Perioperative control of paroxysmal hypertension using esmolol with alpha-blockade in a child with a germline mutated paraganglioma

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Summary

The use of antihypertensive medications in patients with pheochromocytomas and paragangliomas (PCC/PG) is usually a challenge. We report a case of familial paraganglioma that was successfully treated by esmolol and other antihypertensive medications without associated perioperative complications. Our patient was an 11-year-old girl who presented with classic symptoms and signs of PCC/PG and a CT scan of the abdomen that showed a right-sided paravertebral mass. Her father was diagnosed with paraganglioma a few years ago. Prazosin had been started but she continued to experience uncontrolled paroxysms of blood pressure (BP). She was known to have asthma; hence, she developed serious bronchospasm with atenolol. She was, therefore, switched to esmolol that successfully controlled her BP in addition to prazosin and intermittent doses of hydralazine prior to laparoscopic surgery with no side effects of medications or postoperative complications. Esmolol could be a good alternative to routinely used beta-blockers in children with PCC/PG with labile hypertension and related symptoms in the pre and intra-operative periods. It is titratable, effective, and can be weaned rapidly helping to avoid postoperative complications. Further larger studies on the use of esmolol in children with PCC/PG are needed to confirm our observation.

Learning points:

- In addition to alpha-blockers, esmolol could be a good alternative for routinely used beta-blockers to control paroxysmal hypertension and tachycardia in the pre- and intra-operative periods.
- Esmolol is titratable and an effective beta-blocker. It can be weaned rapidly helping to avoid postoperative complications in children with PCC/PG.
- Children with PCC/PG and other comorbidity like asthma may particularly benefit from the use of esmolol due to no or less side effects on airway resistance and the advantage of rapid titration of the medication compared to other beta-blockers.

Background

Pheochromocytomas and paragangliomas (PCC/PG) are rare neuroendocrine catecholamine-secreting tumors that originate from the paraganglionic cells of the autonomic nervous system. Most PCC/PG are considered to be benign. However, about 25% of PG and 10% of PCC are malignant (1). PCC/PG can be familial when they present as unilateral, solitary, frequently found in the abdomen and thorax, and secrete norepinephrine and/or dopamine in 34–70% of patients (2). The clinical presentation is usually variable as a result of the hemodynamic and metabolic actions of catecholamines that are secreted by these tumors. Hemodynamically, these tumors might lead to secondary endocrine hypertension due to catecholamine-releasing properties (3). Most of these tumors are diagnosed by biochemical testing of high catecholamine levels in addition to localizing the tumor by imaging. It was thought that only 10% of these tumors are familial but the improvement of genetic testing has led to more identification of cases and increasing prevalence (4). Approximately, 60% of PCC/PG are associated with germline mutations in children (5). Mutations affecting succinate dehydrogenase (SDH) complex subunit genes (SDHA, SDHB, SDHC, SDHD) and one of the SDH complex factor genes (SDHAF2) render patients more predisposed to PCC/PG with variable risks (6). SDHB is the most commonly mutated gene in children that usually result in extra-adrenal sympathetic tumors with a high risk of metastasis (1, 7). SDH complex gene mutations are also associated with renal cell carcinoma as well as gastrointestinal stromal tumors (8).

Surgical resection is the optimal treatment for these tumors (9). However, the outcome is dependent on appropriate preoperative management. It is crucial to control the blood pressure (BP) preoperatively in order to avoid hypertensive crisis intra-operatively, and equally important to maintain stable BP postoperatively (3). Hypertensive crises might lead to mortality or severe morbidities such as myocardial ischemia, arrhythmias, or cerebral hemorrhage (10). The choice of medications used in the perioperative management of patients with PCC/PG to control paroxysmal hypertension can be challenging. However, adequate use of alpha-blockade in these patients before surgery was emphasized in previous reports (11, 12). For every patient, the blood pressure needs to be optimized initially using alpha-blockades such as phenoxybenzamine or prazosin. Then, a beta-blocking agent such as propranolol or atenolol should be added to control tachycardia and BP (3, 9). Some patients might develop a serious reaction to these beta-blockers due to

comorbid conditions such as asthma and allergic reaction. Therefore, there is a need for a safe and effective alternative to these medications; especially in cases with comorbidity such as asthma. Esmolol, because of its short duration of action and relative lack of airway resistance, may be preferred over other beta-blockers like propranolol and atenolol in patients with asthma who require i.v. beta-blocking agents such as children with PCC/PG (13).

