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Original Research

Perioperative hemodynamics and outcomes of patients on metyrosine undergoing resection of pheochromocytoma or paraganglioma

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HIGHLIGHTS

- Metyrosine, a catecholamine synthesis inhibitor, is an expensive treatment used before resection of pheochromocytoma.
- Does this profound adrenergic blockade affect perioperative hemodynamic instability, and consequently outcomes?
- Due to availability of large number of patients in the Mayo Clinic Pheochromocytoma Registry we explore these outcomes.
- Postoperative outcomes were similar between patients who received metyrosine vs other less expensive adrenergic blockers.

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ABSTRACT

Introduction: To describe outcomes of patients with metyrosine (MET) pretreatment for abdominal surgical resection of pheochromocytoma or paraganglioma (PCC/PGL) compared with patients who had phenoxybenzamine (PBZ) pretreatment.

Methods: Retrospective review of perioperative outcomes for PCC/PGL patients treated with MET and propensity-matched comparison of MET and PBZ (MET + PBZ) with PBZ alone.

Results: MET preparation was given in 63 cases (26 laparoscopic and 37 open, of which 55 also received PBZ). All patients had wide perioperative hemodynamic oscillations. Patients with open procedures required more intravenous fluids and blood transfusions; 35% required postoperative vasopressor infusions for hypotension and 38% developed acute kidney injury. One laparoscopic procedure required postoperative vasopressor infusion, and 12% of patients developed acute kidney injury. Forty-five MET + PBZ patients were propensity-matched with PBZ-only patients. Intraoperatively, MET + PBZ patients had lower minimum systolic and diastolic blood pressures than PBZ-only patients (median systolic, 74 vs 80 mm Hg, $P = 0.01$; median diastolic, 42 vs 46 mm Hg, $P = 0.005$) and larger intraoperative blood pressure oscillations (median systolic range, 112 vs 93 mm Hg, $P = 0.06$; median diastolic range, 58 vs 51 mm Hg, $P = 0.02$). Postoperative vasopressor infusion use was similar between MET + PBZ and PBZ only (16% vs 11%, $P = 0.76$). Major outcomes were not different between regimens.

Conclusion: Large hemodynamic oscillations were present in our PCC/PGL patients treated with MET + PBZ. These patients had a wider range of intraoperative blood pressure variations than PBZ-only patients. No differences in postoperative comorbid outcomes were found between MET + PBZ and PBZ-only groups.

Abbreviations: AKI, acute kidney injury; CCB, calcium channel blocker; DM, diabetes mellitus; IQR, interquartile range; MET, metyrosine; MET + PBZ, metyrosine and phenoxybenzamine; PBZ, phenoxybenzamine; PCC, pheochromocytoma; PCC/PGL, pheochromocytoma or paraganglioma; PGL, paraganglioma.

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1. Introduction

The surgical course of resections of metabolically active pheochromocytoma (PCC) or paraganglioma (PGL) is characterized by hemodynamic instability. PIN these patients preoperative pharmacologic blockade of the adrenergic system has long been used to reduce extreme perioperative blood pressure and heart rate oscillations [1]. The blockade is believed to be central to the low mortality and morbidity rates of these procedures in the modern era [2–4].

At our institution, nonselective α-antagonist phenoxybenzamine (PBZ) is the mainstay of preoperative pharmacologic management, which can be supplemented with β-adrenergic blockers or calcium channel blockers (CCBs), or both, when blood pressure or heart rate stays higher than the desired limits [4]. Less frequently, patients with high tumor activity who do not respond satisfactorily to these treatments also receive a tyrosine hydroxylase inhibitor, metyrosine (MET), as a catecholamine synthesis inhibitor and, in our institution, typically in conjunction with PBZ [5]. Theoretically, simultaneous use of MET and PBZ (MET + PBZ) may blunt the response to exogenous catecholamines and interfere with the ability to maintain adequate blood pressure following tumor resection [6]. In contrast, a recent retrospective study found that preoperative MET therapy improved intraoperative hemodynamic stability and decreased cardiovascular complication rates in patients undergoing PCC/PGL resection compared with PBZ-only preparation [7].

The objective of our study was to describe perioperative outcomes of patients with PCC/PGL undergoing abdominal resection and treated with MET. To achieve this objective, the study designs were a descriptive case series of patients pretreated with MET and a propensity-matched analysis comparing patients receiving MET + PBZ with patients receiving PBZ-only.

