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Predictors of hemodynamic instability during surgery for pheochromocytoma

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Abstract

Background—Resection of pheochromocytoma is often associated with hemodynamic instability (HDI). We examined patient and tumor factors that may influence HDI. The effect of pre-treatment with non-selective alpha-blockade phenoxybenzamine (PXB) vs. selective alpha-blockade on HDI and outcomes was also evaluated.

Methods—The records of 91 patients who underwent adrenalectomy between 2002 and 2013 were retrospectively reviewed. HDI was determined by: number of intraoperative episodes of systolic blood pressure (SBP) >200mmHg, those greater than or less than 30% of baseline, heart rate >110 and the need for postoperative vasopressors. Fishers exact, t-test and regressions were performed.

Results—Among the 91 patients, 78% received PXB, 18% selective alpha-blockade and 4% no adrenergic blockade. Patient demographics, tumor factors and surgical approach were similar among the blockade groups. On multivariate analysis increasing tumor size was associated with a significant rise in the number of episodes of SBP >30% (RR 1.40) and an increased postoperative vasopressor requirement (OR 1.23). Open adrenalectomy and use of selective blockade were associated with an increased number of episodes of SBP >200mmHg (RR 27.8 and RR 20.9, respectively). Open adrenalectomy was also associated with increased readmissions (OR 12.3), complications (OR 5.6), use of postoperative vasopressors (OR 4.4) and hospital stay (4.6 days longer). There were no differences in other HDI measurements or postoperative outcomes among the blockade groups.

Conclusions—Tumor size, open adrenalectomy and type of alpha-blockade were associated with intraoperative HDI during pheochromocytoma resection. Selective blockade was associated with significantly more episodes of intraoperative hypertension but no perioperative adverse outcomes.

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Introduction

Pheochromocytoma is defined as a tumor arising from catecholamine producing chromaffin cells in the adrenal medulla. Almost all adrenal pheochromocytomas produce, store, metabolize and secrete catecholamines.[1] According to the degree of catecholamine secretion patients may experience arrhythmias, myocardial infarction or stroke.[2] Previous studies have demonstrated that higher catecholamine levels, tumor size, alpha-blockade type, hydration status and procedure type may be associated with perioperative hemodynamic instability (HDI) during pheochromocytoma resection.[3-6]

At the First International Symposium on Pheochromocytoma in 2005, it was recommended that all patients with biochemical confirmation of pheochromocytoma should receive appropriate preoperative medical management to block the effects of catecholamine release during surgical extirpation.[7] Excessive catecholamine release is thought to occur during manipulation of the tumor, even in asymptomatic normotensive patients, and can lead to hypertensive crisis, arrhythmia and stroke. The practice of alpha-blockade began at our institution in 1967 [8] but was first described in the literature in 1956 when Priestly and colleagues reported on a series of 51 pheochromocytomas removed without mortality. The lack of mortality was attributed to the routine intraoperative use of alpha-blockade.[9] Due to wide-ranging practices and lack of randomized control trials or large prospective cohort studies, there is no consensus and no specific recommendations regarding the preferred drug to be used for preoperative blockade. However, alpha-blockade, calcium channel blockade or angiotensin receptor blockade have all been named as options.[7]

The goal of preoperative management is to normalize blood pressure, heart rate (HR) and prevent surgically induced catecholamine storm and its consequences on the cardiovascular system.[10] However even when adequate alpha-blockade has been instituted HDI remains common during pheochromocytoma resection. The current low mortality of pheochromocytoma resection is thought to be a result of adequate preoperative blockade, volume repletion and anesthetic and pharmacologic advances yet prospective randomized data are lacking.[11]

At our institution, there are two regimens utilized to achieve preoperative blockade, nonselective alpha-blockade with phenoxybenzamine (PXB) or selective alpha-blockade with doxazosin, prazosin or terazosin. PXB is the most recognized and widely used alpha-blocker for pheochromocytoma resection. However, some studies suggest that selective blockade with its improved side effect profile and wider availability can control blood pressure perioperatively as effectively as PXB and avoid prolonged postoperative hypotension.[3, 12, 13] Other authors have reported either no difference or more episodes of intraoperative hypertension with the use of selective blockade when compared to PXB.[14-16]

This study examines our center's experience with adrenal-based pheochromocytoma resections in an attempt to identify patient and tumor factors predictive of HDI. We also evaluate the effectiveness of selective alpha-blockade compared to the classically used non-selective blocking agent PXB.

