ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TURKEY

CASE REPORT
Endocrinol Res Pract. 2024;28(2):133-136

Perioperative Blood Pressure Control in Pheochromocytoma: The Role of Intravenous Urapidil

ABSTRACT

Pheochromocytomas are rare tumors derived from chromaffin cells of neural crest origin in the adrenal medulla. These neoplasms typically synthesize and secrete catecholamines. Excessive secretion of catecholamines can lead to severe and potentially fatal hypertensive crises. Our study presents 2 cases where blood pressure control was achieved using intravenous urapidil infusion before and during pheochromocytoma surgery. Case 1 was a 54-year-old male patient who received preoperative doxazosin and nebivolol. Urapidil infusion was started at a dose of 5 mg per hour 72 hours before the surgery and titrated by 1 mg per hour to control blood pressure. The patient's blood pressure remained stable during the intraoperative and postoperative periods. Case 2 was a 52-year-old female patient who received preoperative doxazosin and propranolol. Urapidil infusion was initiated 72 hours before the surgery, and blood pressure control was maintained before and after the operation. Considering both cases, urapidil may be a cost-effective alternative to phenoxybenzamine and phentolamine for optimizing blood pressure before and during pheochromocytoma surgery.

Keywords: Blood pressure, hypertension, perioperative period, pheochromocytoma

Introduction

Pheochromocytomas are rare tumors with a low incidence that originate from chromaffin cells of the adrenal medulla, which are of neural crest origin. These neoplasms typically synthesize and secrete catecholamines.[1]

The excessive secretion of catecholamines can lead to severe and potentially life-threatening hypertensive crises. However, as approximately 30% of cases may lead to normotensive or orthostatic hypotension, pheochromocytomas can have a clinically silent course. Therefore, 24-hour continuous blood pressure monitoring is critical in identifying these cases and providing effective treatment.[2] Previously, high mortality rates ranging from 24% to 50% have been reduced to as low as 0%-6% with effective perioperative treatment in contemporary times.[3]

The European and American Endocrine Societies provided recommendations for the perioperative management of pheochromocytoma in 2014. According to these recommendations, initiating alpha-blockade is mandatory even in normotensive patients to prevent unpredictable perioperative hemodynamic instability.[4] However, existing studies on this topic are retrospective, small-scale, and produce conflicting results. Based on the available data, there are no prospective, randomized studies demonstrating the most effective alpha-blocker for ensuring hemodynamic stability during surgery.[5,6]

Our study aimed to present 2 cases in which blood pressure stability was achieved before and during pheochromocytoma surgery through the intravenous infusion of urapidil for blood pressure control.

Case Presentations

Case 1

A 54-year-old male without prior medical issues arrived at the emergency department with complaints of abdominal pain and hematuria. An abdominal CT scan revealed a 9 cm mass near the left kidney and pancreas, necessitating further investigation for potential surgery. Laboratory tests revealed normetanephrine/24 h = 565 µg (Reference range: 88-444 µg/24

Egemen Tural[1]

Levent Özsarı[2]

[1]*Department of Family Medicine, Haydarpaşa Numune Training and Research Hospital, İstanbul, Turkey*
[2]*Departments of Endocrinology and Metabolism, Haydarpaşa Numune Training and Research Hospital, İstanbul, Turkey*

Corresponding author:
Egemen Tural
egementural1@gmail.com

Received: October 26, 2023
Revision Requested: November 29, 2023
Last Revision Received: November 30, 2023
Accepted: December 11, 2023
Publication Date: January 29, 2024

Cite this article as: Tural E, Özsarı L. Perioperative blood pressure control in pheochromocytoma: The role of intravenous urapidil. *Endocrinol Res Pract.* 2024;28(2):133-136.

DOI: 10.5152/erp.2024.23378

h), metanephrine/24 h = 610 µg (reference range: 52-341 µg/24 h), and calcitonin <2 pg/mL (reference range: 0-8.4 pg/mL). Subsequent Ga-68 positron emission tomography–computed tomography (PET-CT) imaging confirmed a heterogeneous, hypodense semisolid mass measuring 68 × 93 mm in the left adrenal gland, consistent with pheochromocytoma. Before the patient's preoperative admission, they received a daily dose of 4 mg doxazosin mesylate and 5 mg nebivolol to manage blood pressure.

