

Urapidil in the Preoperative treatment of pheochromocytoma: How safe is it?

Pheochromocytoma is a rare catecholamine-secreting neuroendocrine neoplasm that arises from the chromaffin cells of adrenal medulla. Common clinical presentations vary from headache, perspirations, pallor and tremors to life threatening hypertensive crisis. Surgical resection is the curative treatment of pheochromocytoma but carries a risk of perioperative fluctuations of haemodynamics due to serum catecholamines levels variations. Hypertensive surges may occur during endotracheal intubation, carbon dioxide insufflations during laparoscopic adrenalectomy and tumor manipulation followed by hypotensive episodes after tumor resection due to fall in serum catecholamines levels.^[1-3]

Management of pheochromocytoma in perioperative period is important to attenuate hypertensive crisis intraoperatively and prevent hypotensive crisis after tumor resections. Various drugs like α blockers, calcium channel blockers and β blockers have been described for preoperative pharmacological interventions. Despite widespread use of various perioperative drugs used, α blockade remains the mainstay of preoperative blood pressure control. Phenoxybenzamine, a non-selective irreversible $\alpha 1$ and $\alpha 2$ antagonist, has been traditionally used in preoperative period, but carries significant disadvantages of postural hypotension, tachycardia, sedation and prolonged post tumor resection hypotension. Selective $\alpha 1$ competitive blockers like prazosin and terazosin have a shorter duration of action with minimal chronotropic effects but need careful dose titration due to possible postural hypotension. No consensus or guidelines has yet been adopted to establish any regimen of α blockade due to inter individual variability, relative rarity of the tumor and variations in different study models. Urapidil is a competitive selective short acting $\alpha 1$ blockade. Its high bioavailability, high clearance and short elimination life has favored its use as a new drug of choice in preoperative optimization of pheochromocytoma patients. Intravenous Urapidil has an average half-life of 2.4- 4 hours as compared to phenoxybenzamine (half-life of 24 hours)^[4] In this issue, Tauzin-Fin P *et al.* compared the efficacy of intravenous urapidil in the perioperative period in 79 cases of pheochromocytoma surgery with oral alpha blockers, and concluded that intravenous urapidil regulates hemodynamic disturbances, corresponds to surgical imperative and contributes to shorter length of hospital stay.^[5]

The preoperative use of intravenous urapidil was first described by Steib A *et al.*^[6] in 7 consecutive patients in a prospective open study undergoing pheochromocytoma resection and evaluated bolus versus continuous infusion dosages of urapidil. They proposed urapidil as an effective drug for controlling hypertensive surges during tumor dissection and emphasized on future studies to determine its role in post tumor resection hemodynamic collapse. The preoperative use of intravenous urapidil was also described by Tauzin-Fin^[7] and colleagues in a case series of 9 patients who received urapidil for 3 days. They claimed that acute variations in blood pressure were managed by additive drugs. No patient developed hypertension and hypotension. The same group also used urapidil in a consecutive case of 18 patients in laparoscopic resection^[4] of pheochromocytoma, and maintained similar findings and insisted the use of urapidil in both open and laparoscopic resection of tumor. A case report by Jankovic *et al.*^[8] described the use of intravenous urapidil for preoperative preparation of a pheochromocytoma in a patient posted for urgent surgical removal of the mass. The patient was admitted 3 days prior to the surgery and invasive blood pressure monitoring began after stopping all his previous antihypertensive abruptly and intravenous urapidil infusion along with magnesium sulphate infusions was started and continued intraoperatively also. Infusions were stopped after the main vein of tumor was clamped and no boluses of fluids and vasopressors were required. This case report raised the possibility of successful immediate preoperative preparation of pheochromocytoma patients in 3 days. Although this idea has not been validated in large randomized controlled trials. Low incidence of the pheochromocytoma has limited large prospective or randomized controlled studies in these groups of patients.

Retrospective study by Nils Habbe *et al.*^[9] investigated clinical course of 30 pheochromocytoma patients undergoing surgical resection and compared pretreatment of these patients with oral phenoxybenzamine and selective short acting urapidil. They observed no differences in intraoperative hypertension or hypotension in the two groups. The median hospital stay was longer for phenoxybenzamine group (median stay - 17 days) compared to urapidil group (median stay -11 days), and concluded urapidil as a new agent to decrease the cost and length of hospital stay of patients undergoing surgical resection of pheochromocytoma. P Gosse *et al.*^[10] compared the usual dose and the maximum dose of urapidil, tolerated by patient during preparation and resection of pheochromocytoma. The patients posted for pheochromocytoma underwent a pre-operative preparation over 3 days by intravenous urapidil in range of 10-15 mg/hour. One group received maximal