Methods

After obtaining institutional review board approval, a retrospective review of the medical records of 91 patients undergoing adrenalectomy between April 2002 and September 2013 for pathologically confirmed pheochromocytoma was performed.

Preoperative variables

Demographic data and vital signs were recorded. Pre-blockade systolic and diastolic blood pressure (SBP and DBP) and HR were defined as those obtained prior to initiation of alpha-blockade. Urine and/or plasma catecholamine and metanephrine values were recorded and normalized by dividing the absolute value by the respective upper limit of normal and quantified as the number of times above the upper limit of normal. For the analysis epinephrine and norepinephrine were grouped with their respective metabolites metanephrine and normetanephrine and were subsequently referred to as epinephrine or norepinephrine. The cohort was divided into two groups according to the type of preoperative alpha-blockade utilized; non-selective blockade with PXB (2/2002-9/2013), or selective blockade with doxazosin, prazosin or terazosin (7/2004-9/2013). Selective blockade has been utilized more recently at our institution (in 12 of 16 patients since 2011) however there are no set criteria of patient or tumor factors to guide prescribing practices and the decision is based on provider preferences. All patients received at least two weeks of pretreatment. The starting dose of PXB was 10 milligrams twice to three times daily and was titrated in 10 milligrams increments to desired effect. The starting dose of doxazosin (the most commonly used selective blocker) was 1 milligram daily and was titrated in 1 milligram increments to desired effect. Patients were considered adequately blocked by the treating physician when the patient reported orthostatic symptoms and the SBP was consistently <135 mmHg. Preoperative baseline SBP and HR were defined as those values recorded after blockade and within the week prior to operative intervention.

Intraoperative variables

American Society of Anesthesiologists physical status (ASA), procedure type, operative time, total fluid administered, estimated blood loss (EBL), blood transfusion and tumor size were recorded. Procedure type was defined as either endoscopic or open. Endoscopic adrenalectomy (EA) (n=71) included the anterior transperitoneal laparoscopic (n=55), posterior retroperitoneoscopic (n=14) and endoscopic converted to open approach (n=2). Indications for open adrenalectomy were based on surgeon preference and included size >6-10cm, cortical sparing procedures, re-operative adrenalectomy, large bilateral tumors, adjacent organ resection (i.e. kidney, spleen, small bowel) or tumor invasion of the IVC. Hemodynamic instability (HDI) measurements collected included: number of episodes of SBP >200mmHg, episodes of SBP greater than 30% above and below baseline, as well as number of episodes of HR > 110 beats per minute (bpm). The use of intraoperative beta blockade, vasodilators and vasopressors was also collected.

Postoperative variables

Vasopressor and fluid requirement, length of stay (LOS), complications, all cause readmission and death within 30 days were recorded. Postoperative vasopressor requirement

was defined as the need for intravenous vasopressors to sustain blood pressure for >30 minutes and was recorded for the first 24 hours after surgery. Postoperative fluid requirement was defined as the total amount of intravenous fluid administered over the first 24 hours.

Statistical analysis

Statistical analysis was performed using STATA version 13.0.[17] Patient demographics, tumor characteristics, procedure type and perioperative outcome variables were compared using fisher's exact and student's t-test with unequal variances. Predictors of HDI were analyzed using unadjusted and adjusted regressions. Each HDI outcome (# of episodes of SBP >200mmHg, # of episodes of SBP greater than 30% above or below baseline and # of episodes of HR >110) was modeled separately by negative binomial regression with duration of surgery as exposure and robust standard error. Postoperative outcomes (postoperative fluid requirement and LOS) were also analyzed using unadjusted and adjusted regression analyses. Postoperative vasopressor requirement, complications, and readmissions were not included in the multivariate analysis due to the low number of occurrences. Missing variables were excluded from the analysis.

