

OPEN Nonselective Compared With Selective α -Blockade Is Associated With Less Intraoperative Hypertension in Patients With Pheochromocytomas and Paragangliomas: A Retrospective Cohort Study With Propensity Score Matching

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BACKGROUND: Both selective and nonselective α -blockade are used for preoperative preparation in patients with pheochromocytomas and paragangliomas (PPGLs). However, the effects of different types of α -blockade on perioperative outcomes remain inconclusive. This study was designed to assess the association between the choice of α -blockade and the amount of intraoperative hypertension in patients undergoing surgery for PPGLs.

METHODS: In this propensity-matched retrospective cohort study, data of patients who received either selective or nonselective α -blockade preoperatively and underwent surgery for PPGLs were collected. The primary end point was the time-weighted average above the systolic blood pressure (SBP) of 160 mm Hg (TWA-SBP >160 mm Hg), which was calculated as the total area of the SBP-time curve above the SBP of 160 mm Hg and divided by anesthesia duration.

RESULTS: A total of 286 patients were included in analysis; of them, 156 received selective α -blockade and 130 nonselective α -blockade. After propensity score matching, 89 patients remained in each group. Patients who received nonselective α -blockade had a lower TWA-SBP >160 (median 0.472 mm Hg, interquartile range [IQR], 0.081–1.300) versus those who received selective α -blockade (median 1.114 mm Hg, IQR, 0.162–2.853; median difference -0.391 , 95% confidence interval [CI], -0.828 to -0.032 ; $P = .016$); they also had a lower highest SBP during surgery (193 ± 24 mm Hg versus 205 ± 34 mm Hg; mean difference -12 , 95% CI, -20 to -3 ; $P = .008$). Postoperative outcomes did not differ significantly between the 2 groups.

CONCLUSIONS: For patients undergoing surgery for PPGLs, preoperative nonselective α -blockade was associated with less intraoperative hypertension when compared with selective α -blockade. (Anesth Analg 2021;132:140–9)

KEY POINTS

- **Question:** Does the choice of preoperative α -blockade affect intraoperative hemodynamics and postoperative outcomes in patients with pheochromocytomas and paragangliomas?
- **Findings:** Compared with preoperative selective α -blockade, nonselective α -blockade was associated with a reduced risk of intraoperative hypertension but does not change outcomes.
- **Meaning:** Preoperative nonselective α -blocker may be better than selective ones in controlling intraoperative hypertension in patients undergoing surgery for pheochromocytomas and paragangliomas.

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GLOSSARY

ASD = absolute standardized difference; **BP** = blood pressure; **beats/min** = beats per minute; **CI** = confidence interval; **D** = difference; **EQUATOR** = Enhancing the QUALity and Transparency Of health Research; **Hb** = hemoglobin; **HR** = heart rate; **ICU** = intensive care unit; **IQR** = interquartile range; **LOS** = length of stay; **MD** = median difference; **MV** = mechanical ventilation; **OR** = odds ratio; **PPGLs** = pheochromocytomas and paragangliomas; **SBP** = systolic blood pressure; **SD** = standard deviation; **TWA** = time-weighted average outside the specified range; **TWA-HR** = time-weighted average outside the specified heart rate range; **TWA-SBP >160** = time-weighted average of systolic blood pressure >160 mm Hg; **TWA-SBP** = time-weighted average outside the specified systolic blood pressure range

Pheochromocytomas and paragangliomas (PPGLs) are rare catecholamine-secreting tumors originating from chromaffin cells of the adrenal medulla and paraganglia. The prevalence of PPGLs in hospital outpatients with hypertension was reported from 0.1% to 0.6%.¹⁻³ Resection is the main treatment for PPGLs. However, severe and rapid fluctuations in blood pressure (BP) may occur during surgery, which places patients at a significantly increased risk of major morbidities.⁴ In the early period, surgery for PPGLs was associated with a mortality up to 25%.^{5,6} Careful preoperative preparation is recommended to prevent life-threatening events, one of which is α -blockade therapy.^{7,8} Studies indicated that preoperative α -blockade significantly improved intraoperative hemodynamics and reduced postoperative morbidity and mortality in patients undergoing surgery for PPGLs.^{9,10}

Currently, 2 types of α -blockers are used in clinical practice, that is, selective and nonselective α -blockers. Phenoxybenzamine is a noncompetitive, long-acting, and nonselective antagonist of α 1- and α 2-receptors. The noncompetitive property is useful during surgery since the α -blockade remains effective even when excessive release of catecholamines occurs. However, the long-acting effect may increase postoperative hypotension; and the inhibition of α 2-receptor is associated with some side effects, including reflex tachycardia.^{11,12} Doxazosin, terazosin, and prazosin are competitive, short-acting, and selective antagonists of α 1-receptors. The short-acting effect may be beneficial by shortening postoperative hypotension, and the selective α 1-blockade means they cause fewer side effects, such as tachycardia. However, as a result of competitive property, the α -blockade may be ineffective during surges of catecholamine release, which may occur when handling the tumor.^{11,12}

The effects of selective and nonselective α -blockade on hemodynamics and outcomes have been observed in patients undergoing surgery for PPGLs.¹³⁻¹⁸ However, limitations exist in available results. For example, apart from the observational and retrospective natures, the sample sizes were small in most studies and the confounding factors were not corrected. All these weakened the strength

of conclusions. The purpose of this propensity-matched cohort study was to assess the association between the choice of α -blockade and the amount of intraoperative hypertension in patients undergoing surgery for PPGLs.

