RESEARCH ARTICLE

Predictors of hemodynamic instability in patients with pheochromocytoma and paraganglioma

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Abstract

Background and Objectives: Intraoperative hemodynamic instability is common in patients with pheochromocytoma and paraganglioma. The aim of this study was to identify the predictive risk factors of intraoperative hemodynamic instability.

Methods: A total of 428 patients having elective resection of pheochromocytoma and/or paraganglioma at Peking Union Medical College Hospital between January 2014 and July 2019 were included. The association between preoperative parameters and the incidence of intraoperative hemodynamic instability were evaluated. Binary logistic regression was used to assess the predictive risk factors of hemodynamic instability.

Results: Patients with intraoperative hemodynamic instability were more prone to have elevated levels of norepinephrine and epinephrine. Binary Logistic regression showed the risk factors of hemodynamic instability were tumor size >5.0 cm (odds ratio [OR], 1.889; 95% confidence interval [CI], 1.243-2.870; $P = .003$) and five-fold increases of urine epinephrine (OR, 2.195; 95% CI, 1.242-3.880; $P = .007$).

Conclusions: Intraoperative hemodynamic instability is common despite adequate preoperative medical treatment. Tumor size and high level of urinary epinephrine are tumor-related factors for intraoperative hemodynamic instability. Identifying these factors can help clinicians to manage patients more effectively and improve patients' outcomes.

KEYWORDS
hemodynamic instability, paraganglioma, pheochromocytoma, tumor size, urine catecholamine

1 | INTRODUCTION

Pheochromocytoma and paraganglioma are rare catecholamine-secreting tumors. The incidence of pheochromocytoma and paraganglioma is about 0.6 cases per 100 000 person-years.[1] The clinical signs of pheochromocytoma arise from catecholamine excess and the typical triad includes hypertension, palpitation, and tachycardia.

Surgical resection is the main therapy for patients with pheochromocytoma or paraganglioma. And preoperative alpha blockade is recommended for patients with pheochromocytoma and/or paraganglioma, to reverse blood volume contraction, prevents orthostatic hypotension, and reduce the risk of significant hypotension after resection of the tumor. Despite improvements in preoperative management and mini-invasive surgical techniques, intraoperative hemodynamic instability

cannot be avoided. The aim of this study was to identify the possible risk factors for intraoperative hemodynamic instability.

2 | MATERIALS AND METHODS

With the approval of the IRB, we conducted a retrospective review of the electronic medical records of patients who had pheochromocytoma and/or paraganglioma resections at Peking Union Medical College Hospital from January 2014 to July 2019. Patients who were excluded of pheochromocytoma or paraganglioma confirmed by postoperative pathology, patients with the diagnosis of carotid body tumor, and those who had incomplete perioperative data or pregnant patients were not included for analysis. For patients who had multiple operations, only the first surgical procedure was included.

Perioperative data were collected, which included age, sex, body mass index (BMI), American Society of Anesthesiologists physical status (ASA), comorbidities, diagnosis, tumor size, locations, and the presence of metastases.

Except incidental pheochromocytoma or paraganglioma, all patients received at least 2 weeks of alpha-adrenergic blocker and the dosage gradually increased as needed to the target blood pressure (blood pressure less than 130/80 mm Hg while seated and systolic blood pressure no less than 90 mm Hg while standing). β-adrenergic receptor blocker was added for a target heart rate (HR) of 80 beats per minute (bpm). Preoperative medication, which included the types of antihypertensive drugs and the values of urine catecholamine were also recorded. The increase of urine catecholamine was presented as norepinephrine/epinephrine/dopamine ratio, which was the ratio of urine level of catecholamine to the upper limit of normal values.