Results

Demographics and tumor characteristics are presented in Table 1. Overall the median patient age was 52 years, 53% were women and the median tumor size was 4 cm with a range of 0.9 cm to 17 cm. The majority of tumors (94%) were functional and predominantly norepinephrine secreting (62%), however 24% secreted both epinephrine and norepinephrine, and 8% solely epinephrine. In five (6%) patients catecholamine elevations were not detected, two NF-1 patients were suspected to have pheochromocytomas and three patients had atypical imaging or large adrenal masses. Four patients (4%) were not preoperatively treated with alpha blocking agents. This was secondary to the fact that 3 of the 4 patients did not have elevated catecholamines at baseline and one patient did not have catecholamine levels checked preoperatively. According to preoperative blockade type, no significant differences were found in demographics, tumor characteristics at presentation or the duration of preoperative alpha blockade. In addition, there were no significant differences in the median SBP prior to or after preparation with alpha-blockade (Table 1).

Procedure type and perioperative variables are presented in Table 2. The majority of adrenalectomies were performed endoscopically (78%) and there was no difference in the distribution of open and endoscopic procedures amongst blockade groups. The majority of patients were blocked with PXB (78%). Sixteen patients (18%) were blocked with selective agents and 4 patients (4%) were not blocked. The operative time and LOS were significantly longer in the PXB group when compared to the selective blockade group (143 vs. 129 min, p=0.044 and 3 vs. 2 days, p=0.010). Other factors were not significantly different between the two blockade groups.

The univariate analysis of factors predictive of HDI revealed that selective blockade was associated with an increased number of episodes of SBP >200 mmHg (RR: 3.87). No other factors on univariate analysis were associated with intraoperative HDI.

On multivariate analysis controlling for age, BMI, tumor size, norepinephrine and epinephrine levels, preoperative baseline systolic blood pressure, procedure type, type of alpha blockade and EBL; only tumor size, use of selective blockade and open adrenalectomy were associated with episodes of HDI (intraoperative hypertension) (Table 3). Increasing tumor size was associated with more episodes of SBP >30% above baseline (RR 1.40). Open adrenalectomy procedures and use of selective blockade were associated with an increased number of episodes of SBP >200mmHg (RR 27.8 and RR 20.9, respectively).

The univariate analysis of postoperative outcomes is depicted in Table 4. Larger tumor size was associated with increased vasopressor requirement (OR 1.23). Open adrenalectomy was associated with increased vasopressor requirement (OR 4.4), LOS (4.4 days longer than EA), complications (OR 5.6) and readmissions (OR 12.3). Other significant findings in the univariate analysis were no longer significant on the multivariate analysis. On multivariate analysis open adrenalectomy was associated with an increased LOS (4.6 days longer than EA).

There were 9 patients with complications. Two patients had three complications each. The majority (90%) of the patients with complications were in the non-selective blockade group. Complications included: respiratory failure requiring re-intubation (n=4), IVC thrombus (n=1), abdominal fluid collection requiring percutaneous drainage (n=1), popliteal artery occlusion (n=1), retroperitoneal hematoma resulting in symptomatic anemia (n=1), acute kidney injury (n=2), pneumonia (n=2) and urinary retention (n=1). There were four readmissions within 30 days of adrenalectomy due to: pneumonia (n=1), IVC thrombus (n=1), abdominal fluid collection (n=1) and popliteal artery occlusion (n=1). There were no complications related to elevated blood pressure events. There were no mortalities within 30 days of adrenalectomy.

Discussion

Surgical resection of pheochromocytomas has been associated with perioperative HDI. This study finds that patients with larger tumors, who have open procedures or are preoperatively treated with selective alpha-blockade, are more likely to experience HDI. Larger tumors and open procedures were also associated with a significant increase in postoperative vasopressor requirement. However neither tumor size, nor selective blockade and the resulting HDI were associated with increased rate of perioperative complications. Open procedures carried a significant risk of increased postoperative complications.