METHODS

This was a retrospective cohort study. The study protocol was approved by the Clinical Research Ethics Committee of Peking University First Hospital (2018 [47]; Beijing, China). Because all data were collected retrospectively through the electronic medical record system and postoperative follow-up was not performed during the study period, the Clinical Research Ethics Committee agreed to waive written informed consent. However, the privacy of patients was strictly protected. This manuscript adheres to the applicable Enhancing the QUALity and Transparency Of health Research (EQUATOR) guidelines.

Patient Recruitment

Potential participants were screened using the electronic medical records system from January 1, 2006 to October 31, 2017 in Peking University First Hospital (Beijing, China). The inclusion criteria were those who underwent surgery for PPGLs, of which the diagnoses were confirmed by pathological examination. Patients were excluded if they met any of the following criteria: (1) did not receive α -blockade before surgery; (2) with bilateral PPGLs; (3) underwent surgery through a transurethral pathway; (4) incomplete data.

Preoperative Management

All patients received α -blockade therapy preoperatively. In the study center, surgeons tended to administer nonselective α -blockade for patients with more severe conditions (more severe symptoms, larger tumor size, and/or higher catecholamine levels). However, there was not a strict boundary between "severe" and "mild" with respect to the various clinical manifestations of PPGLs.

Initially, doxazosin (4–8 mg, once daily), terazosin (2–4 mg, twice daily), prazosin (1–2 mg, 3 times daily), or phenoxybenzamine (10–15 mg, 3 times daily) was administered. The dose was then titrated to maintain

the BP lower than 160/90 mm Hg. After α -blockade had been achieved, a β -blocker was added when necessary to maintain the heart rate (HR) <90 beats per minute (beats/min). All patients received α -blockade for more than 7 days. In addition, patients were encouraged to take large amounts of fluids and salt before surgery. Metyrosine was, however, not used in the study center.

Anesthesia and Perioperative Care

In the operating room, all patients underwent continuous BP monitoring through an intra-arterial catheter starting before the induction of anesthesia. Arterial blood-gas analysis was done when considered necessary. Other intraoperative monitoring included electrocardiogram, pulse oxygen saturation, end-tidal carbon dioxide, nasopharyngeal temperature, and urine output. Both peripheral and central venous lines were established.

General anesthesia with endotracheal intubation was performed for all patients. As a general practice, propofol and/or etomidate were administered for anesthesia induction; propofol infusion and/or sevoflurane inhalation, with or without nitrous oxide inhalation, were used for anesthesia maintenance. Fentanyl, sufentanil, and/or remifentanyl were administered for analgesia. For patients who underwent open surgery, combined epidural-general anesthesia could be performed, depending on the discretion of anesthesiologists. Epidural block was performed with lidocaine or ropivacaine. Intraoperative use of vasoactive drugs and/or β -blockers was decided by the anesthesiologists. Generally, vasodilators were administered when systolic blood pressure (SBP) was higher than 160 mm Hg and vasopressors were administered when SBP was lower than 90 mm Hg. Phentolamine was the first-choice vasodilator; nicardipine and urapidil were used as adjuvant therapies. Regarding vasopressors, norepinephrine was the first-choice therapy; epinephrine and, in some cases, dopamine were also used, depending on the predominant secretion of PPGLs. Esmolol was administered when HR was faster than 90 beats/min. Fluid infusion and blood transfusion were provided according to routine practice. Before tumor removal, patients were subjected to mild volume overload to attenuate relative hypovolemia after vessel ligation; after tumor removal, fluid infusion was adjusted according to patients' hemodynamics and urine output. Blood transfusion was administered when hemoglobin (Hb) <7.0 g/dL; for patients with comorbid cardiovascular disease, blood transfusion was administered when Hb <10.0 g/dL. The choice of the surgical technique (open versus laparoscopic) was determined by the surgeon. As a general practice, large tumor size (>6 – 8 cm), suspected or proven malignancy, locally advanced cancer, metastases, and tumors located in

the suprahilar or interaortocaval region were indications for open surgery.

At the end of the surgery, patients were transferred to the postanesthesia care unit or intensive care unit (ICU) depending on their clinical and hemodynamic status. Postoperative patient-controlled analgesia was established with intravenous opioids or, for those with an indwelling epidural catheter, with epidural local anesthetics and opioids. Nonsteroidal anti-inflammatory drugs were administered in those without contraindications.

Data Collection and Outcomes

Data were collected retrospectively using the electronic medical records system of the study center. Demographic characteristics included age, sex, height, and weight. Preoperative data included surgical diagnosis, comorbidity (and Charlson Comorbidity Index¹⁹), laboratory test results, and location and diameter of the tumor. Intraoperative data included type and duration of anesthesia, use of vasoactive drugs, fluid infusion and blood transfusion, hemodynamic fluctuations, and type and duration of surgery. Postoperative data included ICU admission, duration of vasopressor use, occurrence of complications, and lengths of stay in ICU and hospital.

Hemodynamic data were obtained from the anesthesia information system, which captured and stored parameters every 10 seconds in a real-time manner. For each patient, the collected hemodynamic data were stored in a separate excel file. Time-weighted average (TWA) outside the specified ranges of SBP (TWA-SBP) or HR (TWA-HR) was calculated to reflect hemodynamic fluctuation. In the present study, TWA was calculated as the summation of SBP or HR excursions outside a predefined range multiplied by recording durations (in 10-second intervals), and divided by the anesthesia duration (from anesthesia induction to operating room discharge, in seconds), in units of mm Hg or beats/min (Supplemental Digital Content 1, Document, <http://links.lww.com/AA/D143>). Although the linear interpolation between points and the trapezoid rule was not used in our study, the accuracy of calculated TWA was acceptable due to the very short data capturing interval. The missing hemodynamic data, which were usually due to arterial blood sampling, arterial catheter flushing and disconnection, and $<1\%$ in total, were replaced by the recorded data 10 seconds before. The TWA was calculated using the Python 3.7.0 software (Python Software Foundation, Beaverton, OR).

