Predictors of perioperative hypertensive crisis in patients with pheochromocytoma: A retrospective study

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Article

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Abstract

Background

Pheochromocytoma is a rare adrenal gland tumor.The definitive treatment is adrenalectomy. Because of its secretory nature, appropriate preoperative treatment is essential to prevent hypertensive crisis(HTC) during surgery.Despite this management,HTC is common and can cause life-threatening complications.

Aim

Our aim was to study variables that may affect HTC despite preoperative management.

Methods

In a retrospective study,among 126 medical records of patients with adrenal tumor who referred to Alzahra hospital, Isfahan,Iran,between 2013 and 2021,52 patients who took proper preparation for surgery were included.

Results

Analysis of these patients showed that 12 patients experienced HTC. Among many potential predictors, we observed in multivariate analysis that patients with tumors size > 33.5mm in imaging were at higher risk for experiencing HTC (P = 0.038,OR:13.1,CI:1.26–135.26); taking amlodipine to help reducing blood pressures(BPs) was another significant predictor (P = 0.05,OR:5.1,CI:0.97–56.74). Mean values of systolic BP(SBP) and diastolic BP(DBP) before surgery in HTC group was more, although it wasn't statistically significant.

Conclusion

Tumor sizes > 33.5mm(imaging)and necessity of administering amlodipine to control BP were predictors of HTC but when reported by pathology,it wasn't significantly different and it suggests that tumor size has no effect on HTC.However, due to rarity of pheochromocytoma, multicenter studies with larger sample size for providing more reliable results are suggested.

Introduction

Pheochromocytoma, a rare catecholamine producing neuroendocrine tumor (with an incidence of 0.8 per 100,000 persons per year in the general population) which originates from medulla part of adrenal gland, is associated with high morbidity and mortality when left untreated. It can either be unilateral or bilateral [1–4]. Symptoms include cardiovascular complications such as hypertension, palpitation, hyperglycemia, decreased intravascular volume, [5, 6] headaches, diaphoresis and in more severe cases, a life-threatening crisis that manifests itself as encephalopathy (caused by high BP), symptoms of neurological deficits and loss of consciousness, metabolic acidosis, and eventually death [7–9].

The approach to diagnosis and surgical treatment is well known, but preoperative management is still diverse [10]. Complete surgical excision is the definitive treatment of pheochromocytoma [11]. Because of its secretory nature, preoperative treatment of patients with pheochromocytoma is essential to prevent perioperative hemodynamic instability [12, 13]. During the surgery, catecholamines may be released by the tumor and cause HTC, cardiac arrhythmias, cerebrovascular accidents, myocardial infarction or ischemia, pulmonary edema, and organ failure. Therefore, preparation before surgery is very important to reduce the risk of complications too [14–17].

Recommendations suggest pretreatment with an α-adrenergic receptor blocker to minimize the vasoconstrictive effects of catecholamines [8, 18]. Phenoxybenzamine (PhB) was approved by the US Food and Drug Administration in 1953 to be used in HTC, especially in patients with high levels of epinephrine and norepinephrine secreting tumors, including pheochromocytoma. It binds covalently to α-adrenergic receptors, which inhibits these receptors in a non-competitive, long-term manner [19]. This drug is the preferred and the first choice drug used to prepare patients before adrenalectomy in many medical centers (in comparison to selective α-1-adrenergic blocking agents (e.g. prazosin, terazosin, or doxazosin)). After adequate α-adrenergic blockade, β-adrenergic blockade is initiated usually 2–3 days before surgery. The β-adrenergic blocker should never be started first, because blockade of peripheral β-adrenergic receptors without α-adrenergic receptor block can cause a further elevation in BP. Calcium channel blocker are as the second drugs in managing these patients [10, 20, 21]. On the second or third day of α-adrenergic blockade, patients are encouraged to start a diet of high sodium content (> 5000 mg daily) because of the catecholamine induced volume contraction and the orthostasis associated with α-adrenergic blockade [21].

Patients are prepared for the surgery when BP is < 120/80 mmHg (seated), with SBP > 90 mmHg (standing) [21, 22]. There are differing opinions about the required PhB dose before surgery. Some references suggest that with sitting BP < 130/80mmHg and standing SBP > 90 mmHg and heart rate range of 60–80 beats/minute, the patient is ready for adrenalectomy [23]. Some references suggest BP < 160/90 mmHg, recommending 0.5 to 4 mg/Kg dosing of PhB [24].

Despite proper preoperative preparation, HTC is unpredictable and common during pheochromocytoma resection. Recent studies have shown predictive values for HTC during surgery but the results are conflicting. They have shown that higher catecholamine levels, large tumors, α–blocker type, hydration status and procedure type (open vs laparoscopic) may be associated with this condition [4, 22, 25–27]. HTC is a stressful event during the surgery because of its probable side effects mentioned earlier. So this study examines our center’s experience with pheochromocytoma resection in an attempt to identify patient/tumor related factors predictive of HTC during surgery.

Materials And Methods

Patients and setting

After institutional ethics approval was obtained, (ethical code: IR.MUI.MED.REC.1399.477, scientific code :399417, ethics committee of Isfahan University of medical sciences) a retrospective single-center study was done. Data were reviewed from patients who were suspected to pheochromocytoma between March, 2013 and October, 2021, in the Alzahra hospital affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. The diagnosis was established by increase in 24-h urine catecholamines more than 2 times of upper limit of normal range or metanephrine > 900μg or 24-h urine metanephrine more than 400μg/day and localizing the tumor in imaging data [28, 24]. Patients with pheochromocytoma who underwent adrenalectomy with appropriate preparation for the surgery were included. As the main treatment is done with α-blockers, we included cases who were prepared with PhB for this procedure.

