Is there an optimal preoperative management strategy for phaeochromocytoma/paraganglioma?

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Abbreviated title: Preoperative management of PPGLs

Key words: Phaeochromocytoma, paraganglioma, preoperative pharmacological management

Word count: 2255

Figures: 1

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Disclosures: No conflicts of interest to disclose for any of the authors

Summary

Phaeochromocytomas and paragangliomas (PPGLs) are catecholamine secreting neuroendocrine tumours that predispose to haemodynamic instability. Currently, surgery is the only available curative treatment, but carries potential risks including hypertensive and hypotensive crises, cardiac arrhythmias, myocardial infarction and stroke, due to tumoral release of catecholamines during anaesthetic induction and tumour manipulation. The mortality associated with surgical resection of PPGL has significantly improved from 20–45% in the early 20th century[1] to 0–2.9% in the early 21st century[2], largely due to availability of effective pharmacological agents and advances in surgical and anaesthetic practice. However, surgical resection of PPGL still poses significant clinical management challenges. Preoperatively, alpha-adrenoceptor blockade is the mainstay of management, although various pharmacological strategies have been proposed, based largely on reports derived from retrospective data sets. To date, no consensus has been reached regarding the 'ideal' preoperative strategy due, in part, to a paucity of data from high quality evidence-based studies comparing different treatment regimens. Here, based on the available literature, we address the *Clinical Question*: Is there an optimal preoperative management strategy for PPGL?

What are the goals of preoperative pharmacological therapy?

At a headline level, normalisation of blood pressure and heart rate, and restoration of intravascular fluid status are the main objectives of preoperative pharmacological management. Current guidelines suggest adrenergic blockade should be initiated 7-14 days prior to surgery[3]. However, the average duration of treatment varies depending on the regimen adopted, and whether inpatient or outpatient therapy is initiated. Most centres report

an average preoperative treatment duration of 2-6 weeks.[4,6,11] Although in some institutions treatment may be started even earlier, there is no evidence to suggest that additional benefit is derived from longer preoperative blockade.[4] Similarly, there is no consensus regarding haemodynamic thresholds that signal adequate blockade, with current published recommendations based largely on non-controlled studies and institutional experience. Roizen and colleagues proposed several indicators of adequate preoperative alpha blockade which included: (1) No in-hospital blood pressure >160/90mmHg for 24 hours prior to surgery; (2) No orthostatic hypotension with blood pressure <80/45mmHg; (3) No ST segment or T wave ECG changes for 1-week prior to surgery; (4) No more than 5 premature ventricular contractions per minute.[5] Subsequently, others have suggested a lower preoperative blood pressure (<130/80mmHg while seated; systolic BP >90mmHg on standing) and controlled heart rate (60-70 beats per minute while sitting)[6], which align with current Endocrine Society recommendations.[3] However, whether preoperative normalisation of systolic blood pressure is mandatory in all patients has been questioned. Lentschener and colleagues have proposed that only patients with hypertension-induced organ dysfunction require systolic blood pressure normalisation prior to surgery, based on their findings that high preoperative systolic BP *per se* is not predictive of perioperative haemodynamic instability.[7]

Do all patients with PPGL require preoperative hypotensive drugs?

Current consensus recommends that all hypertensive patients with biochemically confirmed PPGL should receive preoperative pharmacological management.[3] Similarly, in patients with functional PPGL who are apparently normotensive and asymptomatic, tumour manipulation may provoke an increase in blood pressure and preoperative medical management is therefore

recommended.[3, 8] Preoperative medical treatment may not be required for patients with non-functioning (defined by negative metanephrine screening), parasympathetic-derived head and neck paragangliomas or those with exclusive dopamine-secreting tumours.[9] However intra-operative anaesthetic vigilance and expertise is still required.

Preoperative blockade with alpha-adrenoceptor antagonists is also standard of care for management of PPGL in pregnancy. Phenoxybenzamine (PBZ) is the preferred agent and is safe for the fetus; however, blood pressure control must be carefully monitored to ensure adequate placental perfusion.[6] The optimal timing for surgical resection of a PPGL during pregnancy is generally considered to be in the second trimester, thereby allowing the pregnancy to progress to normal term/delivery thereafter. However, if this is not possible, then treatment with PBZ should continue until the fetus has reached a satisfactory weight;[2] careful discussion between the patient, endocrinologist, obstetrician and anaesthetist regarding the timing of tumour resection and delivery of the baby by Caesarean section will be required.[2]

Which preoperative hypotensive drugs have been used?