Operations were performed under general anesthesia and an arterial line was inserted before induction. Two large-gauge intravenous lines, three-lumen center venous catheter, and a urinary catheter were inserted. The type of operation (laparoscopy, laparotomy, or conversion to laparotomy) was determined by the tumor size, the relationship to vessels, the ability to control bleeding, past history of operation, the possibility of malignancy, and the preference of surgeons. Bolus doses of phentolamine or continuous infusion of nitroprusside were administrated intraoperatively when systolic blood pressure (SBP) >160 mm Hg or 30% above baseline. And continuous infusion of norepinephrine or epinephrine was administrated when SBP <90 mm Hg or 30% below baseline. Bolus doses (10-20 mg) of esmolol was given when HR increased above 90 bpm in patients with coronary artery disease (CAD) and 110 bpm in patients without CAD. Hemodynamic variables, which included maximum and minimum SBP, maximum and minimum diastolic blood pressure (DBP), numbers of episodes of blood pressure 30% above or below the baseline, and HR >110 bpm were recorded.

Baseline blood pressure was defined as blood pressure after blockade and within 1 week before the operation. Hemodynamic instability was defined as more than 10 episodes of SBP above 30% baseline or DBP less than 30% despite vasoactive drugs.[2]

Patients were all sent to intensive care unit postoperatively in our center and transferred to ward after hemodynamic variables were stable.

Intraoperative blood loss, allogenic blood transfusion, the length of hospital stay, and the postoperative complications were also collected.

Postoperative complications were defined according to Clavien-Dindo classification.[3]

Data were analyzed using SPSS 24.0 (IBM Corporation). Continuous variables were presented as means and standard deviations or medians and interquartile ranges. category variables were presented as numbers and percentages. Group comparisons for continuous variables were performed by the Student t test for approximately normally distributed data or the Mann-Whitney U test for non-normally distributed data. Categorical variables were compared using the χ^2 test. P value <.05 (two-tailed tests) was considered significant. Continuous variables with statistical significance ($P < .05$) were transformed to categorical variables by their cut-off points respectively. Binary logistic regression analysis was used to determine predictive risk factors of hemodynamic instability.

3 | RESULTS

428 patients were included for analysis. Demographic data were presented in Table 1. The mean age was 45.5 years old and sex distribution was equal. The majority of patients (342 cases, 79.9%) were ASA physical status II. Two hundred seventy-six patients had unilateral or bilateral pheochromocytoma, while 152 patients had extra-adrenal tumors which included 18 cases of multifocal tumors.

TABLE 1 Demographic characteristics of patients with pheochromocytoma and paraganglioma

Variables	
Gender	
Female	231 (54.0%)
Male	197 (46.0%)
Age, y old	45.5 ± 13.2
BMI, Kg/m^2	24.4 ± 9.1
ASA	
II	342 (79.9%)
III	59 (13.8%)
IV	27 (6.3%)
Diagnosis	
Pheochromocytoma	276 (64.5%)
Bilateral	23 (5.4%)
Paraganglioma	152 (35.5%)
Multifocal	18 (4.2%)
Malignancy	5 (1.2%)
Family history	8 (1.9%)

TABLE 2 Comorbidities and preoperative management and measurements

Variables	
Comorbidities	
Hypertension	132 (30.8%)
Coronary artery disease	10 (2.3%)
Diabetes mellitus	65 (15.2%)
Cerebrovascular disease or accident	10 (2.3%)
Classic triad	
Headache	65 (15.2%)
Palpitations	131 (30.6%)
Profuse sweating	77 (18.0%)
Catecholamine cardiomyopathy	21 (4.9%)
Pheochromocytoma crisis	10 (2.3%)
Urine catecholamine	
Norepinephrine, µg/24 h	285 (66.6%)
Norepinephrine ratio	5.78 ± 9.46
Epinephrine, µg/24 h	101 (23.6%)
Epinephrine ratio	3.68 ± 11.08
Dopamine, µg/24 h	94 (22.0%)
Dopamine ratio	1.16 ± 2.34
Normal	117 (27.3%)
Tumor size, cm	5.0 ± 2.4
Necrosis	158 (36.9%)
Preoperative management	
Nonselective alpha-blocker	411 (96.0%)
Selective alpha-blocker	17 (4.0%)
Beta-blocker	53 (12.4%)
No preparation	8 (1.9%)