Among 126 medical records of patients with adrenal tumor, 74 patients' records were excluded from this study because of indeterminate dose of PhB (2 cases), no PhB being administered (14 cases, which 3 of them were suspected of pheochromocytoma and 11 were diagnosed with another disease), no adrenalectomy being done (8 cases), pheochromocytoma being ruled out (27 cases) and having missing data (23 cases). Important data which are worth to mention, include: 4 cases were diagnosed as aldostronoma, 21 cases with Cushing syndrome and 2 cases with myelolipoma. We also found 3 cases with neurofibromatosis and 3 cases with multiple endocrine neoplasia type 2 (MEN2). Finally, 52 patients who were diagnosed with pheochromocytoma (based on catecholamine levels, imaging, clinical presentation) and underwent surgery with PhB preparation were included in the study.

Preoperative management of patients

We found out that patients diagnosed or strongly suspected with pheochromocytoma, received pharmacological preparation for more than 10 days in most cases. All 52 patients received PhB, as the principal drug for preoperative BP control. Some patients received prazosin too (A competitive α-adrenergic receptor blocker). A β–adrenergic receptor antagonist (metoprolol or propranolol) was also prescribed for most patients 2–3 days before surgery. Angiotensin-converting enzyme inhibitors(ACEIs) or angiotensin receptor blockers(ARBs) and Amlodipine (a calcium channel blocker) were added for more hemodynamic control, if necessary. A high-salt diet and increasing daily fluid intake was administered to prevent hypovolemia (on the 2nd or 3rd day of α-adrenergic blockade). Patients were prepared for the surgery when BP was less than 120/80 mmHg (seated), with SBP greater than 90 mmHg (standing); both targets were modified on the basis of age and comorbid diseases [21, 22].

Data collection

All data were obtained from either electronic or paper medical records. basic demographic and clinical characteristics of patients included age, gender, past medical history and pheochromocytoma associated conditions (diabetes mellitus, hypertension, hypothyroidism, neurofibromatosis, MEN2, ischemic heart disease and previous history of pheochromocytoma).

Preoperative data included: clinical presentation recorded in patients' medical records (palpitation, headache, increased BP, dyspnea and abdominal pain) and the duration of these presentations, tumor

size and localization(size, left or right or both sided which were evaluated by abdominal MRI, CT scan or sonography), preoperative 24-h urine catecholamine levels (which were recorded as level of 24-h urine metanephrine, normetanephrine, epinephrine, norepinephrine, and VMA), preoperative medications, PhB cumulative dose taken in mg and dose taken per day in mg/day, days before surgery that PhB was administered and normal saline serum administered or not, BP on admission and right before surgery detected in operating room.

Preoperative medications included prazosin, propranolol, metoprolol, amlodipine and ACEIs or ARBs. We recorded prazosin, propranolol and metoprolol in mg. About ACEIs, ARBs and amlodipine, we just mentioned whether they were administered or not.

The normal range for 24-h urine metanephrine, normetanephrine, epinephrine, norepinephrine and VMA were < 350, <600, < 10, 14–80 and < 13.6 μg/24h, respectively. These are normal ranges of detecting kits of laboratories in Isfahan.

We included maximum tumor size has been recorded by imaging and pathology reports.

Intraoperative and surgery related data included: type of surgery (open or laparoscopic), HTC during surgery, hypotensive drug administered (we just recorded if it was prescribed or not) and during surgery BP.

Postoperative data included: postoperative BP and pathology of the tumor.

In this study, HTC during surgery was defined as a SBP > 180 mmHg and/or the need for hypotensive agent infusion. Postoperative hypotension was defined as a SBP < 90 mmHg. Hypotension during surgery was defined as BP < 100 mmHg [29, 30]. It's considerable that all patients took PhB in the morning of surgery.

We prepared the main data of all patients in (Table 1).

Statistical analysis

SPSS (Statistical Package for the Social Sciences V. 16, IBM corporation) was used for statistical analysis. The quantitative and categorical data were expressed as mean ± standard deviation and frequency and percentage, respectively. Statistical analysis was performed by chi-squared or Fisher's exact tests to compare categorical variables while the Mann-Whitney U test was used to compare continuous variables between groups. Variables with $P < 0.1$ in the univariate analysis were entered into multivariable logistic regression analysis (binary logistic regression), odds ratio (OR) and 95% confidence interval for OR were reported. Repeated measures ANOVA was used for evaluating and comparing the change in blood pressure (systolic and diastolic) in each group and between two groups during admission, before, during and after surgery. We also used receiver operating characteristic curve (ROC) to examine the best cutoff value of tumor size and reported the sensitivity, specificity, positive and negative

predictive values along with area under the curve (AUC) with 95% confidence interval (95%CI). $P \leq 0.05$ was chosen as statistically significant.

All methods were carried out in accordance with relevant guidelines and regulations. All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Results

The mean age of participants was 45.2 ± 13.5 years and 30 (57.7%) of the patients were women. Mean PhB cumulative dose was 570.19 ± 465.25 mg and mean daily dose was 30.34 ± 27.85 mg/day. Mean time of taking PhB was 19.7 ± 16.5 days.

With PhB doses of less than 20 mg/day, 24-h normetanephrine mean level was 410.10 ± 341.39 µg/24h, 20–35 mg/day, it was 799.20 ± 452.71 µg/24h and with doses more than 35mg/day, it was 1892.43 ± 1116.05 µg/24h (P = 0.007). However, mean levels of 24-h urine metanephrine, epinephrine, norepinephrine and VMA were not different (P > 0.05). With the SBPs less than 130mmHg, mean dose was 26.71 ± 12.35 mg/day, and in BPs from 130mmHg to 160mmHg, it was 34.61 ± 16.50 mg/day and for the SBP more than 160 mmHg, mean dose was 42.16 ± 13.16 mg/day (P = 0.039). PhB dose wasn't different in groups of tumor sizes > 33.5mm and tumor sizes < 33.5mm (P > 0.05).

No patient experienced hypotension during operation or postoperatively. There were no perioperative deaths either.