2. Material and methods

The local Institutional Review Board approved this study. We included only patients who provided authorization for research use of their health records.

2.1. Study aims

Our first aim was to describe the intraoperative course and perioperative complications of selected patients with PCC/PGL who did not have an adequate response to PBZ (or an alternative α-blockade or CCB) for normotension and therefore also received MET. Our second aim was to assess whether outcomes differed for patients treated with MET + PBZ compared with those treated with PBZ-only.

2.2. Study design and patient selection

Patients who underwent resection of abdominal PGLs or PCCs from September 1, 1999, through December 31, 2016, were identified from institutional PCC/PGL registry. In the present study, we included resections of patients with primary or recurrent abdominal PCC/PGL who underwent preoperative treatment with MET. For the propensity-matched analysis, patients who met these criteria but were treated preoperatively with PBZ-only were included as controls. Electronic health records were reviewed for patient demographic characteristics, preoperative preparation, intraoperative treatment and hemodynamic course, and postoperative outcomes.

2.3. Preoperative preparation of PCC/PGL patients

Patients with abdominal, pelvic, or thoracic PCC/PGL undergo pharmacologic preoperative preparation, regardless of clinical biochemistry because even less active tumors release catecholamines during surgical manipulation [4]. At 7–14 days before surgery, patients are premedicated with PBZ to achieve normotension. A β-adrenergic receptor antagonist can be added at 2 or 5 days before surgery if the heart rate stays greater than 80 beats per minute. If these regimens do not result in normotension, a CCB is added. If a large catecholamine release is anticipated during tumor manipulation, MET is added. MET blocks the rate-limiting step of catecholamine synthesis but has a half-life of 3.5 h [8,9]. Our institution has developed a protocol for MET preoperative preparation that typically starts 4 days before surgery: day 1, 250 mg of MET every 6 h; day 2, 500 mg every 6 h; day 3, 750 mg every 6 h; and day 4, 1000 mg every 6 h, with the last dose (1000 mg) given on the morning of the procedure [10]. Other preoperative preparation medications (eg, PBZ, CCB, β-adrenergic blocker) are also administered the morning of surgery.

2.4. Data ascertainment

The electronic health records of patients were abstracted for demographic information (ie, age, sex, and weight and height to calculate body mass index); comorbidities (eg, diabetes mellitus [DM] defined as treatment with insulin or oral antidiabetic medications), coronary artery disease (notation of its presence, prior coronary artery bypass surgery or percutaneous intervention, or prior myocardial infarction), history of congestive heart failure or cardiomyopathy (ejection fraction <40% or a cardiology note in health records of its presence, or both), anemia (hemoglobin ≤12 mg/dL for women and ≤13 mg/dL for men), renal impairment (preoperative creatinine ≥1.4 mg/dL), and preoperative medications for control of blood pressure and heart rate (ie, all types of α- and β-adrenergic receptor antagonists, CCBs, and MET).

Electronic anesthetic records were reviewed for maximum and minimum intraoperative systolic and diastolic blood pressures and heart rate; intravenous fluid administration of crystalloids (normal saline plus lactated Ringer's solution), colloids (ie, fresh frozen plasma, platelets, albumin, and hetastarch), and blood transfusions; duration of anesthesia; and intraoperative infusions of potent vasoactive drugs (ie, nitroprusside, nitroglycerin, β-adrenergic antagonists, mixed α/β-adrenergic antagonists [labetalol], CCBs, phenylephrine, dopamine, norepinephrine, and epinephrine). Intraoperative variability in blood pressure and heart rate was quantified using within-patient range (maximum minus minimum observed values). Tumor size was reported as the larger measured dimension of the excised tumor.

Electronic health records were abstracted for occurrence of major perioperative complications. These included cardiovascular (myocardial infarction), major pulmonary (eg, pneumonia, acute respiratory distress syndrome), acute kidney injury (AKI) (per Acute Kidney Injury Network criteria [11]), thromboembolic (pulmonary embolism or deep venous thrombosis), bleeding (need for blood transfusions), and postoperative hypotension (ie, use of potent vasopressor infusions). Hospital length of stay and death were also recorded.

2.5. Statistical analysis

Data are presented as frequency count and percentage for nominal variables, and mean (SD) or median (interquartile range [IQR]) for continuous variables. During the study period, PCC/PGL resection was performed using open and laparoscopic approaches.