tolerated dose till patient received dizziness or symptoms of orthostatic hypotension or using the moderate doses till a target systolic arterial pressure (SAP) below 135 mm Hg was achieved in supine position. The SAP tended to be lower in the group treated with high doses of urapidil. Whereas the number of hypertensive and tachycardia episodes observed during peritoneal insufflations were significantly higher in the group treated with low doses of urapidil. They also reported a significantly larger area under the curve of median levels of norepinephrine in the group treated with a high dose of urapidil. There has been no clinical trial comparing urapidil and prazosin uses in perioperative management of pheochromocytoma surgeries. However, a comparative study between these two drugs for management of mild to moderate essential hypertension concluded urapidil as a safe and effective alternative to prazosin.^[11]

Preoperative pharmacological preparation of pheochromocytoma patients is the most critical phase of perioperative management. The extent of the release of catecholamines by the tumor during surgery and the hemodynamic consequences depend on the magnitude of the blockade of α_1 receptors before the operation. Therefore, an attempt to induce the highest blockade compatible with an absence of orthostatic hypotension as α -adrenergic vasomotor tone plays an important role in the maintenance of standing blood pressure. A complete blockade increases the risk of hypotension after the removal of the tumor; therefore the use of intravenous α blocking agent with a short duration of action, thereby making urapidil an appropriate agent of choice.

The pharmacokinetics of urapidil has favored its use in pheochromocytoma in initial works of many authors. Short elimination half-life of this drug can prevent hypotension in the post tumor resection phase of perioperative period and help in preparation of actively bleeding adrenal tumors requiring emergency surgery.

In conclusion, various clinical experiences till now suggest urapidil as a safe, simple and cost effective pharmacological alternative for the perioperative management of pheochromocytoma. However, large multicenter randomized control trials are required to correctly establish its role in pheochromocytoma surgeries.

Abhishek Kumar, Nishkarsh Gupta, Anju Gupta¹

Department of Onco-Anesthesiology and Palliative Medicine, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, ¹Department of Anesthesiology, Pain and Critical Care, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence: Dr. Nishkarsh Gupta,
437 Pocket A, Sarita Vihar, New Delhi - 110 076, India.
E-mail: drnishkarsh@rediffmail.com

References

- Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Pheochromocytoma. *Lancet* 2005;366:665-75.
- 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. *J Clin Endocrinol Metab* 2010;95:678-85.
- Kinney MA, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. *J Cardiothorac Vasc Anesth* 2002;16:359-69.
- Tauzin-Fin P, Sesay M, Gosse P, Ballanger P. Effects of perioperative alpha1 block on haemodynamic control during laparoscopic surgery for pheochromocytoma. *Br J Anaesth* 2004;92:512-7.
- Tauzin-Fin P, Barrucand K, Sesay M, Rouillet S, Gosse P, Bernhard JC, et al. Peri-operative management of pheochromocytoma with intravenous urapidil to prevent hemodynamic instability: A 17-year experience. *J Anaesthesiol Clin Pharmacol* 2020;36:49-54.
- Steib A, Collin F, Stojeba N, Coron T, Weber JC, Beller JP. Use of urapidil during surgery for pheochromocytoma. *Ann Fr Anesth Reanim* 1996;15:142-8.
- Tauzin-Fin P, Krol-Houdek MC, Gosse P, Ballanger P. Laparoscopic adrenalectomy for pheochromocytoma. Perioperative blockade with urapidil. *Ann Fr Anesth Reanim* 2002;21:464-70.
- Jankovic RJ, Konstantinovic SM, Milic DJ, Mihailovic DS, Stosic BS. Can a patient be successfully prepared for pheochromocytoma surgery in three days? A case report. *Minerva Anestesiologica* 2007;73:245-8.
- 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;37:1141-6.
- Gosse P, Tauzin-Fin P, Sesay MB, Sautereau A, Ballanger P. Preparation for surgery of pheochromocytoma by blockade of α -adrenergic receptors with urapidil: what dose? *J Hum Hypertens* 2009;23:231-5.
- Kaneko Y. Double-blind comparison of urapidil and prazosin in the treatment of patients with essential hypertension. *Drugs* 1988;35(Suppl 6):156-63.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/joacp.JOACP_328_18

How to cite this article: Kumar A, Gupta N, Gupta A. Urapidil in the Preoperative treatment of pheochromocytoma: How safe is it? *J Anaesthesiol Clin Pharmacol* 2020;36:55-6.

Submitted: 24-Oct-2018 **Revised:** 09-Apr-2019 **Accepted:** 11-Jul-2019
Published: 18-Feb-2020

© 2020 Journal of Anaesthesiology Clinical Pharmacology | Published by Wolters Kluwer - Medknow