Prazosin was administered in 14 patients (26.9%). Seven of them (50%) took it because PhB wasn't available at first. When it became available, taking prazosin was stopped. It was prescribed at least 10 days before surgery. Forty-six patients (88.5%) took propranolol or metoprolol for preparation of the surgery. Four (8.7%) patients took it 1 day before the surgery and for others, it was administered at least 2 days before surgery. Mean time to prescribe B-blocker was 9.2 ± 11.3 days. Twenty-two patients (42.3%) and 15 patients (28.8%) took amlodipine and ACEIs/ARBs respectively before the surgery. Normal saline serum was prescribed for patients to be prepared for the operation but 7 patients (13.5%) didn't take any normal saline. Mean time to prescribe normal saline was 7.4 ± 6.3 days.

Twelve patients (23.1%) experienced HTC during surgery. There was no significant difference in terms of HTC during surgery and history of ischemic heart disease, hypertension, diabetes mellitus, hypothyroidism, neurofibromatosis, MEN2 and previous pheochromocytoma (P > 0.05). ROC analysis's results showed tumor sizes reported by imaging more than 33.5mm differentiate significantly patients with HTC during surgery from non-HTC (P = 0.023, sensitivity = 91.7%, specificity = 42.5%, NPV = 94.1%, PPV = 31.4%, AUC: 0.667, CI:0.499–0.835) (Fig. 3). There was no statistically significant difference in terms of HTC and days to prepare patients (P = 0.447). (did have HTC:16.5 ± 9.6 days vs. didn't have HTC: 20.7 ± 18.0 days) We found out that patients who had HTC during surgery, had higher BPs on all points. (Fig. 1, Fig. 2) Pheochromocytoma panel (including 24-h urine metanephrine, noremetenephrine, epinephrine, norepinephrine and VMA) wasn't different between HTC and no HTC groups (P > 0.05). We

didn't see any difference in side of tumor (right, left or bilateral) and type of surgery between these two groups either ($P > 0.05$). Tumor sizes reported in pathology weren't different in with and without HTC groups (Table 2).

Those variables associated with HTC during surgery with a $P < 0.1$(Table 2) in univariate analysis were entered in multivariable binary logistic regression. Results showed that patients with tumor sizes of more than 33.5mm, are 13.1 times more likely to experience HTC during surgery (OR = 13.1, P = 0.031). Patients who took amlodipine as a help to decrease their BPs, were 5.1 times (OR = 5.1, P = 0.05) more likely to experience HTC during surgery. (Table 3)

Discussion

Adrenalectomy is the recommended method to treat pheochromocytoma [31–33]. The important note is that patients are at risk of hemodynamically instability before, during and after surgery [32]. Therefore, appropriate preparation for the surgery is necessary to prevent complications [32].

In the Azahra hospital of Isfahan, endocrinologists tend to choose PhB to prepare the patients. It provides more preventive effects by irreversible binding to receptors, more immediate effects and a significant hypotensive effect [34]. Use of the drug, could greatly reduce intraoperative hemodynamic instability and patient's death during surgery [35].

The initial PhB dose is once to twice daily, usually 10 mg, with an increase of 10–20 mg in divided doses every 2–3 days. Most commonly, the patient is ready for the surgery within the first 7–14 days after initiation of PhB. The final dose is most typically between 20–100 mg daily [36]. This was the chosen approach to prepare the patients in the Azahra hospital, too.

In our center, mean time of preoperative management was 19.7 ± 16.5 days with the median of 14.0 days. However, researchers have reported median duration of 27.4 days, 16 days, 35 days, 38.8 days and even 14 weeks. [10,30,37– 39]. Our study, like most previous studies, defined the duration of preoperative management from the time of beginning to surgery [29, 36, 37]. We didn't find any difference between this duration and group of patients with and without hemodynamic alteration during surgery ($P = 0.601$), like the study Russel et al., Kiernan et al. and Hongju Liu et al. did. [38, 40, 41] Russel et al. reviewed 14 patients' data who underwent adrenalectomy in a retrospective study from 1980 to 1993 and concluded that longer treatment with PhB can't cause better perioperative BP stability. [40] In Hongju Liu et al.'s study, a total of 253 patients were grouped according to their tumor diameter: diameters of ≥ 8cm, 6 to 8 cm and < 6 cm. They showed that there was no difference in time of preparation for these 3 groups of patients. [41] It suggests that spending long days to prepare patients for the surgery is not necessary and helpful [38, 40, 41]. We should mention that all these studies, used imaging reports to do analyses on tumor size.

In a study, mean PhB dose was 29.4(20–40) mg/day [39]. In this study, Tian et al. studied 102 patients' data who were diagnosed with pheochromocytoma and received surgical treatment from 2001 to 2018 in

China. They took PhB from admission in hospital and they mentioned this mean dose. It was close to our study with the mean dose of 30.34 ± 14.22 mg/day (P = 0.635). There was no difference in PhB dose between groups of tumor size or groups of patients with and without hemodynamic instability during surgery in their study. In some other studies, mean doses were 55.0 ± 22.2 mg/day and 40 ± 23 mg/day [30, 43]. There was no difference in PhB dose between tumor sizes > 33.5mm and tumor sizes ≤ 33.5 groups in our study (P > 0.05). In the Hongju Liu et al.'s study, larger tumors needed more PhB dose [41]. Because pheochromocytoma is a rare disease and most studies are retrospective, we don't know if determining the dose of the drug to prepare patients depends solely on measuring BP or some endocrinologists prefer to prescribe higher doses of PhB for larger tumors. They increase the dose of the drug until it is tolerable. Therefore, perhaps comparing the dose of the drug between different studies only indicates the prescriptions of each physician according to his/her experiences.

We couldn't find any difference between HTC and no HTC groups when the tumor size was determined by pathology unlike when it was determined by imaging. Because pathology gives more accurate measure of tumor size Therefore, it seems that in our study, tumor size isn't different in the 2 groups.

We also found that patients with admit SBPs more than 130mmHg, needed more doses of PhB were needed. A study, which Miahi R and colleagues did in 2008, showed that there was no correlation between this variable and dose of PhB [30]. Their study was a retrospective review of 60 patients with pheochromocytoma who underwent an adrenalectomy after adrenergic blockade using standardized protocol between 1998 and 2007. So we suggest a new item to pay attention managing pheochromocytoma. However, more studies are needed to confirm this finding.

