The Pivotal Role of Antihypertensives in the Preoperative Management of Pheochromocytoma

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Abstract

Pheochromocytomas are rare neuroendocrine tumors with the potential to undergo malignant changes.

These tumors are associated with hemodynamic instabilities and may even lead to cardiomyopathy/heart failure due to catecholamine surge. Preoperative intervention with antihypertensives can curb the morbidity and mortality related to the tumor. Adrenergic receptor blockade is an effective preoperative modality. Phenoxybenzamine, along with metyrosine, should be considered a beneficial synergistic combination for a complication-free surgical intervention of the tumor. Standard preoperative therapeutic strategies and guideline protocols, such as the Roizen's criteria, need to be established for a better overall outcome.

Keywords: *Antihypertensives, pheochromocytoma, preoperative therapeutic strategy, phenoxybenzamine, metyrosine.*

INTRODUCTION AND BACKGROUND

The vigorous preoperative therapeutic preparation for pheochromocytoma is essential for reducing its perioperative morbidity and mortality [1, 2]. Alpha-blockade, a standard preoperative management, prevents intraoperative hemodynamic instability during a pheochromocytoma resection alongside calcium channel blockers [3]. Before the administration of alpha-adrenergic antagonists for the preoperative management of the tumor, statistics reveal a surgical mortality rate ranging from 24% to 50%. However, with a standard preoperative preparation, the surgical mortality rate declines significantly to approximately 3%, highlighting the need for an established guideline protocol to preoperatively intervene and approach the tumor effectively [4].

PHEOCHROMOCYTOMA REVIEW

Tumor Origin, Statistics, and Complications

Pheochromocytoma, a rare tumor arising from chromaffin cells in the adrenal medulla or other paraganglia in the body, has been postulated to be associated with genetic syndromes and mutation. The tumor occurs in about 0.01-0.1% of the hypertensive population [5, 6]. Patients suffering from pheochromocytoma may also develop potentially lethal cardiovascular and other complications, especially in the setting of diagnostic or interventional procedures such as upon the induction of anesthesia or during surgery. Such complications occur due to paroxysmal release of the catecholamines. Physicians need to be aware of the clinical manifestations and complications due to catecholamine surge. Prompt diagnosis and treatment is required in order to minimize catecholamine-related pre-, intra- and postoperative adverse events [7, 8]. According to the Pakistan Heart Journal, even though hypertension remains a common health hazard in both the adult and pediatric age groups in the country, physicians appear to neglect the workup of the secondary causes of hypertension in the hypertensive population. It may be partly due to Pakistani physicians overlooking secondary causes of hypertension that this condition is rarely mentioned/addressed in Pakistan medical literature; this would also explain why it's therapeutic approach is still undetermined [9].

Role of Pre- and Perioperative Evaluation with Tumor Management

The pre- and perioperative evaluation of pheochromocytomas appears to be crucial and entails meticulous anesthetic care [10, 11]. The literature review suggests severe morbidity and mortality in poorly prepared patients. Hypertension is present in 50% of cases with pheochromocytoma [9, 12]. According to Lord MS and Augoustides JG, a tight perioperative hemodynamic control can be achieved with clevidipine, an antihypertensive/dihydropyridine calcium channel blocker, which may offer a survival advantage in the perioperative setting. The drug's implementation in pheochromocytoma management before tumor resection has been described; literature review suggests its wide implementation soon. Clevidipine is a fast onset, rapidly titratable, fast offset drug with proven safety and efficacy for acute perioperative hypertension [10]. Calcium channel blockers have been unanimously regarded to play a beneficial role in patients with hindered renal function and cardiovascular status. Recent studies indicate that nicardipine is being used for its therapeutic efficacy in controlling hypertension specifically in patients with pheochromocytoma [13, 14].

Conventional preoperative preparation is usually done with alpha-adrenergic blockade over 10-14 days; beta-

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adrenergic blockade is used to treat any associated tachyarrythmias. Literature shows that patients can be safely prepared for surgery on an outpatient basis by administering oral phenoxybenzamine, a non-selective alpha blocker [15]. Naranjo *et al.* claim that phenoxybenzamine has been an ideal drug, adequate dosing of which would diminish vasoconstriction and avoid intraoperative hypertensive crises, leading to a better surgical outcome. Despite being hailed as an ideal drug, studies report a substantial risk of developing significant postoperative hypotension which should be labelled as a complication [12, 16].

The literature review notes the withdrawal of phenoxybenzamine from a few countries; selective alpha-1 blockers are used instead during the preoperative preparation for patients with pheochromocytoma. Selective alpha-1 blockers include prazosin, doxazosin and terazosin, with prazosin being the most commonly used drug for this purpose. Preoperative control of symptoms and adequate intraoperative alpha blockage in patients was achieved with prazosin [1]. However, if comparing management with non-selective alpha blockers like phenoxybenzamine, using selective alpha blockers like prazosin may carry a higher risk of intraoperative hemodynamic instability [24].