The primary end point was TWA-SBP >160 mm Hg, that is, TWA of SBP >160 mm Hg. The secondary end points included (1) other intraoperative hemodynamic parameters, including TWA-SBP <90 mm Hg, TWA-HR >100 beats/min, the highest SBP, the lowest

SBP, and the highest HR during surgery; and (2) post-operative outcomes, including ICU admission, use of vasopressors, occurrence of complications, length of hospital stay, and in-hospital mortality after surgery.

Statistical Analyses

Between-group differences of baseline and intraoperative variables for propensity score matching were compared using the absolute standardized differences (ASDs), which are defined as the absolute difference in means, mean ranks, or proportions divided by the pooled standard deviation and calculated with the formula published by Austin.²⁰ An ASD ≥ 0.233 (ie, $1.96 \times \sqrt{(n1 + n2) / (n1 \times n2)}$) was considered imbalanced between the 2 groups. Regarding baseline and intraoperative variables not for propensity score matching, continuous data were compared using the Student *t* test (normal distribution) or Mann-Whitney *U* test (nonnormal distribution); categorical data were analyzed using the χ^2 test. Missing data were not replaced.

Variables that were considered clinically relevant were used for propensity score matching. These variables were selected a priori and included age, sex,²¹ body mass index,^{21,22} preoperative comorbidities,²¹⁻²³ presence of typical symptoms,²⁴ catecholamine-producing tumor,²⁵⁻²⁷ maximal tumor size,^{23-25,28,29} origin of tumor, peak SBP before α -blockade,²⁶ other anti-hypertensive therapy, SBP before surgery, HR before surgery, year of surgery, duration of anesthesia, type of anesthesia (general or combined epidural-general),³⁰ anesthesia induction (propofol or propofol + etomidate), anesthesia maintenance (propofol, sevoflurane, or propofol + sevoflurane), use of N₂O during anesthesia, duration of surgery, type of surgery (open or laparoscopic),^{25,28} and equivalent dose vasopressor.³¹ A logistic regression model was used to calculate propensity scores predicting the probability of being in nonselective α -blockade group. Patients were matched in a 1:1 ratio using the nearest-neighbor matching with caliper widths equal to 0.2 of the standard deviation of the logit of the propensity score. In matched patients, the TWA-SBP >160 mm Hg between groups was compared with the Mann-Whitney *U* test. The median difference (and 95% confidence interval [CI]) between 2 groups was calculated with the Hodges-Lehmann estimator. To evaluate the interactions of baseline and intraoperative variables on the association between preoperative α -blockade and TWA-SBP >160, we used Z test to compare the difference between the 2 regression coefficients from subgroup analysis by using the following equation:

$$Z = \frac{\beta_1 - \beta_2}{\sqrt{SE(\beta_1)^2 + SE(\beta_2)^2}} \cdot^{32}$$

For secondary end points, continuous variables were compared using the Student *t* test (highest

SBP, lowest SBP, highest HR) or Mann-Whitney *U* test (TWA-SBP <90 mm Hg and TWA-HR >100 beats/min). Categorical variables (ICU admission after surgery, mechanical ventilation in ICU, use of vasopressors, occurrence of complications, and in-hospital death) were analyzed using the χ^2 test, χ^2 test with continuity correction, or Fisher exact test. Odds ratio between groups was calculated using the logistic regression analysis. Time-to-event variables (duration of mechanical ventilation, duration of vasopressors, length of stay in ICU, length of stay in hospital after surgery) were calculated with the Kaplan-Meier estimator, with differences between groups assessed by the log-rank test. Patients who died during hospital stay were censored at the time of death.

For each hypothesis, a 2-sided *P* < .05 was considered statistically significant. For the treatment-by-covariate interaction in predefined subgroup analyses, a *P* < .10 was considered statistically significant. Statistical analyses were performed with the SPSS version 22 (SPSS, Inc, Chicago, IL) and the free software package “R” version 2.15.3 including the “Matchit” and the “ROC” plugins.

RESULTS

Participants

A total of 357 patients underwent surgery for PPGLs from January 1, 2006 to October 31, 2017. Among them, 48 were excluded for no preoperative α -blockade, 13 for bilateral tumors, 8 for transurethral surgery, and 2 for incomplete data. Of the remaining 286 patients, 156 received selective α -blockade (146 blocked with doxazosin, 9 with terazosin, and 1 with prazosin) and 130 received nonselective α -blockade (phenoxybenzamine). After propensity matching, 89 patients remained in each group, providing a total sample of 178 patients for analysis (Figure 1).

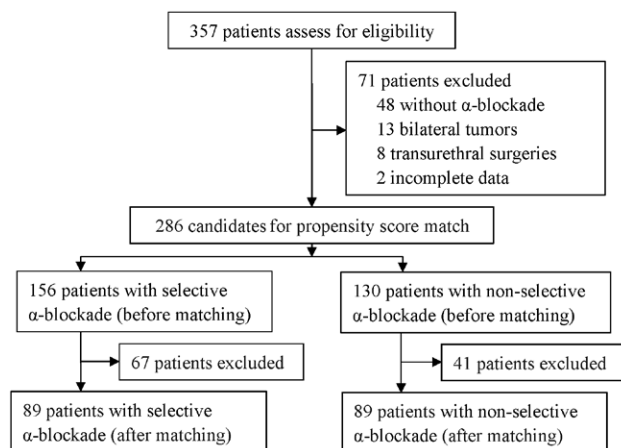


Figure 1. Flowchart of the study.