We noticed that patients with higher levels of 24-h urine normetanephrine, needed more PhB. In the study which Miahi R et al. did [30], there was no significant correlation between the dose of PhB and levels of 24–h urine normetanephrine. Maybe this metabolite could be a predictor of more PhB needed to prepare patients for the surgery.

We also found that with more 24-h urine metanephrine levels, a bigger tumor can be expected, like the study Jennifer C Carr et al. did [42]. They studied 70 patients' data retrospectively and concluded that urine normetanephrine, metanephrine and norepinephrine levels were correlated with bigger sizes of tumor.

Our study showed that despite adequate treatment with PhB and other prescriptions before surgery, HTC wasn't uncommon (12 patients (23.1%)). So it's of great importance to see why patients experienced HTC during adrenalectomy despite this management.

In our study, larger tumors resulted a significant increase in the HTC during surgery (a larger maximal diameter of > 33.5mm reported by imaging, P = 0.023). It was consistent with other studies [22, 38, 44–47]. However, HTC during operation was not correlated with catecholamine levels alone. This may suggest that the intraoperative manipulation of larger tumors causes release of larger amounts of catecholamines than are recorded at baseline, which is consistent with Kiernan et al.'s conclusion of their

study [38]. In another study, H Bruynzeel et al. analyzed data of 73 patients who underwent operation from 1995 to 2007 in a retrospective pattern. They concluded that larger tumor size is a risk factor for hemodynamic instability during surgery. (> 4cm, r = 0.27, P < 0.05) [22] In a retrospective study which Anouk Scholten and colleagues did, 61 pheochromocytoma resections between 2000 and 2010 was done. They concluded that tumor size is an independent risk factor for HTC during surgery (> 3cm, r = 0.39, P = 0.002) [46].

There was no difference in type of surgery between groups of patients with and without HTC during surgery. It is consistent with Davies et al.'s study [47]. They compared 24 patients' data which 12 patients underwent open and 12 patients underwent laparoscopic surgery. They concluded that there was no statistically significant difference between the two groups. However, Kiernan and colleagues studied 91 patients' records and concluded that open surgery was associated with HTC during surgery [38].

As mentioned earlier, we had 12 patients with HTC during surgery. Four of them (33.3%), received PhB less than 20 mg/day. All of them had our criteria of preparation for the surgery but 6 of them (50%) had right before surgery SBP > 130mmHg. For 4 patients, we couldn't find a reason. However, 3 of them (75%) had tumor sizes greater than 50mm. The other one's tumor size was 34mm. It's considerable that all 52 patients were totally prepared and then were sent to operating room and these BPs before surgery, were detected by anesthesiologists.

As mentioned above, all BPs before surgery in patients with HTC were greater than patients without this crisis. A study which Buitenwerf E et al. did, showed that a preoperative SBP < 130 mmHg is associated with less hemodynamic instability during surgery [49]. They did a randomized controlled trial from 2012 to 2017 in Netherlands on a total of 144 patients and concluded this result about preoperative SBP but they didn't mention SBP on admission. It shows that maybe lowering these BPs, could be helpful in preventing HTC during surgery. So increased dose of PhB to decrease these BPs to SBPs < 130mmHg can be a significant predictor of improved intraoperative hemodynamic stability. This conclusion is parallel with the study which Livingstone M et al. did [8]. They reviewed 100 pheochromocytoma resections from 1992 to 2013 and concluded that increased preoperative dose of PhB over the last 10 years' practice have likely contributed to the improvements in perioperative outcomes.

This issue that if taking anti-hypertensive drugs aside from α- and β- blocker, including ACEIs and ARBs or Amlodipine could predict a HTC during surgery was analyzed. We found that patients taking amlodipine to control BP were at more risk for HTC during surgery. Amlodipine, a long acting calcium channel blocker, is mainly used to supplement α- blockers in patients with poor BP control, to obviate the need of increasing the dosage of α-blockers, to replace α-blockers when cause severe side effects and to prevent α-blocker-induced sustained hypotension in patients with only intermittent hypertension. Calcium channel blockers don't cause hypotension or orthostatic hypotension when patient is normotensive [50]. We didn't find a study to focus on this variable. We suggest more and clinical trial studies to evaluate this drug and its effect on HTC during surgery but our recommendation is to reduce the use of amlodipine and instead,

more α–blocker be used as possible as it can be used while preparing the patients for adrenalecomy and more hydration and high sodium diet be administered to prevent probable hypotension of patients.

There were several limitations in our study. First, this was a retrospective study spanning a 9–year period and any retrospective study is limited by the quality and inaccuracy in data reporting. Second, the analysis of HTC during surgery was limited by the small number of patients who experienced this crisis during surgery. (12 patients, 23.1%) Third, the fact that it was a single – center study. Fourth, because of incomplete data recording, we couldn't record patients Body Mass Index (BMI) and therefore, it may have affected some of our data analyses. Finally, our center was a COVID-19 referral center when the epidemic started, so most surgeries couldn't be done and caused a limitation in sample of our study.

Despite these limitations, we could find some analyses that few studies had mentioned, like taking amlodipine and its predictor value of HTC during surgery. One of strength of the study was the relatively good number of patients. We used both imaging and pathology reports to analysis tumor sizes. Also it's worth to mention that this study is the only study which is done in Iran and therefore its data can be helpful for next studies.

Conclusion

This study shows that for patients with tumor sizes of > 33.5mm reported by imaging, it's more probable to cause HTC during surgery but when reported in pathology of tumors, it wasn't significantly different and it suggests that tumor size has no effect on HTC. So probably the nature of the tumor has something to do with catecholamine secreting process. Patients taking amlodipine to control BP were at more risk for HTC during surgery, too. More studies are needed to evaluate this issue but our recommendation is to reduce the use of amlodipine and instead, more PhB be used as possible as it can be used while preparing the patients.