1. Alpha-adrenoceptor antagonists

Phenoxybenzamine (PBZ), a non-competitive α1- and α2-adrenoceptor antagonist, is the most widely used agent for preoperative blockade. Owing to formation of a permanent covalent bond with α-adrenoceptors, PBZ has a long duration of action ($t_{1/2}$ = 24 hours, which tapers following synthesis of new receptors), and may contribute to sustained hypotension following tumour removal. Side effects include nasal congestion, CNS sedation, orthostatic hypotension, reflex tachycardia and, at higher doses, paradoxical hypertension. The starting dose is 10mg twice daily with a recommended maximum daily dose of 1mg/kg, and average

dose requirement of 40-60mg/day.[10] For the majority of patients pre-treatment with PBZ can be undertaken on an outpatient basis.[11] It is important to note, however, that intraoperative hypertensive surges (systolic blood pressure >160mmHg) may still occur in patients deemed to be adequately pre-treated with PBZ[9] (Figures 1A and 1B). In addition, high cost and restricted availability preclude routine use of PBZ in some centres and countries.[12]

Compared with PBZ, selective α_1-adrenoceptor antagonists such as prazosin, terazosin or urapidil, have short half-lives due to competitive inhibition and displacement by endogenous catecholamines. The shorter half-life of selective α_1-adrenoceptor antagonists results in less reflex tachycardia and a shorter duration of post-operative hypotension. In contrast, modified release doxazosin has a longer duration of action ($t_{1/2}$ = 16-36 hours), allowing once daily dosing as well as dose optimisation in the days prior to surgery. In general, doxazosin does not cause reflex tachycardia or significant post-operative hypotension.

Several retrospective studies have reported the benefit of preoperative blockade with PBZ using endpoints such as operative mortality, intraoperative blood pressure excursions and post-operative complications.[4, 15-17] There is no published randomised clinical trial data comparing PBZ with selective alpha-blockade. One retrospective study found no difference in blood pressure or intraoperative/post-operative fluid requirements between patients pre-treated with PBZ versus doxazosin or prazosin.[18] Another retrospective multi-centre study reported higher post-operative inotropic requirements in patients pre-treated with PBZ and higher intraoperative blood pressure readings in those who received doxazosin.[19]

Evidence for efficacy of selective alpha$_1$-adrenoceptor antagonists in the preoperative management of PPGLs exists mainly for doxazosin (DX).[19, 21] In one study DX performed as well as PBZ with respect to intraoperative haemodynamic stability, with fewer reported side-effects, episodes of intraoperative tachycardia and post-operative fluid requirements, and no

difference in mortality.[21] In contrast, other groups observed that pre-treatment with DX resulted in higher systolic blood pressures before and after anaesthetic induction compared with PBZ.[23] Van der Zee and colleagues recently reviewed studies comparing pre-treatment with PBZ versus DX, and concluded that there was no evidence to suggest superiority of one agent over the other, and that alpha-adrenoceptor blockade *per se* was efficacious.[22] In another retrospective series, preoperative treatment with prazosin was associated with no deaths, although significant intraoperative hypertensive surges occurred in 83% of treated patients.[21] Successful surgical outcomes following preoperative urapidil administration have also been reported. However, hypertensive surges occurred at induction and/or tumour manipulation in all patients. Esmolol administration was required to control intraoperative tachycardia in one third of cases.[23]

One retrospective study reported no benefit of preoperative alpha-blockade in normotensive patients with secretory PPGL. It is important to note that the number of subjects in the treatment group was almost twice that of the control group and that a modest dose of DX (4mg) was used in the treatment group. No difference was seen in intraoperative blood pressure in patients treated with DX compared with patients who did not receive alpha-adrenoceptor blockade. There was, however, increased administration of intraoperative inotropes and colloid in the DX-treated group.[25]