Table 1. Baseline Variables Used for Propensity Score Matching

Variables	Full Cohort (n = 286)				Matched Cohort (n = 178)		
	All (n = 286)	Nonselective α -Blockade ^a (n = 130)	Selective α -Blockade ^b (n = 156)	ASD ^c	Nonselective α -Blockade ^a (n = 89)	Selective α -Blockade ^d (n = 89)	ASD ^e
Demographics							
Age (y)	46.1 ± 14.6	43.4 ± 13.2	48.4 ± 15.4	0.373	45.5 ± 13.3	45.1 ± 15.2	0.035
Male gender	130 (45.5%)	58 (44.6%)	72 (46.2%)	0.031	40 (44.9%)	40 (44.9%)	0.000
Body mass index (kg/m ²)	23.4 ± 3.4	23.3 ± 3.5	23.4 ± 3.3	0.045	23.5 ± 3.2	23.8 ± 3.6	0.086
Preoperative comorbidities							
Stroke	13 (4.5%)	8 (6.2%)	5 (3.2%)	0.122	5 (5.6%)	3 (3.4%)	0.093
Epilepsy	1 (0.3%)	1 (0.7%)	0 (0.0%)	0.088	0 (0.0%)	0 (0.0%)	0.000
Coronary artery disease	19 (6.6%)	7 (5.4%)	12 (7.7%)	0.102	4 (4.5%)	6 (6.7%)	0.099
Congestive heart failure	4 (1.4%)	3 (2.3%)	1 (0.6%)	0.111	1 (1.1%)	1 (1.1%)	0.000
Diabetes mellitus	47 (16.4%)	21 (16.2%)	26 (16.7%)	0.014	14 (15.7%)	16 (18.0%)	0.061
Chronic kidney disease	3 (1.0%)	1 (0.8%)	2 (1.3%)	0.058	1 (1.1%)	1 (1.1%)	0.000
Asthma	1 (0.3%)	0 (0.0%)	1 (0.6%)	0.080	0 (0.0%)	0 (0.0%)	0.000
Features of PPGLs							
With typical symptoms ^e	178 (62.2%)	91 (70.0%)	87 (55.8%)	0.411	63 (70.8%)	60 (67.4%)	0.075
Catecholamine-producing tumor	220 (76.9%)	102 (78.5%)	118 (75.6%)	0.068	70 (78.7%)	68 (76.4%)	0.054
Maximal tumor diameter (cm)	5.2 (4.2–7.0)	5.5 (4.5–7.7)	5.0 (4.0–6.5)	0.219	5.0 (4.4–7.4)	5.5 (4.4–7.1)	0.020
Origin of tumor				0.150			0.027
Adrenal gland	232 (81.1%)	101 (77.7%)	131 (84.0%)		71 (79.8%)	70 (78.7%)	
Paraganglia	54 (18.9%)	29 (22.3%)	25 (16%)		18 (20.2%)	19 (21.3%)	
Peak SBP before therapy ^f (mm Hg)	177 ± 39	186 ± 36	168 ± 40	0.498	180 ± 32	180 ± 40	0.012
Other antihypertensive therapy ^g	111 (38.8%)	51 (39.2%)	60 (38.5%)	0.016	34 (38.2%)	34 (38.2%)	0.000
SBP before surgery ^h (mm Hg)	126 ± 15	129 ± 15	124 ± 13	0.281	129 ± 14	127 ± 14	0.094
HR before surgery ^h (beats/min)	76 ± 9	76 ± 9	76 ± 8	0.054	77 ± 8	77 ± 6	0.012

Data are presented as mean ± SD, number of patients (percentage), or median (interquartile range). ASD in bold indicates those of ≥ 0.233 . Abbreviations: ASD, absolute standardized difference; HR, heart rate; PPGLs, pheochromocytomas and paragangliomas; SBP, systolic blood pressure; SD, standard deviation.

^aIndicates phenoxybenzamine.

^bIncludes doxazosin (146 cases), terazosin (9 cases), and prazosin (1 case).

^cAn ASD of ≥ 0.233 was considered unbalanced.²⁰

^dIncludes doxazosin (85 cases) and terazosin (4 cases).

^eContinuous or episodic hypertension with at least 1 of “triad” symptoms (headaches, palpitations, sweating) at the first clinic visit.

^fMeasured before antihypertensive therapy.

^gIncluding of calcium channel blockers, angiotensin-converting enzyme inhibitors, and/or angiotensin II receptor blockers.

^hMeasured the day before surgery in the ward.

Baseline and Preoperative/Intraoperative Data

Before matching, compared with patients who received selective α -blockade, those who received nonselective α -blockade had younger age, more typical symptoms, higher peak SBP before therapy, and higher SBP before surgery; they received more combined epidural-general anesthesia (versus general anesthesia alone); they were given more preoperative β -blockade, more intraoperative fluids, and had more urine output. After matching, the 2 groups were well balanced (Tables 1–3).