We report on a successful experience of using esmolol, in addition to the alpha-blockade, to control labile hypertension of PCC/PG in a child with asthma comorbidity, minimizing perioperative complications.

Case presentation

An 11-year-old girl with a known case of bronchial asthma was referred from a district hospital that affiliates to our tertiary center in Riyadh for further investigations of paroxysms of tachycardia, hypertension, and sweating. Her symptoms started 5 months prior to presentation with attacks of palpitations, chest pain, headache, flushing, and abdominal pain. The frequency of her attacks progressed over the last month. She had a history of polyuria and polydipsia. The family history was impressive for neuroendocrine tumors. For instance, the patient's father was diagnosed with retroperitoneal mass, her paternal aunt had PCC, and also her brother was diagnosed with a benign intestinal tumor. Her BP was maintained with the use of prazosin 0.05 mg/kg/day at the referring hospital, and she was clinically and vitally stable when admitted to our hospital. In our tertiary center, her management was guided by a pediatric multidisciplinary team including Pediatric Intensivist, Endocrinologist, Surgeon, Nephrologist, Oncologist, Radiologist, and Pediatric Anesthetist.

Investigation

Initially, the biochemical and radiological investigations suggested the diagnosis of PCC/PG, and the images did not show evidence of metastasis (Fig. 1 and Table 1). Plasma normetanephrine and 24 h urine norpepinephrine were elevated that helped to make a biochemical diagnosis of PCC/PG (Table 1). MIBG showed avid focus in the right-sided paraspinal retroperitoneal mass at the level of lower pole of the right kidney compatible with a paraganglioma.

Treatment

Hypertension was treated by using esmolol, prazosin, and intermittent doses of hydralazine in our patient. Atenolol

Figure 1
Preoperative imaging showing right-sided paraganglioma.

was given initially; however, the patient developed an allergic bronchospasm reaction. Therefore, esmolol (1000 mg) infusion was used as an alternative to atenolol and gradually titrated to a dose of 50 $\mu\text{g/kg/min}$. That was effective in controlling the tachycardia and the BP in addition to prazosin at 0.1 mg/kg/day in four divided doses (i.e. 0.8 mg per dose every 6 h) and also an intermittent use of i.v. hydralazine push of 3 mg when the systolic BP exceeded 130 mm of mercury. A successful control of the paroxysms of hypertension and tachycardia using the above agents was achieved a week prior to surgery (Fig. 2). Following control of paroxysmal hypertension, an exploration laparotomy was performed to remove the right-sided paraspinal abdominal paraganglioma. Postoperatively, the pain was controlled with minimal settings of epidural anesthesia (Bupivacaine hydrochloride 0.1%) then epidural injections of fentanyl citrate (50 $\mu\text{g/mL}$) until day 2 after the operation. The patient remained

hemodynamically stable after the removal of tumor with BP maintained between 109–120/60–67 mm of mercury. She required noradrenaline infusion (0.05 $\mu\text{g/kg/min}$) for only 8 h postoperatively; after which, no episodes of hypotension were recorded.

Outcome and follow-up

The diagnosis was confirmed later by histopathology and the genetic test (Fig. 3). Her genetic study showed a heterozygous p.R90 pathogenic mutation in the SDHB gene confirming the diagnosis of familial paraganglioma. Her family was counseled regarding the risks of tumour recurrence as well as the development of renal cell carcinoma and gastrointestinal stromal tumor. They were also told about the need for life-long tumor surveillance.

