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Original Article

Predictors of Hypotension after Adrenalectomy for Pheochromocytoma

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The management of blood pressure is a significant concern for surgeons and anesthesiologists performing adrenalectomy for pheochromocytoma. We evaluated clinical factors in pheochromocytoma patients to identify the predictors of postoperative hypotension. The medical records of patients who underwent adrenalectomy for pheochromocytoma between 2001 and 2017 were retrospectively reviewed and clinical and biochemical data were evaluated. Of 29 patients, 13 patients needed catecholamine support in the perisurgical period while 16 patients did not. There were significant differences in median age, tumor size, and blood pressure drop (max-min) between the 2 groups (68 vs 53 years old, $p=0.045$; 50 vs 32 mm diameter, $p=0.022$; 110 vs 71 mmHg, $p=0.015$ respectively). In univariate logistic analysis, age > 65.5 years, tumor size > 34.5 mm, urine metanephrine > 0.205 mg/day and urine normetanephrine > 0.665 mg/day were significant predictors of prolonged hypotension requiring postoperative catecholamine support. Tumor size and urine metanephrine and urine normetanephrine levels were correlated with postoperative hypotension. These predictors may help in the safe perioperative management of pheochromocytoma patients treated with adrenalectomy.

Key words: urinary metanephrine, urinary normetanephrine, adrenalectomy, pheochromocytoma

Pheochromocytomas arising from chromaffin cells in the adrenal medulla and paraganglia secretes catecholamines that result in widespread sympathetic derangement of homeostasis. Clinical symptoms due to the tumor's overproduction of catecholamines include tachycardia, high blood pressure, sweating and headache. The standard treatment for pheochromocytoma is surgical resection. During surgery and the perioperative period, blood pressure fluctuates significantly due to changes in plasma levels of catecholamines secreted by the tumor. Thus, the management of blood pressure in adrenalectomy for pheochromocytoma becomes a significant concern for surgeons and anesthesiologists. The fluctuation has 2 parts. Just before the drainage veins are clamped, blood pressure rises due to tumor manipulation and the resultant catecholamine surge; then, after clamping, the blood pressure drops precipitously. In some patients, hypotension persists even postoperatively, and intensive care may be required. However, the fluctuation in blood pressure varies from patient to patient, and not all cases show large fluctuations. If we can determine beforehand which patients will likely have persistent postoperative hypotension, perioperative management could be made more safe and predictable. Several studies have reported predictors of postoperative hypotension, but there is no consensus on related factors [1-4]. To identify the predictors of postoperative hypotension, we reviewed our series of adrenalectomy for pheochromocytoma.

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Materials and Methods

We reviewed the medical records of all patients who underwent adrenalectomy at Ehime University Hospital and were pathologically diagnosed as having pheochromocytoma between 2001 and 2017. All adrenalectomy cases were pheochromocytomas; there were no paragangliomas. Preoperative capacity loading with saline was performed in all cases and circulating blood volume was maintained. In order to increase circulating blood volume, a 500-1,000 mL saline drip was started from 3 h prior to operation in all patients. Use of doxazosin was determined by an endocrinologist. Postoperative hypotension was defined as the necessity of catecholamine supplementation to maintain systolic blood pressure (SBP) 90 mmHg at any time during hospital recovery. Blood pressure fluctuation is especially large at the time of clamping the drainage veins. We used SBP as the blood pressure and defined blood pressure fluctuation as the difference between the maximum blood pressure prior to vein clamping and the minimum blood pressure after clamping. Patients were divided into 2 groups: Group 1, who needed catecholamine support postoperatively and Group 2, who did not need catecholamine at all. Patients' background, surgical outcomes, and biochemical data were compared between the 2 groups. The statistical difference between the two groups was examined by the Mann-Whitney *U* test. Next, we found appropriate cutoff points for continuous variables. We selected these cutoffs by identifying predictor variable values on receiver operating characteristic curves. The value with the maximum sensitivity and minimal loss of specificity was chosen. Finally, we selected candidate variables with *p*-values < 0.05 based on univariate analyses.