Primary and Secondary End Points

Patients who received nonselective α -blockade had lower TWA-SBP >160 mm Hg (median 0.472 mm Hg, interquartile range [IQR] 0.081–1.300) than those who received selective α -blockade (median 1.114, IQR, 0.162–2.853; median difference –0.391 mm Hg, 95% CI, –0.828 to –0.032; $P = .016$). Significant interaction effects were observed between the choice of preoperative α -blockade and age (<50 vs ≥ 50 years, P for interaction = .024) and typical symptoms (no versus yes, P for interaction = .032), indicating that patients with higher age and typical symptoms might get more

benefit from preoperative nonselective α -blockade (Figure 2).

Regarding secondary end points, patients who received nonselective α -blockade had lower highest SBP (193 ± 24 mm Hg) than those who received selective α -blockade (205 ± 34 mm Hg; mean difference –12 mm Hg, 95% CI, –20 to –3; $P = .008$). Other intraoperative hemodynamic variables, as well as postoperative outcomes, did not differ significantly between the 2 groups. Two patients (1 in each group) died during hospital stay after surgery, both were attributed to a large retroperitoneal tumor (>20 cm), massive bleeding, and persistent hypotension (Table 4, Supplemental Digital Content 2, Document, <http://links.lww.com/AA/D143>).

DISCUSSION

Results of this retrospective cohort study with propensity score matching showed that, for patients with PPGLs, the use of nonselective α -blockade before surgery was associated with a reduced risk of intraoperative hypertension when compared with selective α -blockade.

Table 2. Intraoperative Variables Used for Propensity Score Matching

Variables	Full Cohort (n = 286)				Matched Cohort (n = 178)		
	All (n = 286)	Nonselective α-Blockade ^a (n = 130)	Selective α-Blockade ^b (n = 156)	ASD ^c	Nonselective α-Blockade ^a (n = 89)	Selective α-Blockade ^d (n = 89)	ASD ^c
Year of surgery				0.196			0.080
2006–2009	69 (24.1%)	37 (28.5%)	32 (20.5%)		23 (25.8%)	26 (29.2%)	
2010–2013	66 (23.1%)	26 (20.0%)	40 (25.6%)		18 (20.2%)	18 (20.2%)	
2014–2017	151 (52.8%)	67 (51.5%)	84 (53.8%)		48 (53.9%)	45 (50.6%)	
Duration of anesthesia (min)	179 (135–245)	180 (140–258)	178 (130–233)	0.211	183 (143–263)	185 (136–250)	0.016
Type of anesthesia				0.342			0.067
General	172 (60.1%)	66 (50.8%)	106 (67.9%)		54 (60.7%)	51 (57.3%)	
Epidural + general	114 (39.9%)	64 (49.2%)	50 (32.1%)		35 (39.3%)	38 (42.7%)	
Anesthesia induction				0.053			0.054
Propofol	221 (77.3%)	102 (78.5%)	119 (76.3%)		67 (75.3%)	69 (77.5%)	
Etomidate + propofol	65 (22.7%)	28 (21.5%)	37 (23.7%)		22 (24.7%)	20 (22.5%)	
Anesthesia maintenance				0.147			0.075
Propofol	109 (38.1%)	48 (36.9%)	61 (39.1%)		34 (38.2%)	31 (34.8%)	
Sevoflurane	115 (40.2%)	57 (43.8%)	58 (37.2%)		37 (41.6%)	40 (44.9%)	
Propofol + sevoflurane	62 (21.7%)	25 (19.2%)	37 (23.7%)		18 (20.2%)	18 (20.2%)	
Use of N ₂ O during anesthesia	253 (88.5%)	117 (90.0%)	136 (87.2%)	0.094	79 (88.8%)	78 (87.6%)	0.037
Duration of surgery (min)	123 (78–177)	125 (88–214)	123 (73–159)	0.231	120 (87–215)	134 (88–173)	0.025
Type of surgery				0.050			0.000
Open	104 (36.4%)	49 (37.7%)	55 (35.3%)		36 (40.4%)	36 (40.4%)	
Laparoscopic	182 (63.6%)	81 (62.3%)	101 (64.7%)		53 (59.6%)	53 (59.6%)	
Equivalent dose vasopressor ^e	2 (0–64)	8 (0–70)	0 (0–64)	0.153	8 (0–38)	4 (0–80)	0.005

Data are presented as mean ± SD, number of patients (percentage), or median (interquartile range). ASD in bold indicates those of ≥0.233.

Abbreviations: ASD, absolute standardized difference; SD, standard deviation.

^aIndicates phenoxybenzamine.

^bIncludes doxazosin (146 cases), terazosin (9 cases), and prazosin (1 case).

^cAn ASD of ≥0.233 was considered unbalanced.²⁰

^dIncludes doxazosin (85 cases) and terazosin (4 cases).

^eEquivalent dose = (dopamine dose) + (epinephrine dose × 100) + (norepinephrine dose × 100).³¹

Table 3. Baseline and Intraoperative Variables Not Used for Propensity Score Matching