Magnesium, intriguingly, has also been acclaimed to have a positive role in preoperative preparation by directly inhibiting the catecholamine receptors. Despite its favorable action, its clinical application remains limited [13].

Combination Therapy *versus* Single Therapy?

Nicholas *et al.* suggest esmolol, an antihypertensive/beta-1 receptor blocker, as a treatment for hemodynamic alteration encountered perioperatively in a 35-year-old female with a right adrenal pheochromocytoma [17]. The use of the latter has gained considerable popularity in the literature. An analysis by Perry *et al.* reports an efficacious combination of two drugs, phenoxybenzamine and metyrosine. This report discourages the traditional method of administering a single antihypertensive. In this analysis, twenty-five patients were intervened with phenoxybenzamine and metyrosine (an antihypertensive/tyrosine hydroxylase inhibitor) before undergoing surgical intervention. Nineteen patients received a combination of both drugs, and the rest only phenoxybenzamine. The results demonstrated better surgical management with the combination rather than the single drug alone. When combined, the two drugs were found to have better blood pressure control, a reduction in blood loss, and the need for less intraoperative fluid replacement [4]. Similar positive findings with combination drug regimens have also been previously reported [18].

Metyrosine in combination with Phenoxybenzamine has also been highlighted throughout the literature for its proven beneficial role in managing elevated blood pressures as a positive duo in both morbidities including pheochromocytoma and sympathetic Paraganglioma collectively referred to as the PPGL syndrome [19, 20]. This drug synergism could therefore ultimately revolutionize the therapeutic world of pheochromocytoma management.

Antihypertensives: A Necessity for Adrenalectomy?

Despite a widely accepted and published role of anti-hypertensives in pre- and perioperative circumstances, an interesting conclusion came from a 10 year study on 60 patients with pheochromocytoma, who underwent surgery successfully without preoperative alpha-adrenergic blockade [21]. Another study showed that patient survival can be achieved even without a comprehensive preoperative antihypertensive preparation in the tumor population [13]. Antihypertensives may be administered just prior to surgical intervention in order to avoid side effects due to prolonged use of the drugs preoperatively and still lead to a positive outcome.

Considering the recent literature, it appears mandatory to signify the rationale of alpha blockade implementation before tumor resection where the surgery could lead to a catastrophic guarded prognosis due to tremendous emission of catecholamines triggering intraoperative hemodynamic instability. This highlights the need for a standard protocol to be established irrespective of the patient subset chosen for tumor removal and the implementation of the traditional application of preoperative antihypertensive therapy as a recommendation ultimately signifying the essential role of the latter in the pre-surgical intervention phase [13].

No specific criterion has been delineated to classify a specific patient subset exposure to the preoperative antihypertensive regimen, however, patients with co-morbidities such as Diabetes and Cerebrovascular ailments acquire the need for a vigilant pre-interventional therapeutic window period [22].

Guideline-based Approach for Tumor Removal

Before being clinically “accepted” for surgery, 5-15 days of preoperative preparation with optimal alpha-blocking drugs, increased oral fluids and salt intake, and intravenous fluids may be required by a patient as per Endocrine Society Clinical Practice Guidelines. A high-sodium diet and fluid intake were recommended by the Guidelines to converse catecholamine-induced blood volume contraction preoperatively and prevent severe hypotension after tumor removal [1].

Dr. Pacak states the initiation of a preoperative adrenergic blockade when dealing with pheochromocytomas to normalize blood pressure, heart rate, and other organs’ function; restore volume depletion; and prevent a patient from surgery-induced catecholamine storm and its consequences on the cardiovascular system [7]. This, in turn, has been reinforced by a criterion known as the Roizen criterion, which has been objectively utilized to gauge the efficacy of adequate pre-operative alpha blockade and includes the following: No in-hospital blood pressure >160/90 mmHg for 24 h before surgery, No orthostatic hypotension with blood pressure <80/45 mmHg, No ST or T wave changes for 1-week before surgery and no more than five premature ventricular

contractions per minute. According to Ramakrishna H, these criteria have remained consistently reliable. Poorer outcomes have been reported when patients have not met these criteria before tumor resection [23]. This highlights a strategy that could be implemented to achieve more successfully managed cases in the future.

CONCLUSION

Physicians should be aware about managing pheochromocytomas with great caution. Roizen's criteria needs to be implemented as a standard to reduce perioperative mortality and complications. Hemodynamic instabiltiies are frequent with the tumor's presence and require effective preoperative intervention such as the preoperative adrenergic blockade. Hypotension may be a postoperative complication when using non-selective alpha blockers like phenoxybenzamine. In comparison, using selective alpha blockers carries a higher risk of intra-operative hemodynamic instability. Phenoxybenzamine and metyrosine used in combination appear to play a positive role in the management of the disease. General consensus needs to be established to sort the subset requiring preoperative antihypertensive therapy and their management.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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