For all statistics, IBM SPSS Statistics Version 21 (IBM, Armonk, NY, USA) was used. This study was approved by the institutional review board of Ehime University (IRB number 1905012).

Results

We evaluated 29 patients who underwent adrenalectomy for pheochromocytoma. Thirteen patients were assigned to Group 1 and 16 to Group 2. The background of all patients, surgical outcomes, and the comparison of clinical and biochemical factors between the 2 groups are shown in Table 1. The surgical approach differed based on the case. Three patients who were started with laparoscopic surgery were converted to laparotomy during the surgery. The reason for open conversion was bleeding in 2 cases and omentum adhesion in 1 case. Most of the patients in group 1 had a small amount of blood loss. Only one patient had bleeding from renal vein, and the amount of intraoperative blood loss was 2,190 mL. There were significant differences in tumor size and blood pressure fluctuation between the 2 groups (68 vs 53 years old, $p = 0.045$; 50 vs 32 mm diameter, $p = 0.022$; 110 vs 71 mmHg, $p = 0.015$ respectively). Some cases did not require preoperative administration of doxazosin; these were included in Group 2. According to the preoperative biochemical data, urinary metanephrine and urinary normetanephrine levels were significantly correlated with postoperative catecholamine support (0.54 vs 0.09 mg/day, $p = 0.008$; 1.94 vs 0.50 mg/day, $p = 0.018$ respectively).

Clinical variables significantly associated with prolonged hypotension requiring postoperative catecholamine support included larger tumor size, blood pressure fluctuation, higher urinary metanephrine and higher urinary normetanephrine levels. When optimum cutoffs for continuous variables were selected using the area under the curve (AUC) derived from the receiver operating characteristic curve, the following 3 preoperative dichotomous variables were selected as predictors: tumor size > 34.5 mm (AUC = 0.75), urinary metanephrine > 0.205 mg/day (AUC = 0.837), urinary normetanephrine > 0.665 mg/day (AUC = 0.816) (Fig. 1). In univariate logistic analysis, these factors were significant predictors of prolonged hypotension requiring postoperative catecholamine support (Table 2).

Discussion

The aim of this study was to identify preoperative predictors of cases with persistent hypotension after adrenalectomy for pheochromocytoma. Other studies have reported frequencies of hypotension after adrenalectomy for pheochromocytoma was about 50% [1,5]. In this study, 44.8% of patients needed catecholamine supplementation after surgery, which was not significantly different from other reports. According to our study, there were three predictors of persistent postoperative hypotension. Tumor size, urinary metaneph-

Table 1 Comparison of characteristics in patients who needed catecholamine support after surgery and those who did not