Oral antihypertensive treatment switched to urapidil infusion 72 hours before the operation, starting at 5 mg per hour intravenously. The dosage was increased by 1 mg per hour for 3 days to maintain systolic blood pressure above 90 mmHg. Urapidil infusion ceased right after the adrenal vein clamping during the operation. Blood pressure was monitored 6 times daily while on intravenous urapidil, with systolic pressure ranging from 143 mm Hg to 120 mm Hg (Table 1). The tumor, with an approximate diameter of 10 cm, was excised through an open surgical operation. After the operation, a similar monitoring routine continued from hours 25-72 without extreme blood pressure spikes (>180 mm Hg) or drops (<80 mm Hg).

The pathology report indicates large irregular nests as poor prognostic markers, according to the 2022 WHO Classification of Neuroendocrine Neoplasms.[7] Additionally, a tumor diameter larger than 6 cm increases the risk of malignant behavior, according to the 2023 European Society of Endocrinology guidelines.[8] Other poor prognostic markers such as necrosis, marked pleomorphism, vascular invasion, increased mitosis (>3/10 hpf), and Ki-67 proliferation index (>20/200×) were not detected.

Written informed consent was taken from the patient to publish this case report.

Case 2

A 52-year-old female patient with no chronic medical conditions was presented at the emergency department due to high blood pressure. Diagnostic evaluations in the emergency department led to the discovery of a mass in the left adrenal gland, measuring 44 × 38 mm, with a cystic area at the center. Subsequent Ga-68 PET-CT imaging confirmed a mass consistent with pheochromocytoma in the left adrenal gland. Urine tests showed Normetanephrine/24 h = 2035 µg (reference range: 88-444 µg/24 h) and metanephrine/24 h = 225.66 µg (reference range: 52-341 µg/24 h), leading to the planning of an operation. Before the operation, the patient received a daily dose of 6 mg of doxazosin mesylate and 40 mg of propranolol hydrochloride for blood pressure control during hospitalization.

Doxazosin mesylate and propranolol hydrochloride were discontinued 72 hours before the surgery. Then, urapidil at 5 mg per hour intravenously was initiated. The urapidil dosage was increased by 1 mg per hour for 3 days to maintain systolic blood pressure above 90 mm Hg. During the operation, urapidil infusion stopped during adrenal vein clamping. While on intravenous urapidil, blood pressure was monitored 6 times daily, with systolic pressure ranging from 148 mm Hg to 108 mm Hg, ensuring stable blood pressure (Table 1). The tumor was excised through an open surgical operation.

After the operation, a similar monitoring routine from hours 25 to 72 revealed no extreme blood pressure spikes (>180 mm Hg) or drops (<80 mm Hg).

The pathology report reveals that large irregular nests are the only identified poor prognostic markers based on the 2022 WHO Classification of Neuroendocrine Neoplasms.[7] There is no evidence of other poor prognostic markers, including necrosis, marked pleomorphism, vascular invasion, increased mitosis (>3/10 hpf), and Ki-67 proliferation index (>20/200×).

Written informed consent was taken from the patient to publish this case report.

Discussion

Our study found that intravenous urapidil in both pheochromocytoma cases during the perioperative period effectively controlled blood pressure without complications. While there is limited research in this area, a 17-year study by Tauzin Fin et al[9] demonstrated the effectiveness and safety of urapidil in managing pheochromocytoma patients perioperatively. Similarly, a study by Reinisch et al[10], which included 20 patients, supported the safe use of intravenous urapidil

Table 1. The 72-hour Blood Pressure Monitoring Results of the 2 Cases During Urapidil Infusion Before Surgery