Also all SBPs before surgery in patients with HTC were greater than patients without HTC. It shows that maybe lowering these SBPs, could be helpful in preventing HTC during surgery. So increasing doses of PhB to decrease the SBPs to < 130mmHg can be a significant predictor of improved intraoperative hemodynamic stability.

Declarations

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

1. Randle RW, Balentine CJ, Pitt SC, Schneider DF, Sippel RS. Selective Versus Non-Selective Alpha-Blockade Prior to Laparoscopic Adrenalectomy for Pheochromocytoma. Ann Surg Oncol. 2017;24(1):244-50.
2. Tischler A.S., de Krijger R.R. Phaeochromocytoma. In: Lloyd R.V., Osamura R.Y., Kloppel G., editors. WHO Classification of Tumors of Endocrine Organs. 4th ed. IARC Press; Lyons, France: 2017. pp. 183–189
3. van der Horst-Schrivers ANA, Kerstens MN, Wolffenbuttel BHR. Preoperative pharmacological management of phaeochromocytoma. Neth J Med. 2006; 64(8): 290–295
4. Kinney MA, Narr BJ & Warner MA. Perioperative management of pheochromocytoma. Journal of Cardiothoracic and Vascular Anesthesia 2002 16 359
5. Lentschener C, Gaujoux S, Tesniere A, et al. Point of controversy: perioperative care of patients undergoing pheochromocytoma removal-time for a reappraisal? Eur J Endocrinol. 2011; 165(3): 365–373.
6. Soltani A, Pourian M, Davani BM. Does this patient have Pheochromocytoma? a systematic review of clinical signs and symptoms. J Diabetes Metab Disord. 2015; 15:6.
7. Baguet JP, Hammer L, Mazzuco TL, Chabre O, Mallion JM, Sturm N, et al. Circumstances of discovery of phaeochromocytoma: A retrospective study of 41 consecutive patients. Eur J Endocrinol. 2004; 150:681–6.
8. Livingstone M, Duttchen K, Thompson J, Sunderani Z, Hawboldt G, Sarah Rose M, et al. Hemodynamic Stability During Pheochromocytoma Resection: Lessons Learned Over the Last Two Decades. Ann Surg Oncol. 2015;22(13):4175-80.
9. Bajwa SS, Bajwa SK. Implications and considerations during pheochromocytoma resection: A challenge to the anesthesiologist. Indian J Endocrinol Metab. 2011;15 Suppl 4: S337-44.
10. Malec K, Miśkiewicz P, Witkowska A, Krajewska E, Toutounchi S, Gałązka Z, et al. Comparison of phenoxybenzamine and doxazosin in perioperative management of patients with pheochromocytoma. Kardiol Pol. 2017;75(11):1192-1198.
11. Andrew D. Ludwig, Daniel I. Feig, Mary L. Brandt, M. John Hicks, Megan E. Fitch, Darrell L. Cass, Recent advances in the diagnosis and treatment of pheochromocytoma in children, The American Journal of Surgery, Volume 194, Issue 6, 2007, Pages 792-797.
12. Neumann HP, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J Med 2002; 346:1459–66.
13. Neumann HP, Pawlu C, Peczkowska M, et al. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. JAMA 2004; 292:943–51.
14. K. Pacak, G. Eisenhofer, H. Ahlman, S.R. Bornstein, A.P. Gimenez-Roqueplo, A.B. Grossman et al. Pheochromocytoma: recommendations for clinical practice from the First International Symposium. October 2005. Nat. Clin. Pract. Endocrinal. Metab. 3(2), 92–102 (2007)

15. Zhu Y, He HC, Su TW, Wu YX, Wang WQ, Zhao JP, et al. Selective alpha1-adrenoceptor antagonist (controlled release tablets) in preoperative management of pheochromocytoma. Endocrine. 2010;38(2):254-9.
16. Almeida CEC, Silva M, Carvalho L & Almeida CMC. Adrenal giant cystic pheochromocytoma treated by posterior retroperitoneoscopic adrenalectomy. International Journal of Surgery Case Reports 2017 30 201–204
17. Babic B, Patel D, Aufforth R, Assadipour Y, Sadowski SM, Quezado M, Nilubol N, Prodanov T, Pacak K & Kebebew E. Pediatric patients with pheochromocytoma and paraganglioma should have routine preoperative genetic testing for common susceptibility genes in addition to imaging to detect extra-adrenal and metastatic tumors. Surgery 2017 161 220–227
18. Lenders JWM, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF Jr. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014; 99:1915-1942.
19. Inchiosa MA, Jr. Anti-tumor activity of phenoxybenzamine and its inhibition of histone deacetylases. PLoS One. 2018;13(6): e0198514
20. Garg MK, Kharb S, Brar KS, Gundgurthi A, Mittal R. Medical management of pheochromocytoma: Role of the endocrinologist. Indian J Endocrinol Metab. 2011;15 Suppl 4(Suppl4): S329-36.
21. William F Young, MScElectron Kebebew, Treatment of pheochromocytoma in adults, In Lynnette K Nieman, Sally E Carty (Eds.), UpToDate. (2018)
22. Bruynzeel H, Feelders RA, Groenland TH, van den Meiracker AH, van Eijck CH, Lange JF, et al. Risk Factors for Hemodynamic Instability during Surgery for Pheochromocytoma. The Journal of clinical endocrinology and metabolism. 2010; 95(2):678–85.
23. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. (2014) 99:1915–42.
24. Dennis Kasper, Anthony Fauci, Stephen Hauser, Dan Longo, J. Jameson, Joseph Loscalzo- Harrison's principles of internal medicine, 19th ed. [monograph on the Internet]. New York: The McGraw-Hill Companies, Inc.; 2015
25. Conzo G, Musella M, Corcione F, Depalma M, Stanzione F, Della-Pietra C, et al. Role of preoperative adrenergic blockade with doxazosin on hemodynamic control during the surgical treatment of pheochromocytoma: a retrospective study of 48 cases. The American surgeon. 2013; 79(11):1196–202.
26. Kim HH, Kim GH, Sung GT. Laparoscopic adrenalectomy for pheochromocytoma: comparison with conventional open adrenalectomy. Journal of endourology / Endourological Society. 2004; 18(3):251–5.
27. Kim JH, Lee HC, Kim SJ, Yoon SB, Kong SH, Yu HW, et al. Perioperative hemodynamic instability in pheochromocytoma and sympathetic paraganglioma patients. Sci Rep. 2021 Sep 17;11(1):18574.