	Needed catecholamine support after surgery, n = 13	Did not need catecholamine support after surgery, n = 16	*P* value
Age, median, years old	68 (33–76)	53 (20–73)	.045
Gender, male/female (number)	8/5	7/9	.339
BMI, median, kg/m^2	21.4 (15.8–26.8)	22.7 (16.0–27.7)	.531
Tumor size, median, mm diameter	50 (30–90)	32 (16–150)	.022
Tumor side, right/left/bilateral (number)	4/9/0	4/11/1	.528
Approach, laparoscopic/laparotomy/thoracoabdominal	10/3/0	13/2/1	.381
Surgical time, median, min	201 (135–565)	293 (115–410)	.232
Blood loss, median mL	10 (10–2,190)	70 (10–900)	.589
Postoperative hospitalization, days blood pressure fluctuation, median, mmHg	8 (7–16)	8.5 (4–15)	.722
(Subtract minimum sBP after tumor resection from maximum sBP before tumor resection)	110 (43–230)	71 (16–152)	.015
Preoperative cumulative dose of doxazosin, median, mg	216 (64–590)	60.5 (0–1,440)	.110
Duration of catecholamine need, median, hours	20 (1–94)		
Serum adrenaline, median, pg/mL	0.08 (0.02–3.18)	0.06 (0.02–2.04)	.525
Serum noradrenaline, median, pg/mL	1.43 (0.23–17.77)	1.11 (0.21–11.60)	.905
Serum dopamine, median, pg/mL	0.035 (0.02–0.29)	0.05 (0.02–0.09)	.536
Urinary adrenaline, median, μg/day	13.4 (8.0–215.4)	28.6 (1.5–456.8)	.847
Urinary noradrenaline, median, μg/day	270.9 (101–4,240)	433.9 (53.4–2,132.1)	.898
Urinary dopamine, median, μg/day	840 (435.9–9,018,9)	496.6 (39–1,963)	.088
Urinary VMA, median, mg/day	7.60 (0.77–18.73)	4.08 (0.38–10.32)	.252
Urinary metanephrine, median, mg/day	0.54 (0.10–17.14)	0.09 (0.02–2.10)	.008
Urinary normetanephrine, median, mg/day	1.94 (0.65–8.59)	0.50 (0.06–63.7)	.018
Changes between pre- and post operative levels of urinary metanephrine, median, mg/day	−0.23 (−14.51–−0.02)	−0.45 (−2.08–+0.01)	.069
Changes between pre- and post operative levels of urinary noremtanephrine, median, mg/day	−1.42 (−8.42–−0.52)	−0.325 (−63.4–−0.02)	.069

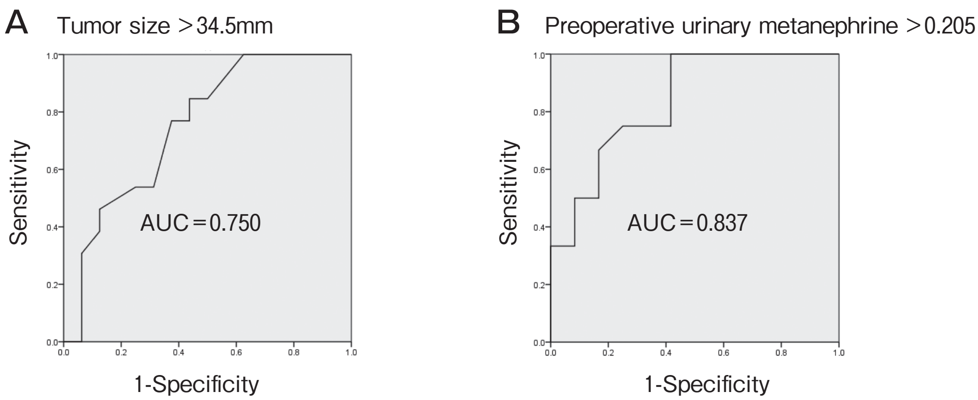
Table 2 Univariate analysis of predictors for catecholamine needs

Variables	Univariable analysis		
	Odds	95%CI	*P* value
Tumor size > 34.5 mm	4.29	0.84–21.8	0.079
Preoperative urinary metanephrine > 0.205	6.67	1.15–38.8	0.035
Preoperative urinary normetanephrine > 0.665	17.6	1.71–181.3	0.016

rine, and urinary normetanephrine were significantly correlated with postoperative catecholamine support. Previous reports have cited blood circulation volume, operation time, and the intraoperative catecholamine index as predictors of postoperative hypotension [1-4]. However, catecholamines originating elsewhere than the pheochromocytoma also affects blood pressure during surgery; some reports therefore state that prediction of fluctuations in blood pressure is difficult [6-8].

Tumor size has been noted as a predictor of significant blood pressure fluctuations in other reports [1, 4, 6, 7, 9]. It is suggested that catecholamine outflow due to compression of the tumor may increase with size because large tumors have many collateral vessels and the tumor is manipulated for a long time [4, 6, 7, 9].