TABLE 3 Intraoperative parameters and hemodynamics and postoperative outcomes

Parameters	
Operation	
Laparoscopy	356 (83.2%)
Laparotomy	56 (13.1%)
Conversion to laparotomy	16 (3.7%)
Length of operation	135.6 ± 73.0
Length of anesthesia	180.8 ± 75.8
Intraoperative blood loss >1000 mL	174 (40.7%)
Allogenic transfusion	33 (7.7%)
SBPmax >160 mm Hg	305 (71.3%)
SBPmax >200 mm Hg	100 (23.4%)
HR > 110 bpm	218 (50.9%)
SBP maximal	171 ± 25
SBP minimum	89 ± 11
DBP maximal	91 ± 14
DBP minimum	51 ± 8
MAP < 60 mm Hg	75 (17.5%)
SBP > 30% baseline	255 (59.6%)
DBP < 30% baseline	287 (67.1%)
Hemodynamic instability	134 (31.3%)
Intraoperative administration of phentolamine	209 (48.8%)
Intraoperative infusion of norepinephrine	285 (66.6%)
Intraoperative infusion of epinephrine	25 (5.8%)
Intraoperative infusion of nitroprusside	251 (58.6%)
Continuous infusion of vasopressor at the end of operation	221 (51.6%)
Postoperative outcomes	
Length of stay	6.8 ± 6.5
Complications	37 (8.6%)

Hypertension was the most common comorbidities in patients with pheochromocytoma and paraganglioma (see Table 2). The prevalence of headache, palpitations, and profuse sweating was 15.2% (65 cases), 30.6% (131 cases), and 18.0% (77 cases) respectively. Twenty-one patients (4.9%) were diagnosed as pheochromocytoma cardiomyopathy and pheochromocytoma crisis was the first clinical manifestation in 10 patients. Norepinephrine was the most common elevated urine catecholamine and 117 patients (27.3%) had a normal level of urine catecholamine. Nonselective alpha-blocker (phenoxybenzamine) was commonly used as the preoperative drug, while selective alpha-blockers (doxazosin, prazosin, or terazosin) were only used in 17 patients (4%). Fifty-three patients used β-adrenergic receptors blocker to control tachycardia preoperatively. Eight patients did not have preoperative alpha-blocker due to intraoperative diagnosis. The mean diameter of the tumor was 5.0 ± 2.4 cm and necrosis was presented in 158 (36.9%) patients on CT image.

A total of 83.2% (356 patients) had an operation under laparoscopy and 56 patients had laparotomy, the conversion rate from laparoscopy to laparotomy was 3.7% (see Table 3). One hundred seventy-four patients had intraoperative blood loss larger than 1000 mL and the allogenic transfusion rate was 7.7%. The mean length of hospital stay was 6.8 days. The incidence of complications was 8.6% and there was no death perioperatively.

Three hundred five (71.3%) patients experienced at least one episode of SBP > 160 mm Hg and 100 (23.4%) patients had at least one episode of SBP > 200 mm Hg. The proportions of patients who experienced at least one episode of SBP > 30% and DBP < 30% baseline were 59.6% and 67.1% respectively. Seventy-five patients experienced at least one episode of mean arterial pressure (MAP) less than 60 mm Hg. The mean maximal and minimum SBP were 171 ± 25 mm Hg and 89 ± 11 mm Hg, and the mean maximal and minimum DBP were 91 ± 14 and 51 ± 8 mm Hg respectively. Two hundred eleven patients were still on continuous vasopressor infusion by the end of the operation. The incidence of hemodynamic instability was 31.3% (134 patients).