2. Beta-adrenoceptor antagonists

β-adrenoceptor antagonists are contraindicated in the absence of effective α_1-receptor blockade due to the risk of a potentially fatal hypertensive crisis secondary to unopposed alpha-adrenoceptor stimulation.[6] Preoperative use of β-blockers is generally reserved for prevention and treatment of cardiac arrhythmias and reflex tachycardia, and no evidence exists to support the routine use of beta-blockade in the management of noradrenaline-

secreting tumours in the absence of arrhythmias.[1] However, preoperative use of β-blockers should be considered in the management of tachycardia or tachyarrhythmias induced by adrenaline-secreting PPGL. Cost and dosing schedules may need to be considered when choosing a beta-adrenoceptor antagonist (the latter to maximise compliance).

3. Calcium channel antagonists

Calcium channel antagonists (CCB) inhibit noradrenaline-mediated calcium influx into vascular smooth muscle thereby inducing coronary and peripheral artery relaxation to control hypertension, tachyarrhythmias and possibly coronary vasospasm.[14] These agents cause minimal hypotension and may be best suited for normotensive patients with paroxysmal hypertension or intolerance to alpha-adrenoceptor antagonists.[6]

Brunaud *et al* compared patients treated with nircardipine with patients treated with PBZ and beta-blockade and found that intraoperative mean systolic blood pressure and incidence/duration of hypertensive surges was lower in PBZ-treated patients.[26] However, postoperatively, PBZ-treated patients had an increased incidence of hypotension and greater fluid requirements. No difference in overall haemodynamic stability was observed between groups.[25] Similarly, Siddiqi *et al* reported no difference in haemodynamic stability between patients treated with either nicardipine or PBZ, although patients pre-treated with the former had a smaller mean tumour size and lower metanephrine levels.[24] Finally, in another retrospective series, nicardipine monotherapy was associated with low mortality rates but increased incidence of intraoperative hypertensive episodes.[25]

4. α-methyl-para-tyrosine (Metyrosine)

Metyrosine competitively inhibits tyrosine hydroxylase, the enzyme that regulates the rate-limiting step of catecholamine biosynthesis[14], to reduce catecholamine levels. Metyrosine is most often used in conjunction with alpha-blockade, and in combination may reduce both

intraoperative haemodynamic instability and postoperative cardiovascular morbidity. However, high cost, limited availability and intravenous route of administration restrict routine use. Metyrosine has been reported to provide improved haemodynamic stability and reduced postoperative fluid requirements, although no differences in surgical outcome.[28,29,30] It is important to note however, that hypertensive crises may still occur with metyrosine monotherapy.[5]

When should add-on therapy be considered?

Add-on therapy should be considered when blood pressure is not adequately controlled with a single agent or the patient is intolerant of escalating doses of monotherapy. In either setting, metyrosine or CCB can be used effectively as add-on therapies to alpha-adrenoceptor antagonists and, in combination, have been found to provide superior haemodynamic stability in some studies.[26, 28] Add-on therapy should also be used to treat tachycardia or cardiac arrhythmias, with beta-adrenoceptor antagonists the preferred agents.

When should pre-operative alpha-blockade be discontinued?

Limited data exists to inform this decision and discontinuation of treatment the night prior versus the morning of surgery is guided by the choice of alpha-blockade and half-life of the agent. For example, PBZ has a longer half-life and in patients scheduled for an early morning theatre slot treatment is generally continued until the evening prior to surgery; however, this approach is not universal with some clinicians advising a final dose on the morning of surgery. Where a selective alpha-blocker with a shorter duration of action is used, the last dose is usually administered on the day of surgery.

Do all patients require preoperative fluid replacement?

There is no randomised controlled evidence to support a role for routine preoperative fluid replacement. However, retrospective data suggests that fluid and salt replacement may limit postural hypotension and post-operative hypotension[3] by optimising intravascular status. If patients are unable to tolerate a high fluid intake orally, administration of intravenous fluids for 24-48 hours before surgery is often advised. However, the requirement for preoperative intravenous fluid has been queried, as Lentschener and colleagues observed no difference in mortality when intravenous fluids were given on an 'as needed' basis only, as guided by arterial blood pressure[7], indicating that 'prophylactic' administration of intravenous fluids may not improve outcomes in PPGL surgery when appropriate anaesthetic expertise is readily available.