This study revealed that tumor size was independently associated with an increased number of episodes of SBP >30% above baseline. Larger tumors have been shown to result in a significant increase in the number and duration of intraoperative hypertensive episodes as a consequence of increased catecholamine release.[3, 11, 18, 19] However, in the current study, when controlling for other factors catecholamine levels alone were not associated with HDI. This suggests that the intraoperative manipulation of larger tumors may lead to the release of larger amounts of catecholamines than are recorded at baseline. Induction of anesthesia and tumor manipulation have been shown to increase catecholamine release but our study did not measure catecholamine release at the time of tumor removal.[7, 20] Not surprisingly, larger

tumor size was associated with increased postoperative vasopressor requirement, which was likely needed to relieve the hypotension that develops after removal of a very large and hormonally active tumor.

On multivariate analysis the strongest predictor of an increased number of episodes of SBP >200mmHg was open adrenalectomy (RR 27.8). This finding agrees with prior reports showing that patients undergoing open pheochromocytoma resections have increased episodes of hypertension [5, 21] when compared to the endoscopic approach. Open adrenalectomy was also associated with an increase in postoperative vasopressor and fluid requirement. We were unable to include postoperative vasopressor use in a multivariate model, but this finding can be partially attributed to the fact that the most common indication for an open adrenalectomy is a large tumor and tumor size was also associated with increased vasopressor and fluid requirement. In agreement with other studies, open adrenalectomy was also associated with an increased LOS, complications and readmissions.[22]

In this series, selective blockade was associated with more frequent intraoperative episodes of SBP >200mmHg, however there was no difference in the other HDI measurements or clinical outcomes. Our results support prior findings that the use of selective blockade is sometimes associated with increased intraoperative hypertension.[3, 4, 15] The observed increased number of episodes of intraoperative hypertension may be attributed to the mechanisms of action of the selective alpha-blockade, which are competitive inhibitors and therefore can be overcome by a large surge in catecholamines. This is an important factor to consider in providing anesthetic care to patients who are preoperatively treated with selective alpha-blockade. While the increased number of episodes of SBP >200mmHg is concerning because of the potential increase risk of cardiovascular and cerebrovascular events associated with these pressures,[23] we and others have not been able to document any of such complications.[3, 4, 13-15] Weingarten and colleagues compared the intraoperative and postoperative course of patients undergoing pheochromocytoma resection at two large tertiary care centers with differing approaches to preoperative blockade (n=49 vs. n=24) and found more episodes of intraoperative hypertension with selective blockade compared to non-selective blockade but no difference in outcomes.[15] Zhu and colleagues compared perioperative HDI of 67 patients, 31 treated with PXB and 36 with doxazosin and found that the intraoperative SBP was higher in the group treated with doxazosin but there was less variability in the intraoperative and postoperative SBP, thus they concluded that greater hemodynamic stability was achieved with selective blockade.[16] Other studies report no difference in HDI or outcomes between non-selective and selective blockade. [3, 12, 13] Most recently, Agrawal and colleges compared 15 patients blocked with PXB to 17 patients blocked with prazosin and found an increased and greater number of hypertensive episodes (SBP>220mmHg) and a higher median maximum intraoperative SBP in patients blocked with prazosin.[14] They report no difference in outcomes or complications, however they conclude that PXB is superior to prazosin due to the lower number of intraoperative hypertensive episodes.