As biochemical factors, urinary metanephrine and urinary normetanephrine showed significant differences between the 2 groups. Various studies on biochemical factors have been reported so far. Serum adrenaline, urinary noradrenaline, and urinary VMA are also regarded as predictors of intraoperative blood pressure fluctuations [1-4]. Metanephrine and normetanephrine are metabolites of adrenaline and noradrenaline, respectively, and VMA is the final metabolite of both.



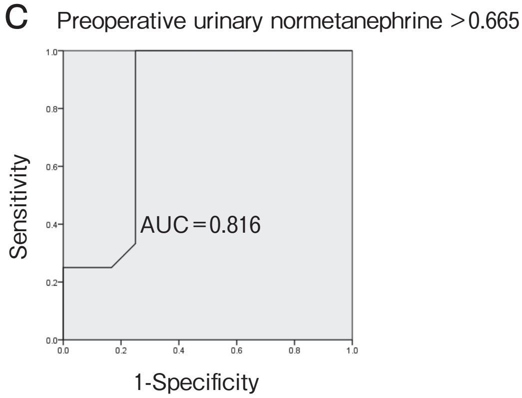


Fig. 1 Receiver operating characteristic curve of each continuous variable as a candidate predictor. The three predictive variables were (**A**) tumor size >34.5 mm, (**B**) preoperative urine metanephrine >0.205 ug/day, and (**C**) preoperative urine normetanephrine >0.665 ug/day. Each value was chosen to have the maximum sensitivity combined with the minimal loss of specificity.

Adrenaline and noradrenaline have several minutes of half-life and depend largely on the patient's diet and exercise. Similarly, urinary VMA tends to be affected by diet and medicine. Therefore, measurements of these factors are not constant over time, and one-time measurements sometimes show false negatives.

By contrast, urinary metanephrine and urinary normetanephrine are highly stable, and there have been cases diagnosed as pheochromocytoma because of the high urinary levels of metanephrine and normetanephrine even if urinary catecholamines are in the normal range. From these facts, it was agreed that urinary metanephrine and urinary normetanephrine are useful for the diagnosis of pheochromocytoma, but their utility as a predictive factor for postoperative hypotension is divided. Namekawa *et al*. showed that urinary normetanephrine could be a predictor of postoperative hypotension in univariate analysis [1]. Furthermore, their multivariate analysis showed that intraoperative catecholamine index and surgery time were significantly related to postoperative hypotension, and they reported that urinary normetanephrine strongly correlated to both [1]. In our study, urinary metanephrine and urinary normetanephrine were significantly correlated with postoperative hypotension in univariate logistic analysis. Age also showed significant differences between the 2 groups, but we did not consider it as a good predictor. As ageing, calcification occurs in the vascular wall, and vascular compliance decreases. Therefore, elderly people both with and without pheochromocytoma may have greater perioperative blood pressure fluctuations. Thus we decided to exclude age as a candidate predictor.

There are a few limitations to this study. The number of cases was small and it was a retrospective examination. Details of perioperative management, such as anesthesia method and administration of antihypertensive medication other than doxazosin, for example ARBs and Ca blockers, were not constant across all subjects. Only very recently did laboratory tests for plasma free metanephrine fractions become covered by Japanese insurance. In future studies, it will be possible to use the data of plasma free metanephrine fraction, and thus another factors may be identified as a reliable predictor of postoperative hypotension.

In conclusions, tumor size, urinary metanephrine and urinary normetanephrine levels were especially correlated with postoperative hypotension. These predictors may help in the safe perioperative management of pheochromocytoma patients treated with adrenalectomy. Further research with a greater number of cases and more purposeful study design, *i.e.*, a prospective study designed to maintain a constant dose of preoperative doxazosin and more explicit criteria for starting and stopping postoperative catecholamines, may yield more conclusive results.

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