	Case 1 (Systolic/Diastolic Blood Pressure in mm Hg)	Case 2 (Systolic/Diastolic Blood Pressure in mm Hg)
Day 1	140/80	115/68
	125/75	111/63
	130/70	126/83
	139/89	116/70
	121/63	128/92
	129/82	110/64
Day 2	120/70	108/62
	120/70	128/74
	143/86	122/80
	143/91	122/74
	131/81	125/78
	127/75	130/80
Day 3	123/83	138/82
	130/90	140/92
	135/90	120/75
	126/86	127/79
	132/87	148/85
	120/75	143/91

MAIN POINTS

- In patients diagnosed with pheochromocytoma scheduled for surgery, the initiation of alpha-blockade is imperative, even in normotensive cases, to preempt unpredictable perioperative hemodynamic instability.
- Phenoxybenzamine is commonly employed to maintain perioperative hemodynamic stability in individuals with pheochromocytoma.
- Urapidil's remarkable bioavailability, substantial clearance rates, and abbreviated elimination half-life have rendered it a favorable choice in the preoperative optimization of patients afflicted with pheochromocytoma.

in preparing for pheochromocytoma surgery. It indicated that postoperative monitoring could be safely conducted with a moderate number of routine blood pressure measurements (4-6 times on average) without intensive monitoring. Our study aligns with these findings, as we achieved effective blood pressure control without complications during the surgeries.

Urapidil is a competitive, short-acting α1 blocker that also functions as a central serotonin receptor agonist. Its high bioavailability, rapid clearance, and short elimination half-life make it an appealing option for preoperative optimization in pheochromocytoma patients. Intravenous urapidil has a notably shorter half-life (2.4-4 hours) compared to phenoxybenzamine, which has a half-life of 24 hours.[11]

The short elimination half-life of this medication has been suggested to help prepare patients with adrenal tumors, which can lead to post-tumor resection hypotension and active bleeding requiring emergency surgery.[12]

Habbe et al[13] conducted a study with 30 pheochromocytoma patients undergoing surgical resection, splitting them into 2 groups: 19 received oral phenoxybenzamine, while 11 received urapidil. They found no significant differences in intraoperative hypertension or hypotension between the 2 groups. However, the phenoxybenzamine group had a longer average hospital stay. This led them to suggest urapidil as a potential agent for reducing hospitalization duration and costs in pheochromocytoma surgical resection compared to phenoxybenzamine. In our study, both patients received urapidil treatment, and we did not make any comparisons with patients using other medications. It is important to acknowledge this limitation as a constraint in our research.

Gosse et al[14] compared patients' tolerated normal dose of urapidil (13.8 ± 3.6 mg/h) to the maximum dose (48.6 ± 47.4 mg/h) with 18 patients in each group. They conducted preoperative preparation and intraoperative comparisons for pheochromocytoma resection. Preoperative preparation involved 3 days of intravenous urapidil administration before the surgery. The group treated with high urapidil doses showed lower systolic blood pressure. Moreover, the group receiving lower urapidil doses had a significantly higher number of hypertensive and tachycardic episodes during peritoneal insufflation. In Tauzin-Fin's[9] study, urapidil dosages started at 5 mg per hour 72 hours before the operation and increased until patients experienced dizziness or their orthostatic systolic blood pressure dropped below 90 mm Hg. In our study, similar to Tauzin-Fin et al, we initiated urapidil at 5 mg per hour for our cases 72 hours before the surgery and gradually increased it by 1 mg per hour to control the blood pressure while closely monitoring the patients.

The literature has indicated a connection between tumor size and intraoperative hypertensive episodes.[15] Kwon et al[16] established a critical threshold of 42.5 mm for tumor size. Tauzin-Fin et al[9] similarly linked tumor sizes exceeding 41 mm to elevated catecholamine release, suggesting the potential for hypertensive peaks during surgery. However, in our study, despite both cases having tumors larger than 42.5 mm, we did not observe any intraoperative hypertensive peaks. This divergence could be attributed to individual patient factors or other clinical variables.

In the perioperative management of pheochromocytoma, there is limited research on the use of intravenous urapidil. A limitation of our study could be the inability to conduct an extensive literature review before our research. Another limitation is that the intravenous urapidil regimen applied in studies related to the subject, initiated 72 hours before the surgery, may be considered a relatively long period, potentially leading to an extended preoperative hospital stay.