This study has several limitations. First, any retrospective study is limited by the quality and inconsistency of data in the medical record. Hemodynamic parameters were obtained from

the anesthetic care record, which is updated every five minutes. This may have resulted in decreased accuracy of our counting variables. Second, we were unable to quantify clearly whether the recorded hemodynamic changes resulted from patient factors, tumor factors, type of blockade and/or the influence of the anesthesia provider. To attempt to address this, we examined the use of vasopressors, vasodilators and beta-blockade intraoperatively and found no significant difference between blockade groups however due to sample size we were unable to include them in our multivariate analysis. Third, there was variability in the dose, duration of and criteria to determine when pre-operative blockade was adequate. This effect could not be analyzed. Additionally, the analysis of HDI was limited by the small number of patients with events of interest, for example only 18% (16 patients) had episodes of SBP >200mmHg. The multivariate analysis results should be interpreted with caution, as the confidence intervals are wide due to small sample size and low event numbers. These wide confidence intervals imply that the significance of the outcome variables may change with even a small change to the data set. Finally, due to the low sample size we may be unable to detect severe but low frequency events, such as stroke, myocardial infarction and arrhythmias. As this is a rare disease and a randomized control trial may not be feasible a meta-analysis of all previously published results may be useful to identify and analyze rare outcomes.

In conclusion, tumor size, operative approach and selective alpha-blockade were associated with intraoperative hemodynamic instability during pheochromocytoma resection. Preoperative selective blockade was associated with significantly more episodes of intraoperative SBP>200 mmHg when compared to phenoxybenzamine and caution must be taken intraoperatively to reduce these hypertensive episodes. This and other studies have failed to show a significant increase in adverse outcomes when selective blockade is used.

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Synopsis

A retrospective review of 91 patients undergoing adrenalectomy for pheochromocytoma was performed to determine the factors associated with perioperative hemodynamic instability.

Table 1
Patient Demographics and Tumor Characteristics

	Total n=91*	Non-Selective α Blockade n=71	Selective α Blockade n=16	p-value
Age	52 (36-60)	53 (36-61)	47 (40-56)	0.456
Gender				0.580
Male	43 (47%)	32 (45%)	9 (56%)	
Female	48 (53%)	39 (55%)	7 (44%)	
BMI	27.5 (25-30)	27.5 (25-30)	27.7 (23-29)	0.809
ASA				0.372
2	17 (19%)	11 (16%)	5 (31%)	
3	65 (71%)	52 (73%)	10 (63%)	
4	9 (10%)	8 (11%)	1 (6%)	
Familial Syndrome				1.00
Yes	22 (24%)	17 (24%)	4 (25%)	
No	69 (76%)	54 (76%)	12 (75%)	
Tumor Size (cm)	4 (2.5-6.5)	4.2 (3-6.5)	3.8 (2.5-6.8)	0.902
+ Functional tumor				1.000
Yes	82 (94%)	65 (96%)	16 (100%)	
No	5 (6%)	3 (4%)	0 (0%)	
**# Elevated Epinephrine				0.539
Yes	60 (71%)	47 (69%)	13 (71%)	
No	24 (29%)	21 (31%)	3 (19%)	
**+ Elevated Norepinephrine				1.000
Yes	75 (86%)	60 (88%)	15 (94%)	
No	12 (14%)	8 (12%)	1 (6%)	
Pre-blockade SBP	137 (130-153)	137 (130-150)	161 (131-170)	0.180
Preoperative baseline SBP	133 (120-143)	135 (123-146)	129 (120-140)	0.829
Duration of alpha-blockade (days)	34 (17-51)	35 (19-52)	38 (15-52)	0.6966

Median values with interquartile range (IQR)

ASA, American Society of Anesthesiologists Physical Status Classification System; SBP, systolic blood pressure; BMI, body mass index;

*, includes patients without blockade;

+Four patients did not have catecholamine levels available;

#Three additional patients were missing epinephrine levels but had norepinephrine levels available;