Our patient was followed in oncology and endocrine clinics. She showed an excellent improvement in her general condition apart from infrequent episodes of palpitation that were assessed by a cardiologist who reassured the family. The screening for tumor recurrence included urine and blood tests for catecholamine levels every 4 months that was normal and a whole-body MRI imaging twice a year that was also reassuring of no recurrence.

Discussion

Preoperative management using alpha- and beta-blockade is crucial to prevent intra-operative complications in PCC/PG. Combination of both is usually preferred for better control of BP. Phenoxybenzamine, a long-acting non-selective alpha-blockade, has been widely used since 1950s. In addition, prazosin, a selective alpha 1 blockade,

Table 1 Initial pre- and postoperative levels of catecholamines.

Initial Result	Plasma	Urine
Preoperatively	<i>Catecholamines (HPLC[†])</i> Adrenaline < 0.106 nmol/L ($n = \text{up to } 0.435$) Noradrenaline 99.7** nmol/L ($n = \text{up to } 2.89$) Dopamine < 0.130 nmol/L ($n = \text{up to } 0.377$) Results from another laboratory: <i>Catecholamines (LC-MS/MS[‡])</i> Metanephrine*** < 50 ng/L ($n < 90$) Normetanephrine*** 3760** ng/L ($n < 129$, borderline up to 320 ng/L)	<i>Catecholamines (HPLC)</i> Adrenaline/creatinine 12.6 $\mu\text{g/g Creat}^*$ ($n < 18$) Noradrenaline/creatinine 1030** $\mu\text{g/g Creat}$ ($n = 5\text{--}53$) Dopamine/creatinine 260 $\mu\text{g/g Creat}$ ($n = 69\text{--}552$) Creatinine 4.22 mmol/L ($n = 2.56\text{--}20.0$)
Postoperatively	<i>Catecholamines (LC-MS/MS)</i> Metanephrine < 50 ng/L ($n < 90$) Normetanephrine 123 ng/L ($n < 129$, borderline up to 320 ng/L)	<i>Catecholamines (HPLC)</i> Adrenaline/creatinine 1.8 $\mu\text{g/g Creat}$ ($n < 18$) Noradrenaline/creatinine 28.7 $\mu\text{g/g Creat}$ ($n = 5\text{--}53$) Dopamine/creatinine 547 $\mu\text{g/g Creat}$ ($n = 69\text{--}552$) Creatinine 19.7 mmol/L ($n = 2.56\text{--}20.0$)

*Creat, creatinine; **High levels of catecholamines; ***Metanephrine and normetanephrine – adrenaline and noradrenaline; [†]HPLC, high performance liquid chromatography; [‡]LC-MS/MS, liquid chromatography mass spectrometry.

Figure 2
Pre-operative paroxysms of hypertension and tachycardia in our patient.

has also been favorably used due to its short duration of action resulting in fewer side effects postoperatively (14). Beta blockade should never be used prior to initiating alpha-blockade agents as they might exacerbate vasoconstriction by blocking its vasodilator component, leading to hypertensive crisis. Nonetheless, beta-blockade is generally used after alpha-blockade to suppress the alpha-blocker-induced tachycardia, and they also help in control of BP (15). There is no evidence to support the use of beta 1 blockers such as atenolol over the non-selective beta-blockers, which include propranolol. Some previous reports suggested the use of esmolol in adults but there were only a few reports in Pediatrics (16, 17). Esmolol showed a good effect as adjuvant therapy to alpha-blockers and its very short half-life of approximately 9 min facilitated an easy titration, which helped to avoid postoperative hypotension that usually requires prolonged use of presser agents.