28. Dluhy RG, Lawrence JE, Williams GH. *Larsen: Williams Textbook of Endocrinology.* 14th ed. Saunders; 2019. Pheochromocytoma
29. van der Zee PA, de Boer A. Pheochromocytoma: a review on preoperative treatment with phenoxybenzamine or doxazosin. Neth J Med. 2014 May;72(4):190-201.
30. R. Mihai, G. P. Sadler, and H. Bridge, "Adrenergic blockade with phenoxybenzamine and propranolol in a cohort of 60 patients undergoing surgery for phaeochromocytoma," *European Journal of Anaesthesiology*, vol. 25, no. 6, pp. 508–510, 2008.
31. Mannelli M. Management and treatment of pheochromocytomas and paragangliomas. Ann N Y Acad Sci. 2006; 1073: 405–416.
32. Li J, Yang CH. Improvement of preoperative management in patients with adrenal pheochromocytoma. Int J Clin Exp Med. 2014; 7(12).
33. Conzo G, Musella M, Corcione F, et al. Laparoscopic adrenalectomy, a safe procedure for pheochromocytoma. A retrospective review of clinical series. Int J Surg. 2013; 11(2): 152–156.
34. Weingarten TN, Cata JP, O'Hara JF, Prybilla DJ, Pike TL, Thompson GB, et al. Comparison of two preoperative medical management strategies for laparoscopic resection of pheochromocytoma. Urology 2010 76 6–11.
35. Zhu Y, He HC, Su TW, Wu YX, Wang WQ, Zhao JP, Shen Z, Zhang CY, Rui WB & Zhou WL. Selective α 1 -adrenoceptor antagonist (controlled release tablets) in preoperative management of pheochromocytoma. Endocrine 2010 38 254
36. Yoham AL, Casadesus D. Phenoxybenzamine. [Updated 2021 Jul 23]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan.
37. R. E. Goldstein, J. A. O'Neill, G. W. Holcomb et al., "Clinical experience over 48 years with pheochromocytoma" *Annals of Surgery*, vol. 229, no. 6, pp. 755–766, 1999.
38. C. M. Kiernan, L. Du, X. Chen et al., "Predictors of hemodynamic instability during surgery for pheochromocytoma," *Annals of Surgical Oncology*, vol. 21, no. 12, pp. 3865–3871, 2014.
39. Tian J, Bao Z, Yuan Y, Fang D, Zhan Y, Wang T, et al. The Duration of Preoperative Administration of Single *α*-Receptor Blocker Phenoxybenzamine before Adrenalectomy for Pheochromocytoma: 18 Years of Clinical Experience from Nationwide High-Volume Center. Biomed Res Int. 2019 Nov 16; 2019:2613137.
40. Russell WJ, Metcalfe IR, Tonkin AL, Frewin DB. The preoperative management of phaeochromocytoma. Anaesth Intensive Care. 1998 Apr;26(2):196-200.
41. Liu H, Li B, Yu X, Huang Y. Perioperative management during laparoscopic resection of large pheochromocytomas: A single-institution retrospective study. J Surg Oncol. 2018 Sep;118(4):709-715.
42. Carr JC, Spanheimer PM, Rajput M, Dahdaleh FS, Lal G, Weigel RJ, Sugg SL, Liao J, Howe JR. Discriminating pheochromocytomas from other adrenal lesions: the dilemma of elevated catecholamines. Ann Surg Oncol. 2013 Nov;20(12):3855-61.

43. Falhammar H, Kjellman M, Calissendorff J. Treatment and outcomes in pheochromocytomas and paragangliomas: a study of 110 cases from a single center. Endocrine. 2018 Dec;62(3):566-575.
44. Kinney MA, Warner ME, vanHeerden JA, Horlocker TT, Young WF Jr, Schroeder DR, et al. Perianesthetic risks and outcomes of pheochromocytoma and paraganglioma resection. Anesthesia and analgesia. 2000; 91(5):1118–23.
45. Guerrero MA, Schreinemakers JM, Vriens MR, Suh I, Hwang J, Shen WT, et al. Clinical spectrum of pheochromocytoma. Journal of the American College of Surgeons. 2009; 209(6):727–32.
46. Scholten A, Vriens MR, Cromheecke GJ, Borel Rinkes IH, Valk GD. Hemodynamic instability during resection of pheochromocytoma in MEN versus non-MEN patients. European journal of endocrinology / European Federation of Endocrine Societies. 2011; 165(1):91–6.
47. Araujo-Castro M, Garcia Centeno R, López-García MC, Lamas C, Álvarez-Escolá C, Calatayud Gutiérrez M, et al. Risk factors for intraoperative complications in pheochromocytomas. Endocr Relat Cancer. 2021 Sep 8;28(11):695-703.
48. Davies MJ, McGlade DP, Banting SW. A comparison of open and laparoscopic approaches to adrenalectomy in patients with phaeochromocytoma. Anaesth Intensive Care. 2004 Apr; 32(2):224-9.
49. Buitenwerf E, Osinga TE, Timmers HJLM, Lenders JWM, Feelders RA, Eekhoff EMW, et al. Efficacy of α-Blockers on Hemodynamic Control during Pheochromocytoma Resection: A Randomized Controlled Trial. J Clin Endocrinol Metab. 2020 Jul 1;105(7):2381–91.
50. Garg MK, Kharb S, Brar KS, Gundgurthi A, Mittal R. Medical management of pheochromocytoma: Role of the endocrinologist. *Indian J Endocrinol Metab*. 2011;15 Suppl 4(Suppl4): S329-S336.