In conclusion, for preoperative blood pressure optimization in pheochromocytoma surgery, urapidil is considered an alternative to the routinely used phenoxybenzamine, considering its cost-effectiveness. However, further research is needed to establish the necessity of alpha-blockade pretreatment in pheochromocytoma surgery and determine the preferred pretreatment regimen.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.T., L.Ö.; Design – E.T., L.Ö.; Supervision – E.T., L.Ö.; Materials – L.Ö.; Data Collection and/or Processing – E.T., L.Ö.; Analysis and/or Interpretation – L.Ö.; Literature Search – E.T.; Writing – E.T.; Critical Review – E.T., L.Ö.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

References

1. Gunawardane PTK, Grossman A. Phaeochromocytoma and paraganglioma. *Adv Exp Med Biol*. 2017;956:239-259. [CrossRef]
2. Mazza A, Armigliato M, Marzola MC, et al. Antihypertensive treatment in pheochromocytoma and paraganglioma: current management and therapeutic features. *Endocrine*. 2014;45(3):469-478. [CrossRef]
3. Conzo G, Pasquali D, Colantuoni V, et al. Current concepts of pheochromocytoma. *Int J Surg*. 2014;12(5):469-474. [CrossRef]
4. Lafont M, Fagour C, Haissaguerre M, et al. Per-operative hemodynamic instability in normotensive patients with incidentally discovered pheochromocytomas. *J Clin Endocrinol Metab*. 2015;100(2):417-421. [CrossRef]
5. van der Zee PA, de Boer A. Pheochromocytoma: a review on preoperative treatment with phenoxybenzamine or doxazosin. *Neth J Med*. 2014;72(4):190-201.
6. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. *Lancet*. 2005;366(9486):665-675. [CrossRef]
7. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol*. 2022;33(1):115-154. [CrossRef]
8. Fassnacht M, Tsagarakis S, Terzolo M, et al. European Society of Endocrinology Clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol*. 2023;189(1):G1-G42. [CrossRef]
9. Tauzin-Fin P, Barrucand K, Sesay M, et al. Perioperative management of pheochromocytoma with intravenous urapidil to prevent hemodynamic instability: a 17-year experience. *J Anaesthesiol Clin Pharmacol*. 2020;36(1):49-54. [CrossRef]
10. Reinisch A, Holzer K, Bojunga J, Bechstein WO, Habbe N. Patients' Safety and feasibility of intravenous urapidil in the pretreatment of pheochromocytoma patients in a normal ward setting - an analysis of 20 consecutive cases. *Acta Endocrinol (Buchar)*. 2016;12(4):475-480. [CrossRef]
11. Tauzin-Fin P, Sesay M, Gosse P, Ballanger P. Effects of perioperative alpha1 block on haemodynamic control during laparoscopic surgery for phaeochromocytoma. *Br J Anaesth*. 2004;92(4):512-517. [CrossRef]
12. Kumar A, Gupta N, Gupta A. Urapidil in the preoperative treatment of pheochromocytoma: how safe is it? *J Anaesthesiol Clin Pharmacol*. 2020;36(1):55-56. [CrossRef]

13. Habbe N, Ruger F, Bojunga J, Bechstein WO, Holzer K. Urapidil in the preoperative treatment of pheochromocytomas: a safe and cost-effective method. *World J Surg*. 2013;37(5):1141-1146. [CrossRef]
14. Gosse P, Tauzin-Fin P, Sesay MB, Sautereau A, Ballanger P. Preparation for surgery of phaeochromocytoma by blockade of alpha-adrenergic receptors with urapidil: what dose? *J Hum Hypertens*. 2009;23(9):605-609. [CrossRef]
15. Bruynzeel H, Feelders RA, Groenland TH, et al. Risk factors for hemodynamic instability during surgery for pheochromocytoma. *J Clin Endocrinol Metab*. 2010;95(2):678-685. [CrossRef]
16. Kwon SY, Lee KS, Lee JN, et al. Risk factors for hypertensive attack during pheochromocytoma resection. *Investig Clin Urol*. 2016;57(3):184-190. [CrossRef]