What is the value of perioperative management?

Even when preoperative blockade is carefully managed, and optimal alpha-adrenoceptor blockade and fluid replacement is deemed to have been achieved, intraoperative haemodynamic instability can still occur as illustrated in Figures 1A and 1B. Moreover, in some instances, such as emergency surgery in patients with a known phaeochromocytoma, it may not be possible to establish adequate preoperative blockade prior to surgery; however safe clinical outcomes can still be achieved. Figure 1C illustrates such a case, suggesting that perioperative management may actually be more critical for achieving good clinical outcomes than administration of preoperative hypotensive drugs. This thesis is supported by recent reports which reason that adequate control of intraoperative hypertension can be achieved through meticulous blood pressure monitoring, careful surgical practice and

administration of fast-acting hypotensive agents when necessary.[32, 33] Consistent with this, several studies have shown that in the perioperative period, continuous blood pressure monitoring, administration of vasoactive and anti-arrhythmic drugs, and careful fluid management all contribute to improved patient outcomes.[7, 10, 11]

Conclusions

There is a lack of available randomised clinical trial data to support decision-making on pre-operative management of PPGL. Currently, however, 'PRESCRIPT' (see clinicaltrials.gov), a randomised, multi-centre open label clinical trial is recruiting subjects to determine whether preoperative treatment with PBZ or DX is superior with regards to minimising intraoperative haemodynamic instability. Until these data are reported, current recommendations and available evidence support PBZ (or, where not available, DX) as first line preoperative pharmacological therapy in patients with PPGLs. In the majority of cases, a short period of preoperative blockade with PBZ, combined with active fluid management, allows surgery to proceed uneventfully. However, even when the patient's clinical status is deemed to have been 'optimised' prior to surgery, significant intraoperative blood pressure excursions may still occur. There is growing evidence that perioperative anaesthetic expertise is critical for successful management of patients with PPGL undergoing surgery, and we believe that this may in fact be the single most important factor-governing outcome.

ACKNOWLEDGEMENTS

BC, RC and MG are supported by the National Institute for Health Research Cambridge Biomedical Research Centre.

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FIGURE LEGEND:

Fig. 1 Intraoperative haemodynamic changes in three patients undergoing adrenalectomy for phaeochromocytoma.