Tables

Tables 1 to 3 are available in the Supplementary Files section

Figures

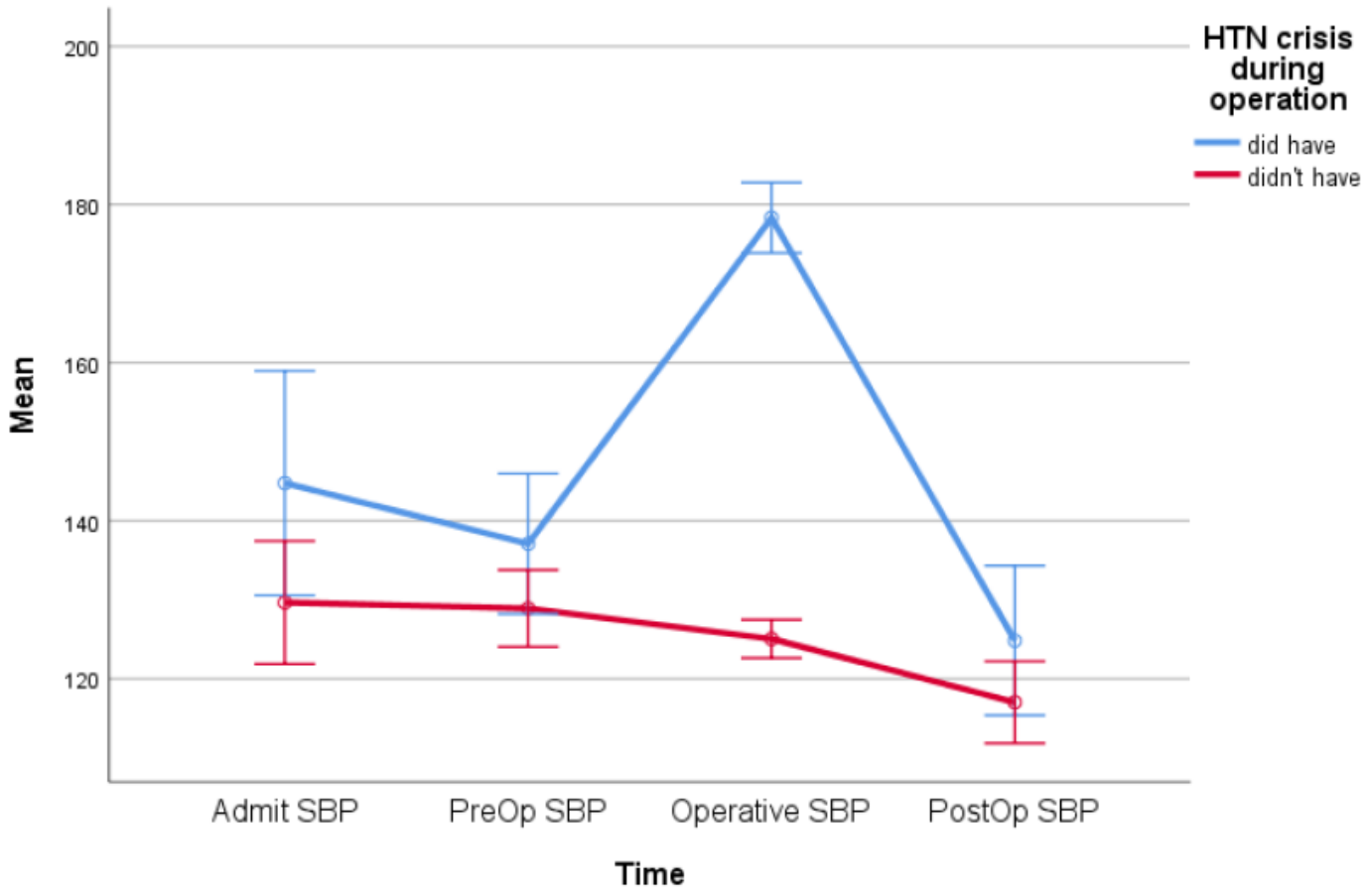

Figure 1

Systolic blood pressures (SBPs) of different times in patients with and without hypertensive crisis during surgery.

Mean SBPs in different times: SBP on admission, PreOp: in the day of surgery, Operative: on operative room during surgery and PostOp: postoperatively. HTN – Hypertension