**, Normalized: see text for details

Table 2
Procedure Type and Perioperative Variables

	Total n=91	Non-Selective α Blockade n=71	Selective α Blockade n=16	p-value
Procedure type				0.506
Endoscopic	71 (78%)	55 (77.5%)	14 (87.5%)	
Open	20 (22%)	16 (22.5%)	2 (12.5%)	
* Operative time (min)	138 (105-217)	143 (107-230)	129 (89-164)	0.044
* EBL (mL)	100 (5-200)	100 (5-200)	88 (5-175)	0.801
Intraoperative vasopressor				1.000
Yes	74 (81%)	57 (80%)	13 (80%)	
No	17 (19%)	14 (20%)	3 (20%)	
Intraoperative vasodilator				0.776
Yes	55 (60%)	44 (62%)	11 (69%)	
No	36 (40%)	27 (38%)	5 (31%)	
Intraoperative fluid (mL)	3375 (2300-4500)	3500 (2300-5000)	3225 (2625-4000)	0.558
Blood transfusion				0.668
Yes	9 (10%)	7 (10%)	2 (12.5%)	
No	82 (90%)	64 (90%)	14 (87.5%)	
*# episodes SBP >200 mmHg	0.47±1.4	0.29±1.05	1.38±2.47	0.103#
*# episodes SBP >30% above baseline	3.02±6.89	3.12±7.54	3.31±4.22	0.895#
*# episodes SBP <30% below baseline	6.78±8.12	7.42±8.58	4.43±5.17	0.078#
Postoperative vasopressors	10 (11%)	7 (9.8%)	3 (18.8%)	0.383
Fluid requirement 24 Hrs. postoperatively (mL)	3960 (2650-5655)	3950 (2800-5600)	3920 (1500-5095)	0.390
* LOS (days)	3±3	3±3	2±1	0.010
Complications				1.000
Yes	9 (10%)	8 (11%)	1 (6%)	
No	82 (90%)	63 (89%)	15 (94%)	
Readmission				0.563
Yes	4 (4%)	3 (4%)	1 (6%)	
No	87 (96%)	68 (96%)	15 (94%)	

Reporting median values with interquartile range (IQR) unless otherwise indicated;

* Mean values with standard deviation;

[#]analysis based on mean values, not counting variables and did not consider duration of surgery.

Min, minutes; mL, milliliter; SBP, systolic blood pressure; Hrs., hours; LOS, Length of hospital stay;

Table 3

Factors Predictive of Intraoperative Hypertension: Multivariate Analysis*

	# episodes SBP >200 mmHG	# episodes SBP >30% above baseline
Tumor size	--	RR: 1.40 CI: 1.01-1.95 p=0.041
Procedure type		--
Endoscopic	RR: 1.00	
Open	RR: 27.8 CI: 4.78-162.6 p< 0.001	
Blockade type		--
Non-selective	RR: 1.00	
Selective	RR: 20.9 CI: 6.07-72.1 p <0.001	

SBP, systolic blood pressure; mmHG, millimeters of mercury; RR, rate ratio; --, not significant; CI, 95% confidence interval;

*Multivariate analysis included Age, BMI, epinephrine and norepinephrine levels, preoperative baseline SBP, EBL in addition to the above listed factors. Only factors shown above were significant predictors of intraoperative hypertension

Table 4

Postoperative Outcomes: Univariate Analysis

	Postoperative vasopressor requirement	Postoperative fluid requirement (mL)	LOS (days)	Complications	Readmissions
Tumor size	OR: 1.23 CI: 1.01-1.50 p= 0.039	Coeff: 158 CI: 23-292 p= 0.022	Coeff: 0.38 CI: 0.14-0.61 p= 0.002	--	--
Procedure type					
Endoscopic	OR: 1.00	Reference	Reference	OR: 1.00	OR: 1.00
Open	OR: 4.4 CI: 1.12-17.3 p= 0.034	Coeff: 1658 CI: 664-2652 p= 0.001	Coeff: 4.44 CI: 2.43-6.45 p< 0.001	OR: 5.58 CI: 1.32-23.5 p =0.019	OR: 12.3 CI: 1.19-127.8 p =0.035
Blockade type	--	--		--	--
Non-selective			Reference		
Selective			Coeff: -1.26 CI: -2.21- -0.32 p= 0.009		

mL, milliliter; LOS, length of stay; --, not significant; OR, odds ratio; Coeff, coefficient; CI, 95% confidence interval