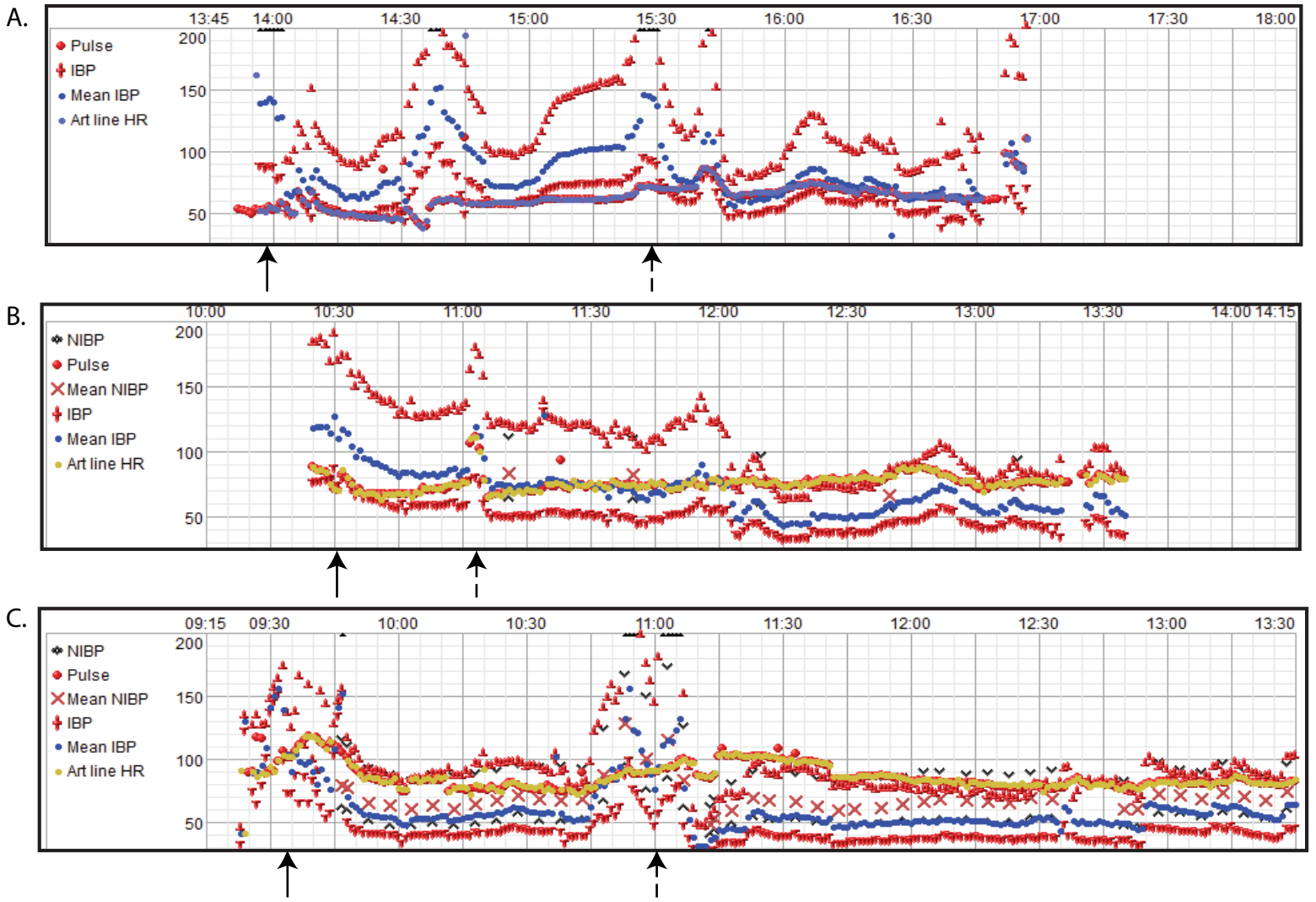
(A) 68-year old man (70kg): plasma metadrenaline 1,283 pmol/L (RR: 0–600) and normetadrenaline 1,086 pmol/L (RR: 0–1000). Computed tomography (CT) imaging revealed a 9.0 x 4.5cm phaeochromocytoma. Preoperative blockade was established with phenoxybenzamine over a five-week period (maximum tolerated dose 20mg twice daily) and propranolol (10mg thrice daily) in accordance with published guidelines.[3] A minimum 2.5L oral fluid intake per day was advised while taking phenoxybenzamine. He also received 5L of 0.9% sodium chloride intravenously in the 48 hour period prior to surgery. There were no postoperative complications.

(B) 72-year old man (85.2kg): plasma metadrenaline 427 pmol/L (RR: 0–600) and plasma normetadrenaline 17,187 pmol/L (RR: 0–1000). CT revealed a 12.5 x 11.5cm right-sided phaeochromocytoma. Preoperative blockade was established with phenoxybenzamine over a seven-week period (maximum tolerated dose 20mg twice daily). As the patient was clinically hypovolemic at initiation of phenoxybenzamine treatment, 3L of oral fluid intake per day was supplemented with 2L of 0.9% sodium chloride intravenously as an outpatient on our endocrine day unit, and a further 6L of intravenous fluid in the 48h preoperatively. There were no postoperative complications.

(C) 75-year old man (65.8kg): plasma metadrenaline >18,000pmol/L (RR: 0–600) and plasma normetadrenaline 10,120 pmol/L (RR:0–1000). CT revealed a 5 x 7cm right-sided phaeochromocytoma. The patient declined medical or surgical management. However, shortly afterwards he presented with acute small bowel obstruction necessitating emergency surgery in the absence of preoperative blockade. A right adrenalectomy was performed during the same procedure. There were no postoperative complications.

Key: Art line, arterial line; HR, heart rate; IBP, invasive blood pressure; NIBP, non-invasive blood pressure; solid arrow indicates time of anaesthetic induction/intubation; dashed arrow signifies the point at which the PPGL was removed.

Figure 1.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