Variables	Full Cohort (n = 286)				Matched Cohort ^a (n = 178)		
	All (n = 286)	Nonselective α-Blockade ^b (n = 130)	Selective α-Blockade ^c (n = 156)	P	Nonselective α-Blockade ^b (n = 89)	Selective α-Blockade ^d (n = 89)	P
Preoperative laboratory test							
Hemoglobin (g/L)	135 ± 18 [3]	134 ± 19 [2]	136 ± 16 [1]	.368	134 ± 20 [1]	135 ± 16	.821
Creatinine (mmol/L)	76 ± 19 [2]	77 ± 24 [1]	76 ± 14 [1]	.428	77 ± 27	75 ± 13 [1]	.526
Albumin (g/L)	43 ± 4 [2]	43 ± 4 [1]	42 ± 4 [1]	.216	43 ± 4	42 ± 4 [1]	.936
Glucose (mmol/L)	5.9 ± 1.9 [2]	6.0 ± 1.6 [1]	5.9 ± 2.2 [1]	.805	5.9 ± 1.6	5.8 ± 1.6 [1]	.610
Preoperative β-blockade	69 (24.1%)	39 (30.0%)	30 (19.2%)	.034	27 (30.3%)	23 (25.8%)	.505
Charlson Comorbidity Index ^e	2 (2–3)	2 (2–3)	2 (2–3)	>.999	2 (2–3)	2 (2–3)	.799
Intraoperative vasodilators							
Use of esmolol	200 (69.9%)	96 (73.8%)	104 (66.7%)	.187	61 (68.5%)	62 (69.7%)	.871
Dose of esmolol ^f (mg)	160 (80–350)	240 (100–490)	130 (60–258)	.002	200 (85–480)	160 (68–273)	.160
Use of phentolamine	188 (65.7%)	91 (70.0%)	97 (62.2%)	.165	62 (69.7%)	60 (67.4%)	.747
Dose of phentolamine ^f (mg)	10 (4–25)	10 (2–22)	10 (4–26)	.297	8 (2–22)	14 (5–36)	.022
Use of nicardipine	89 (31.1%)	39 (30.0%)	50 (32.1%)	.709	29 (32.6%)	30 (33.7%)	.873
Use of urapidil	30 (10.5%)	13 (10.0%)	17 (10.9%)	.805	10 (11.2%)	11 (12.4%)	.816
Intraoperative fluids							
Fluid infusion (mL)	3200 (2475–4800)	3625 (2500–5463)	3100 (2125–4200)	.010	3200 (2500–5500)	3210 (2500–4800)	.897
Blood transfusion ^g	54 (18.9%)	27 (20.8%)	27 (17.3%)	.456	16 (18.0%)	20 (22.5%)	.455
Estimated blood loss (mL)	100 (50–500)	150 (60–600)	100 (50–490)	.052	100 (50–550)	150 (50–550)	.797
Urine output (mL)	500 (200–900)	600 (300–1000)	475 (200–800)	.003	600 (300–1000)	500 (200–900)	.264

Data are presented as number of patients (percentage), or median (interquartile range). Numbers in square brackets indicate patients with missing data. P value in bold indicates those of <.05.

Abbreviations: HR, heart rate; SBP, systolic blood pressure.

^aThe following covariates were used for matching: age, sex, body mass index, preoperative comorbidities, with typical symptoms, catecholamine-producing tumor, maximal tumor diameter, origin of tumor, peak SBP before α-blockade, other antihypertensive therapy, SBP before surgery, HR before surgery, year of surgery, duration of anesthesia, type of anesthesia, anesthesia induction, anesthesia maintenance, use of N₂O during anesthesia, duration of surgery, type of surgery, and equivalent dose vasopressor.

^bIncludes doxazosin (146 cases), terazosin (9 cases), and prazosin (1 case).

^cIndicates phenoxybenzamine.

^dIncludes doxazosin (85 cases) and terazosin (4 cases).

^eCalculated according to the version without age.¹⁹

^fResults of patients who received the drug.

^gIncluding allogeneic blood and autologous blood transfusion.