TABLE 4 Risk factors of intraoperative hemodynamic instability

	Hemodynamic instability (n = 134)	No hemodynamic instability (n = 294)	P
Gender			.531
Female	69 (51.5%)	162 (55.1%)	
Male	65 (48.5%)	132 (44.9%)	
Age	44.6 ± 13.2	46 ± 13.2	.294
BMI	23.9 ± 3.1	24.6 ± 10.8	.463
ASA			.058
II	98 (73.1%)	244 (83.0%)	
III	24 (17.9%)	35 (11.9%)	
IV	12 (9.0%)	15 (5.1%)	
Diagnosis			.461
Pheochromocytoma	88 (65.7)	188 (63.9%)	
Bilateral	13 (9.7%)	10 (3.4%)	
Paraganglioma	46 (34.3%)	106 (36.1%)	
Multifocal	5 (3.7%)	13 (4.4%)	
Malignancy	0	5 (1.7%)	.331
Family history	5 (3.7%)	3 (1.0%)	.115
Recurrence	1 (0.7%)	5 (1.7%)	.670
Comorbidities			
Hypertension	43 (32.1%)	89 (30.3%)	.735
Coronary artery disease	4 (3.0%)	6 (2.0%)	.512
Diabetes mellitus	27 (19.4%)	39 (3.1%)	.083
Cerebrovascular disease or accident	3 (2.2%)	7 (2.4%)	1.000
Pheochromocytoma crisis	6 (4.5%)	4 (1.4%)	.078
Urine catecholamine			
Norepinephrine	99 (73.9%)	186 (63.3%)	.036
Epinephrine	49 (36.6%)	52 (17.7%)	.000
Dopamine	30 (22.4%)	64 (21.8%)	.900
Norepinephrine ratio	5.60 ± 7.12	5.86 ± 10.10	.795
Epinephrine ratio	5.48 ± 13.47	2.87 ± 9.72	.024
Dopamine ratio	0.99 ± 0.98	1.23 ± 2.76	.331
Tumor size, cm	5.5 ± 2.1	4.8 ± 2.4	.003
Preoperative management			
Nonselective alpha blocker	130 (97%)	281 (95.6%)	.600
Selective alpha blocker	2 (1.5%)	15 (5.1%)	.107
Beta blocker	20 (14.9%)	33 (11.2%)	.342
No preparation	2 (1.5%)	6 (2.0%)	1.000
Operation			.078
Laparoscopy	108 (80.6%)	248 (84.4%)	
Laparotomy	20 (14.9%)	36 (12.2%)	
Conversion to laparotomy	6 (4.5%)	10 (3.4%)	

The analysis of preoperative parameters and intraoperative hemodynamic instability are shown in Table 4. The proportion of increased norepinephrine and epinephrine were higher in patients who had intraoperative instability. The epinephrine ratio and tumor size were associated with a higher risk of hemodynamic instability. The cut-off point of tumor size was established every 1 cm (1 cm, 2 cm,

3 cm, etc). Only the number of patients whose tumor size was large than 5.0 cm was found to be statistically different between the two groups. Five was the cut-off value of epinephrine ratio determined by the same method. Binary logistic regression showed the independent risk factors of hemodynamic instability were tumor size >5.0 cm (odds ratio [OR], 1.889; 95% confidence interval [CI], 1.243-2.870;

P = .003) and five-fold increases of urine epinephrine (OR, 2.195; 95% 1.242-3.880; *P* = .007).

4 | DISCUSSION

Pheochromocytoma is a rare endocrine tumor and the majority of patients need operation. Surgical resection of pheochromocytoma and paraganglioma are associated with risks. Intraoperative hemodynamic instability is still a big concern for anesthesiologists, surgeons, and endocrinologists, since it has been proven to be associated with morbidity.[4,5] Our study showed that tumor size large than 5.0 cm and five-fold increases of urine epinephrine were predictive risk factors of intraoperative hemodynamic instability.

Previous reports about the predictive risk factors for intraoperative hemodynamic instability were conflicting, due to no standard definition of intraoperative hemodynamic instability. The results of different studies were not comparable. And different medical centers have a significant influence on intravenous hemodynamic instability,[5] which suggests the standardization of perioperative medical, anesthetic, and surgical management are necessary.

Intubation, the creation of pneumoperitoneum, and the manipulation of tumors intraoperatively will result in intraoperative hypertension. Hypotension after tumor resection is due to a sudden decrease in serum levels of catecholamines, relatively low intravenous blood volume, and down-regulation of α and β adrenergic receptors caused by chronic increased levels of catecholamines. To evaluate intraoperative hemodynamics, we combined the parameters of both rise and drop in blood pressure, since reduced blood pressure after tumor resection was associated with outcome.[6] We used 30% above or below baseline instead of SBP >200 mm Hg or MAP < 60 mm Hg as previous reports, because we hope to increase the vigilance of both anesthesiologists and surgeons. In our experience, the incidence of hemodynamic instability was still as high as 31.3% despite the adequate preoperative alpha blockade.