Patients are commonly admitted 24–36 h prior to surgery and are given alpha and beta-blockers, as well as, in some cases, a tyrosine hydroxylase inhibitor in the night before surgery (18). Hypotension is a common complication in the immediate postoperative period due to the unopposed effect of long-acting alpha-blockade leading to vascular expansion. This is usually

managed preoperatively with large volume i.v. fluids and consumption of high sodium diet (19). An important initial step in the management is to start with an alpha-blocking agent to reduce the BP then use beta-blockers to achieve heart rate control. The goal of BP reduction is to achieve <50 percentile for age and height. Echocardiography is necessary for the preoperative assessment to rule out dilated cardiomyopathy as a complication of chronic oversecretion of catecholamines (20).

In a previous report, with the use of alpha-blockade, the operative and postoperative complications decreased dramatically from 69% to 3% (17). The preferred agent for the alpha-blockade is phenoxybenzamine because of its long duration of action and a non-competitive blockade of alpha-receptors that favored its use (21). Nonetheless, the downsides of a long half-life duration of phenoxybenzamine are tachycardia and persistent postoperative hypotension. Other alternatives include terazosin, doxazosin, and prazosin that are mainly used in adults (15). Given the rarity of neuroendocrine tumors in pediatric and adult patients; to date, there are no reported randomized controlled trials looking at the superiority of the commonly used subtypes of medications. Although, the short duration of action of prazosin and doxazosin might suggest favoring their use in patients with PCC/PG, none of these alpha-blockers, neither the phenoxybenzamine, is currently evident to be superior in the perioperative management of patients with PCC/PG (22). The decision on a choice probably much depends on individual cases.

For beta-blockade, propranolol is commonly used in patients with PCC/PG following the use of alpha-blockers (23). In our case, the patient was also known to have bronchial asthma, for which propranolol was contraindicated. When atenolol was given, the patient developed serious allergic bronchospasm, so esmolol was given as an alternative. Esmolol is an ultra-short acting, cardio-selective, beta 1 blockade agent. The onset of action is within 1 to 2 min, and its half-life is only 9 min (24). The rapid onset and short half-life enable titration

Figure 3
Gross histopathology of paraspinal paraganglioma following surgical excision.

of the drug to the desired effect facilitating escalation and discontinuation of treatment to avoid postoperative complications. Esmolol has been approved for use only in adults by FDA (25). Nevertheless, it has been used in pediatrics for several indications including arrhythmia (e.g. supraventricular tachycardia), perioperative and postoperative tachycardia, as well as hypertension and hypertensive emergencies (25). It is usually administered as a loading dose of 100–500 µg/kg over 1 min, followed by an infusion of 50–500 µg/kg/min and titrated by 25–50 µg/kg/min (25). In our case, we were able to achieve adequate control of paroxysmal hypertension by using a minimal dose of esmolol in addition to other antihypertensive agents, mainly prazosin, without adverse events.

Conclusion

Esmolol is titrable, effective, and can be weaned rapidly helping to avoid postoperative complications of hypotension in children with PCC/PG after the removal of a catecholamine-secreting tumor. In addition to alpha-blockers, esmolol could be a good alternative to routinely used beta-blockers such as propranolol and atenolol to control the BP and tachycardia in the pre- and intra-operative periods; especially when a patient has comorbidity of asthma.

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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Patient consent

A written informed consent has been obtained from the patient's guardian for publication of the submitted article and accompanying images.

Author contribution statement

A B, W A and S K wrote and drafted the initial manuscript and approved the final manuscript. All other co-authors revised, amended, and approved the finally submitted manuscript. Y K designed Figure 2. M A provided the photo of Figure 3. A B (Pediatric Endocrinologist) named physician of the patient in the treatment center, A H (Pediatric Endocrinologist) named physician of the patient in the referring center, Y K (Intensivist, PICU), T A (Pediatric Oncologist), M A (attending Endocrinologist), M A (Pediatric Surgeon), A A (Pediatric Anesthetist), W A and S K (Medical interns).

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