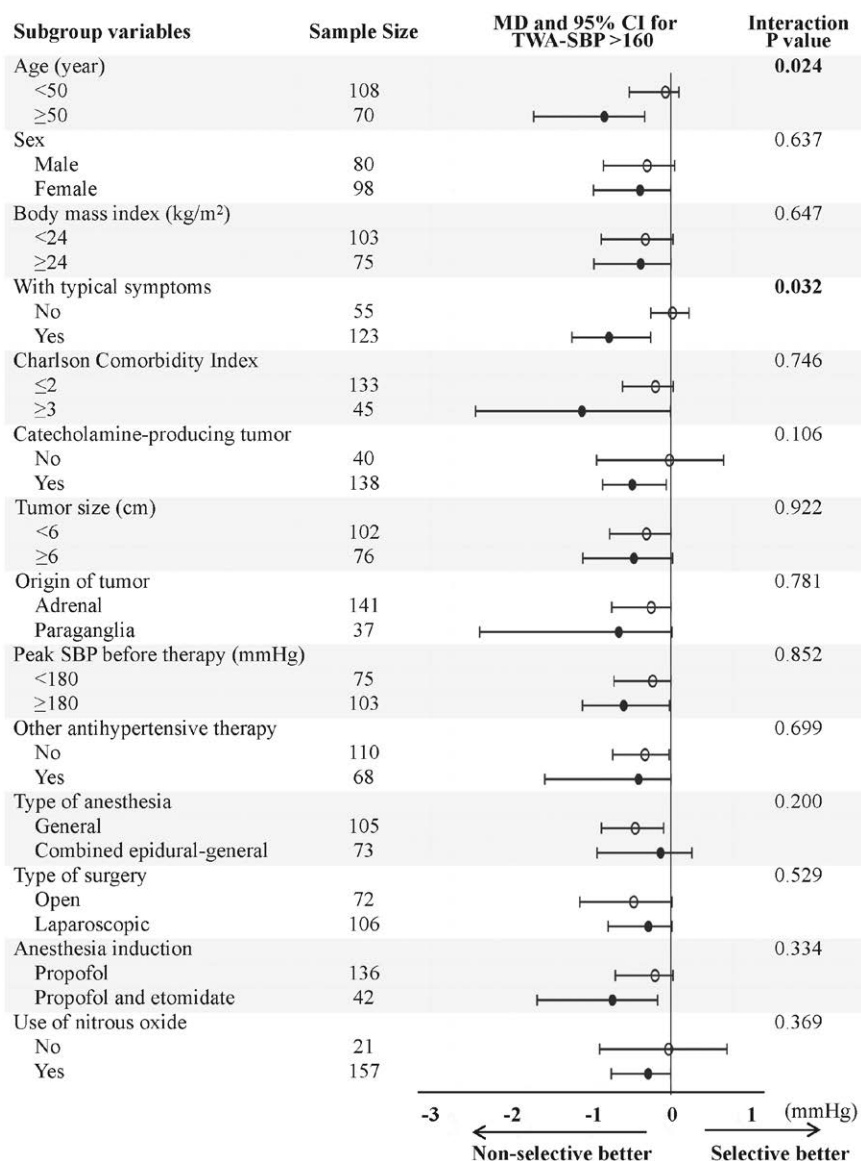


Figure 2. Interactions of baseline and perioperative variables on the association between preoperative α -blockade (selective versus nonselective) and TWA-SBP >160 in the propensity score-matched cohort. P values in bold indicate those of statistical significance. CI indicates confidence interval; MD, median difference; SBP, systolic blood pressure; TWA-SBP >160, time-weighted average of systolic blood pressure >160 mm Hg.

Although PPGLs are different in origin, they both secrete catecholamines and produce similar hemodynamic effects. Endotracheal intubation, creation of pneumoperitoneum, and handling or accidental squeezing of the tumor are common procedures that can provoke instant catecholamine release and hypertensive crises, whereas ligation of tumor veins is often followed by hypotension due to acute decrease of catecholamines concentration. The principles of perioperative management including anesthesia, fluid replacement, and hemodynamic maintenance are similar between PPGLs, so we pooled them together to analyze in the present study, just like many other authors.³³⁻³⁵

In the present study, SBP >160 mm Hg was adopted as the threshold of primary end point since it is high enough to trigger intervention. Several previous studies also adopted this threshold as primary end point³³

or to define hemodynamic instability.^{4,25,36} In our results, a reduced risk of intraoperative hypertension was observed in patients with nonselective α -blockade than in those with selective α -blockade after propensity score matching. This was in line with results in previous observational studies.^{13,28} In a recent randomized controlled trial, Buitenwerf et al³³ also reported that use of phenoxybenzamine significantly reduced the frequency and duration of SBP >160 mm Hg, lowered the maximal SBP, and lessened the requirement of vasodilators when compared with doxazosin. It is true that neutral results were also reported by some authors, possibly due to the small sample size included in the study.¹⁴ When compared with the results of others,^{14,28,33} the maximal SBP during surgery was higher in our patients. These might be attributed to the differences in patient population and perioperative management. For example, the maximal tumor diameter

Table 4. End Points of the Study in Matched Patients^a

Variables	Nonselective α -Blockade ^b (n = 89)	Selective α -Blockade ^c (n = 89)	Difference, OR, or Hazard Ratio (95% CI)	P
Primary end point				
TWA-SBP >160 (mm Hg)	0.472 (0.081–1.300)	1.114 (0.162–2.853)	Median D = -0.391 (-0.828 to -0.032)	.016
Secondary end points				
Intraoperative hemodynamic parameters				
TWA-SBP <90 (mm Hg)	0.125 (0.000–0.530)	0.095 (0.000–0.615)	Median D = 0.000 (-0.028 to 0.031)	.995
TWA-HR >100 (beats/min)	0.098 (0.017–0.371)	0.087 (0.011–0.326)	Median D = 0.005 (-0.002 to 0.057)	.464
Highest SBP (mm Hg)	193 ± 24	205 ± 34	Mean D = -12 (-20 to -3)	.008
Lowest SBP (mm Hg)	81 ± 16	80 ± 17	Mean D = 1 (-4 to 6)	.649
Highest HR (beats/min)	115 ± 17	113 ± 21	Mean D = 2 (-4 to 7)	.522
Postoperative outcomes				
ICU admission after surgery	60 (67.4%)	58 (65.2%)	OR = 1.106 (0.594–2.059)	.751
MV in ICU	41 (46.1%)	42 (47.2%)	OR = 0.956 (0.530–1.723)	.881
Duration of MV ^d (h)	3.0 (1.6–4.4)	3.0 (1.8–4.2)	Hazard ratio = 0.998 (0.643–1.549)	.991
LOS in ICU ^e (d)	1.4 (1.2–1.6)	1.6 (1.2–1.8)	Hazard ratio = 0.953 (0.660–1.374)	.626
Use of vasopressors ^f	17 (19.1%)	23 (25.8%)	OR = 0.678 (0.333–1.379)	.281
Duration of vasopressors ^g (h)	4.0 (0.0–12.1)	8.0 (0.2–15.8)	Hazard ratio = 0.800 (0.411–1.558)	.497
Occurrence of complications	22 (24.7%)	25 (28.1%)	OR = 0.841 (0.431–1.639)	.610
LOS in hospital after surgery (d)	7.0 (6.3–7.7)	6.0 (5.3–6.7)	Hazard ratio = 1.103 (0.816–1.491)	.461
In-hospital death	1 (1.1%)	1 (1.1%)	OR = 1.000 (0.062–16.241)	>.999

Data are presented as median (interquartile range), mean ± SD, number of patients (percentage), or median (95% CI). P value in bold indicates those of <.05. Abbreviations: beats/min, beats per minute; CI, confidence interval; D, difference; HR, heart rate; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; OR, odds ratio; SBP systolic blood pressure; TWA, time-weighted average.

