugs applied to the hypotension resulting. This was a basis for searching for the alternative, intraoperative treatment mode [15, 19]. Ulchaker claims that calcium channel blockers (nicardipine) are as effective and safer when used as the primary mode of antihypertensive therapy, and may be continued during anesthesia by continuous infusion [15]. Such therapy allows more feasible blood pressure control and individual dose adjustment [14, 20].

Pheochromocytoma-induced tachyarrhythmias can also be treated by the use of short-acting β -adrenergic blockers, such as esmolol [14] or landiolol, a novel ultrashort-acting selective β 1-adrenergic blocker with short elimination half-time (4 min in healthy subjects). Landiolol may efficiently control tachycardia [18], whereas episodes of increased blood pressure may be controlled by calcium channel blockers [15]. This drug combination may be used in the preoperative preparation and in the intraoperative course [14].

Short acting antihypertensive agents may be appropriate in the light of hypertensive surges of blood pressure related to the induction of anesthesia, especially in the unrecognized pheochromocytoma [4, 5]. Although such crisis may be resolved by intraoperative phentolamine injections [2], agents of short action, like nitroprusside, landiolol and balanced general anesthesia using propofol and sevoflurane may improve hemodynamic management of phaeochromocytoma patients [18, 21]. These agents could be applicable for immediate control of excessive blood pressure resulting not only from catecholamines secreted by phaeochromocytoma, but also due to the surgical manipulation of normal adrenal tissue and adrenal tumors [10]. In our study, anesthetic balancing was proven as a sufficient method for blood pressure management during surgical manipulation in the other adrenal tumors group.

Hypertension was comparable or even more severe during the laparoscopic adrenalectomy vs. traditional open surgery [11, 22–24]. Although laparoscopic manipulation of the tumor has been shown to slightly elevate plasma catecholamines and mean arterial pressure [25] it offers many advantages over conventional surgery, including less pain, reduced postoperative morbidity, and more rapid return to normal activities [22, 24, 26]. The surgical and anesthesia expertise confirmed laparoscopic resection of phaeochromocytomas as safe and effective method with resultant short ICU and hospital stays [15, 22, 26, 27].

The perioperative hypertension and tachycardia observed in our study were resolved by medical therapy in all patients. Three male patients who were treated by phenoxyben-

zamine preoperatively needed phentolamine injection during open adrenalectomy. Those patients had prolonged ICU stay (6.6 days). A blood pressure monitoring and regulation was the main reason for prolonged ICU stay in phaeochromocytoma patients in our study. ICU stay was significantly reduced in patients who underwent laparoscopic surgery. The mean operative time and outcome in our study correspond to literature reports (160 – 180 minutes, no perioperative deaths). Unexpectedly, the overall hospital stay was significantly longer for both groups of patients [3, 24, 26]. It can mostly be attributed to the preoperative preparation.

This study has some limitations. A small number of patients in this study are a result of low incidence of phaeochromocytoma. A one-year study period was used because of perioperative preparation, anesthetic and surgical management were comparable during this period. A similar, small study sample was reported in the majority of studies related to this type of tumor [5, 25]. Jaroszewski described a series of 47 phaeochromocytoma patients at all 3 Mayo Clinic sites in the ten year period and Bravo reported 132 patients with pheochromocytoma treated at the Cleveland Clinic from 1980 – 1994. [3, 26].

For the purposes of this study, it should have been more appropriate to compare two treatment approaches of the same disease. It was hard to realize since there is a uniform preoperative procedure in the phaeochromocytoma patients established in our hospital. Hence, the study was aimed to find whether some improvements can be introduced. The hypertensive crises, which are the main reason for prolonged preoperative preparation, were not completely avoided by this protocol. Phaeochromocytoma patients were given additional intraoperative doses of antihypertensive drugs and needed 50% higher doses of fentanyl. Higher anesthetic requirement can be attributed to the blood pressure regulation since the same operative procedure was performed in both groups. MAP was significantly lower in the phaeochromocytoma group on admission in the ICU, reflecting prolonged α -blockade caused by phenoxybenzamine in 3 patients with preoperative (MAP2) lower BP. The effect contributed to the postoperative blood pressure decrease and to the prolonged ICU stay in the entire group.

Before preoperative preparation protocols were established, perioperative mortality of phaeochromocytoma patients was significant. Luo reported 8% perioperative mortality before routine preoperative medical preparation was instituted [7]. The adequate preoperative preparation, improved surgical techniques, intraoperative anesthetic management, and postoperative support for vital organ dysfunction significantly reduced perioperative mortality [5, 7]. Whether prolonged α -receptor blockade is still necessary after improved perioperative management was introduced, should be discussed between endocrinologists, surgeons and anesthesiologists involved in the clinical treatment of phaeochromocytoma [5]. A multidisciplinary approach is mandatory. Only through the close collaboration of all specialists, treatment improvements can be introduced in the clinical praxis. Since the pathophysiology of hypertension in patients with adrenal tumors is complex, the perioperative care must be properly adjusted to each patient's characteristics.

Since phaeochromocytoma patients are still having pronounced blood pressure oscilla-

tions even after α -blockade, preemptive intervention with the antihypertensive agents of short duration may be more appropriate. Intraoperative combination of novel anesthetics and vasodilators with rapid onset and short duration in the treatment of hypertension are recommended [5, 20]. These maneuvers may result in decreased systemic catecholamine release and minor blood pressure oscillations. A switching to the laparoscopic surgery with proper surgical manipulation may reduce the duration of hospital stay.

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