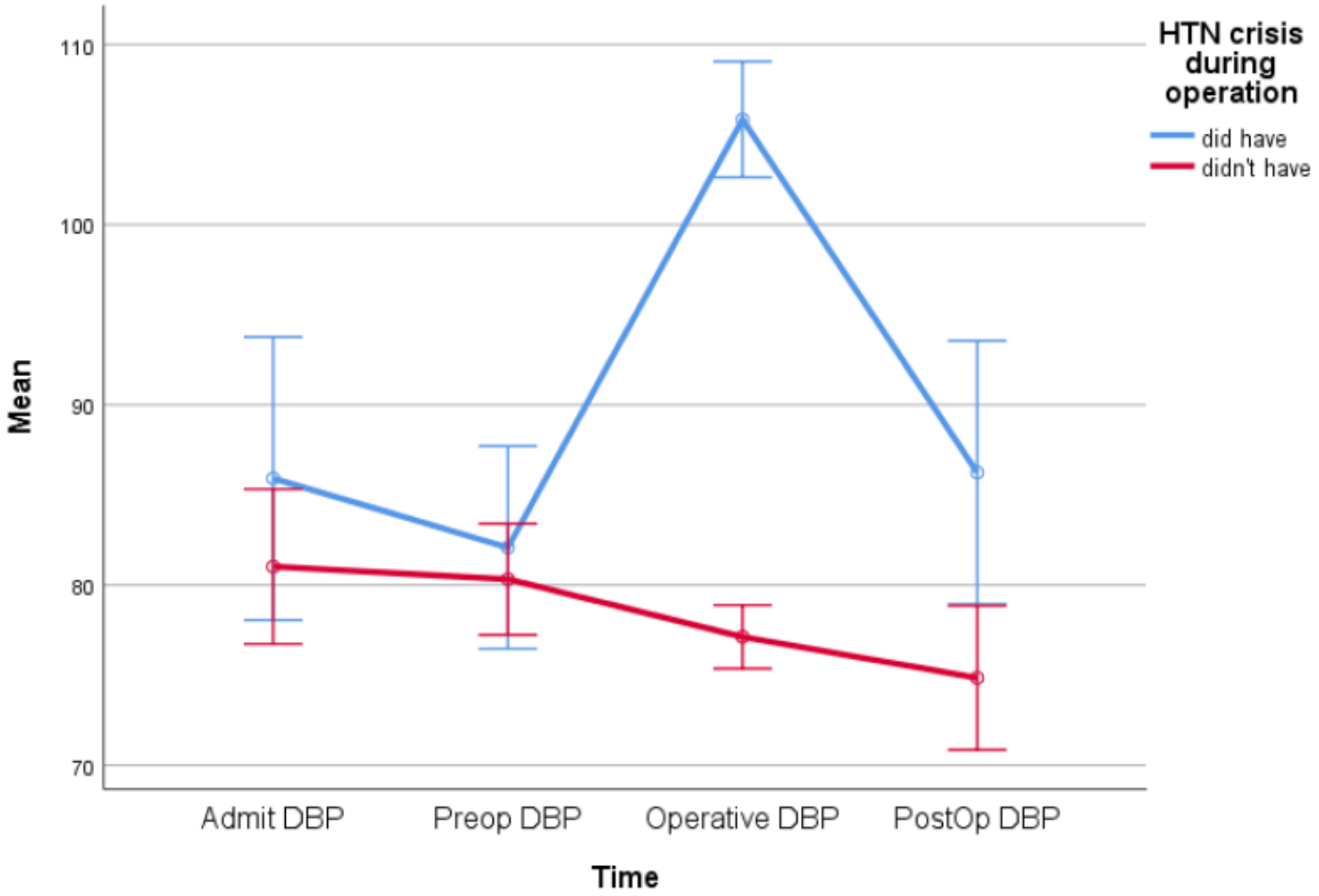

Figure 2

Diastolic blood pressures (SBPs) of different times in patients with and without hypertensive crisis during surgery

Mean DBPs in different times: DBP on admission, PreOp: in the day of surgery, Operative: on operative room during surgery and postoperatively. HTN – Hypertension

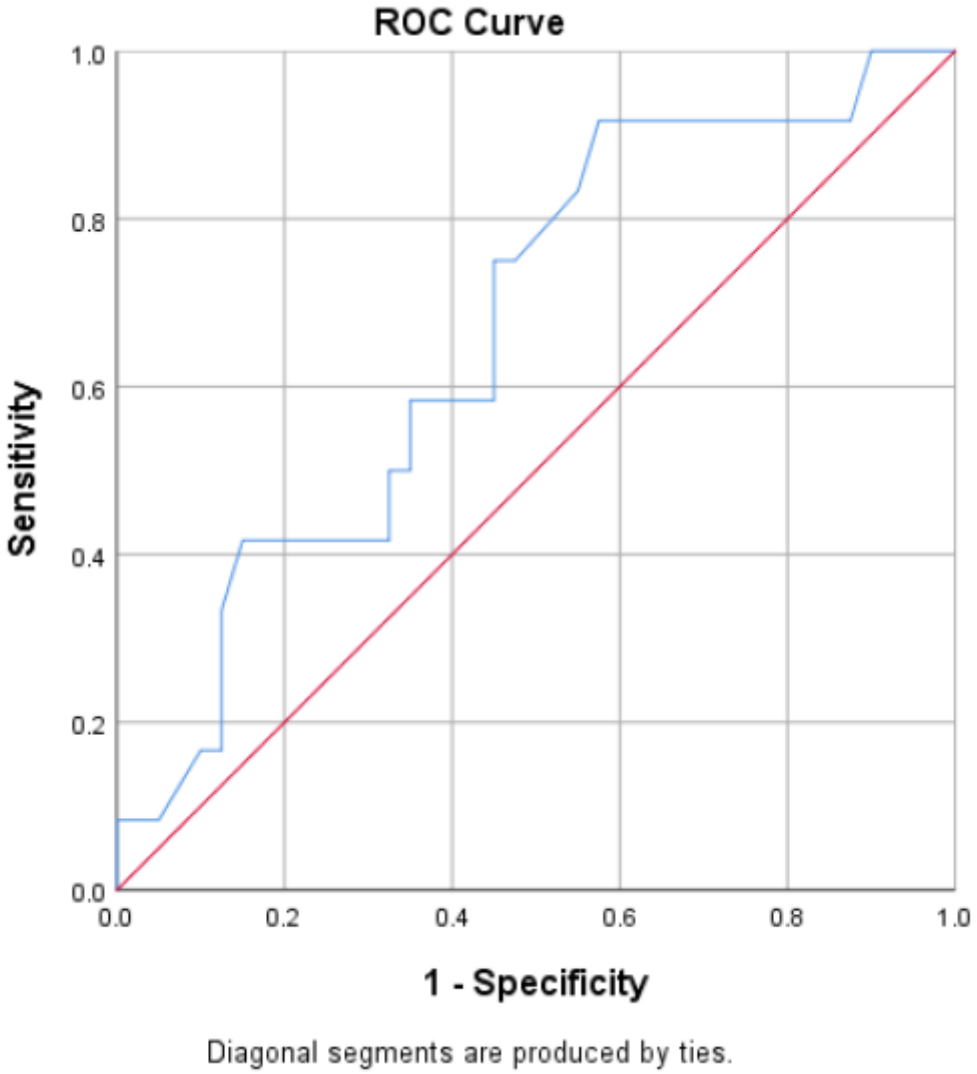

Figure 3

Receiver Operating Characteristic (ROC) curve of hypertensive crisis during surgery by tumor size reported by imaging

Size of tumor in mm has at least one tie between the positive actual state group and the negative actual state group. Area: 0.667, P=0.082, 95% confidence interval: 0.499 – 0.835. (it didn't significantly differ when tumor sizes were reported by pathology)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.png
- Table2.png
- Table3.png