The larger tumor has been reported to be associated with an increased number and duration of episodes of intraoperative hypertension,[6-8] increased requirement of postoperative vasopressin,[7] and postoperative complication.[9,10] Tumor size was related to plasma catecholamine levels[8] and intraoperative manipulation of tumors will cause increased levels of catecholamine release. With the increase of tumor size, the possibility of conversion to open operation[10] and intraoperative blood loss[11] increase. So it is not surprisingly that larger tumors are more prone to have hemodynamic fluctuation perioperatively.

Increased urine or plasma level of catecholamine and/or metabolites has been reported to be associated with intraoperative hemodynamic instability,[8,12-14] prolonged hypotension postoperatively,[15] and adverse perioperative complications. Higher levels of catecholamine indicate a more actively functional tumor and the release of catecholamine would be more during intraoperative manipulation. In our study, increased epinephrine, especially five-fold increase was the predictive factors of hemodynamic instability. Long-term high levels of catecholamine will lead to receptor desensitization, down-regulation, and decreased affinity. Downregulation of β-adrenergic receptors due to chronic elevated levels of epinephrine, will lead to decreased cardiac contractility.[16] Epinephrine is 10 times more metabolically active than norepinephrine and epinephrine-secreting tumors are associated with morbidity and mortality due to cardiogenic shock.

The effects of the operation type on the hemodynamic instability and outcome have been reported previously, but results are conflicting. Laparoscopic approach has been demonstrated as the safe way for pheochromocytoma, with low conversion rate, complication, and mortality.[4,14,17-19] Open operation increases the risk of intraoperative hypertension, length of stay, and complications,[7] while other reports demonstrated no influence of operation type on intraoperative hemodynamic instability.[8,20] In our study, there was no difference between laparoscopic and open operation in intraoperative hemodynamic instability and the conversion rate in our study was only 3.7%. However, preoperative and intraoperative parameters may differ between laparoscopic and open procedures. And our sample size was not powered adequately to do subgroup analysis of the effect of tumor size on the hemodynamic instability stratified by operation type. So we could not exclude the influence of operation type on hemodynamic instability in patients with large tumors and further research is necessary.

Phenoxybenzamine was used as the primary α blocking agent in our studies. Both nonselective alpha-blocker (phenoxybenzamine) and selective blockade have been suggested as the first choice preoperatively.[21] Phenoxybenzamine is a noncompetitive α-blocker, with irreversible action and long duration of effect. However prolonged hypotension after tumor resection and reflex tachycardia are big concerns. The effects of selective α1 blocker may be overcome by lager surge of catecholamines since its inhibition is competitive, with the hemodynamic fluctuation as a big concern. At present, there were no randomized controlled clinical studies comparing the effectiveness of nonselective and selective α blockers. Although it had been demonstrated that selective α1 blocker was associated with better hemodynamic stability when compared to nonselective α blocker,[22] other studies found selective blockade was associated with more episodes of hypertension,[7] hypotension,[23] and more prone to require vasopressor postoperatively.[23] Recently it has been reported that there was no difference of intraoperative hypertension and major complications between patients with or without α-receptor blockade.[24] So the optimal strategy of preoperative α-receptor blockade still needs further research.

The limitations of our study were as follows: First, this is a retrospective study, and selection bias was not avoidable. Second, although we had a relatively large number of patients in our study, the possibility of being underpowered to detect real significant parameters is still existing. Additionally, our center is a large tertiary referral hospital for patients with adrenal tumor and it has a large surgical volume of laparoscopic adrenalectomy, the experience may not be generalized to the whole population of patients or other centers.

Our study demonstrated hemodynamic instability was common in patients with pheochromocytoma or paraganglioma

perioperatively. Large tumor size and increased levels of urine epinephrine were predictive factors of intraoperative hemodynamic instability.

DATA AVAILABILITY STATEMENT

Research data can be available.

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