^aThe following covariates were used for matching: age, sex, body mass index, preoperative comorbidities, with typical symptoms, catecholamine-producing tumor, maximal tumor diameter, origin of tumor, peak SBP before α -blockade, other antihypertensive therapy, SBP before surgery, HR before surgery, year of surgery, duration of anesthesia, anesthesia induction, anesthesia maintenance, use of N₂O during anesthesia, duration of surgery, type of surgery, and equivalent dose vasopressor.

^bIndicates phenoxybenzamine.

^cIncludes doxazosin (85 cases) and terazosin (4 cases).

^dResults of patients who received mechanical ventilation.

^eResults of patients who were admitted to the ICU after surgery. Results are presented as mean (95% CI).

^fIncluding epinephrine, norepinephrine, and/or dopamine.

^gResults of patients who received vasopressors after surgery.

was larger in our patients than in those of Malec et al¹⁴ and Buitenwerf et al,³³ whereas the proportion with preoperative β -blockade was lower in our patients than in those of others.^{14,28,33} Furthermore, we found significant interaction effects between age or typical symptoms and type of preoperative α -blockade on TWA-SBP >160, which indicated that nonselective α -blockade might be more beneficial for patients with higher age and typical symptoms. However, the interaction results from this observational study are only hypothesis generating because confounding has not been controlled for within the subgroups.

The effects of selective and nonselective α -blockade on intraoperative and postoperative hypotension had been evaluated, but with conflicting results. In studies of Randle et al¹⁵ and Bruynzeel et al,²⁵ patients blocked with doxazosin had more intraoperative hypotension and lower postoperative BP than those blocked with phenoxybenzamine, whereas Malec et al¹⁴ did not find any significant differences regarding intraoperative or postoperative BP between patients with selective or nonselective α -blockade. On the contrary, Prys-Roberts and Farndon¹⁶ and Liu et al¹⁷ reported that postoperative BP was significantly lower in patients with nonselective α -blockade (phenoxybenzamine) than in those with selective ones. It should be noted

that all the above studies were observational in nature and, therefore, the confounding effects of baseline and perioperative imbalances could not be excluded, and the sample sizes were small in most of these studies. In the present study, the amount of intraoperative hypotension and the use of vasopressors after surgery did not differ between groups. Similar results were also reported by Buitenwerf et al³³ in their recent randomized trial.

In addition to α -blockade, β -blockade is often administered during preoperative and intraoperative periods for patients with PPGLs. The proportion of patients who received β -blockade in different studies varied from 26.0% to 96.3% due to different types of α -blockade, the threshold of HR control, and patient populations.^{13,15,18,30,36,37} In a systematic review, van der Zee and de Boer¹¹ found that the use of phenoxybenzamine was often accompanied by a β -blocker to control reflex tachycardia when compared with doxazosin. In the present study, patients with nonselective α -blockade received more β -blockade therapy before and during surgery, but the differences no longer existed after propensity score matching. From the available evidence, it seems that Chinese patients received less β -blockade to control the HR before surgery than Western patients.^{13,15,18,30,36,37}

Postoperative outcomes including length of hospital stay and the occurrence of complications had been compared in previous studies. The available evidence did not find significant differences between patients with selective and nonselective α -blockade.^{15,17,28,33} In the present study, although patients with nonselective α -blockade suffered less hypertension during surgery, clinical outcomes did not differ between groups. One possible reason is that, because of the rarity of the tumor, sample sizes of the available studies including ours were small and insufficient to detect the difference. Another possible explanation is that intraoperative hypertension might be less harmful. In the study of Monk et al,³⁸ intraoperative hypotension, but not hypertension, was associated with increased 30-day postoperative mortality. Whether the prevention of intraoperative hypertension can improve outcomes in patients with PPGLs deserves further study.

Adverse side effects should also be considered when choosing the type of α -blockers. The study of Prys-Roberts and Farndon¹⁶ systematically evaluated safety outcomes after administering doxazosin or phenoxybenzamine in patients with pheochromocytoma. Less postural hypotension (100% with phenoxybenzamine versus 7% with doxazosin) and fewer postoperative edema (88% with phenoxybenzamine versus 4% with doxazosin) were documented in patients given doxazosin. However, because of the retrospective nature of the study, we did not report the occurrence of adverse events in our patients. Further studies especially prospective trials with a large sample size are required to confirm our results and clarify the above questions.

The strength of this study included a relatively large sample size for a rare tumor, data obtained from the electronic medical records system and therefore less subject to observer bias, and propensity matching to further minimize bias. However, there are some limitations. There was a surgeon's preference for nonselective α -blockade in more severe cases in the study center, and the study was done over a 12-year period during which changes were made in clinical practice. Although nearest-neighbor propensity score matching was performed, we cannot exclude residual imbalance and bias produced by unrecognized factors in comparing the results between the 2 patient populations. As a retrospective study, we did not collect data regarding the prevalence of side effects, which might be different between patients with selective or nonselective α -blockade. Finally, we did not perform postdischarge follow-up, so the effects of selective versus nonselective α -blockade on longer outcomes remain unknown.

CONCLUSIONS

For patients undergoing surgery for PPGLs, preoperative nonselective α -blockade was associated with less intraoperative hypertension when compared

with selective α -blockade. The choice of preoperative α -blockades does not change postoperative outcomes. Further studies are required to confirm our results. ■■

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DISCLOSURES

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Contribution: This author helped design the study and collect data.

Name: Dong-Xin Wang, MD, PhD.

Contribution: This author helped conceive and design the study, review the original data and the results of analyses, and critically revise the manuscript.

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