



Haemodynamic instability of the pheochromocytoma

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Careful peri-operative management of a patient with a secretory pheochromocytoma or paraganglioma (PPGL) is essential to help minimise peri-operative haemodynamic instability (HDI) and other potential complications of surgical resection. Most practitioners and guidelines advocate pre-operative adrenergic blockade (1). However, along with many other rare conditions, best management is often guided by clinical expertise and experience, and in this particular condition, the vast majority of data are retrospective. As far as the authors are aware, there is only one prospective contemporary study analysing outcomes of pheochromocytoma blockade (2).

The authors from the experienced adrenal unit at Birmingham here analyse retrospective data for 46 patients over a period of 11 years to suggest risk factors for HDI post-adrenalectomy (3). The large number of variables that needs to be considered highlights the difficulties and controversies of managing this condition. Such variables include patient age and co-morbidities, size and site of tumour, genetic status, secretion/co-secretion pattern, surgical approach, choice of alpha-blockade, use or not of beta-blockade, reason and choice of beta-blocker when used, choice of target blood pressure and pulse rate, use of salt loading and pre-operative fluids, type of anaesthesia, volume of fluids, use and choice of peri-operative vasodilators and pressor agents. As a single-centre retrospective study looking at a rare condition, the authors fully acknowledge the changing practice over time (with reference to some of these variables) with a move from mainly open to mainly laparoscopic procedures, a change from phenoxybenzamine

to doxazosin, a move away from routine beta-blockade, and presumably also a trend towards operating on smaller tumours with lower secretion of catecholamines, detected at an earlier stage due to genetic surveillance screening or as incidental radiological findings (4).

There are four main conclusions from the study and all are certainly worthy of note and further discussion. We look at each in turn, combining the first two conclusions.

Conclusions I & II

Conclusions I & II: Intra-operative hypertension is a common event during adrenalectomy for pheochromocytoma, and is more likely in patients with large tumours and very high pre-operative plasma normetanephrine levels. Cardiovascular complications may be prevented by prompt treatment of intra-operative HDI by an experienced anaesthetic team.

These conclusions are important because even with the most judicious and experienced attempts to minimise the risk of hypertensive “escape”, profound hypertension often occurs at key stages of surgery, for example, with induction of anaesthesia. It is for this reason, among many others, that the management of the pheochromocytoma should be undertaken by an experienced team able to combine the skills required to ensure safe pre- and post-operative management and most critically able to meet the potential intra-operative surgical and anaesthetic challenges.

The authors observe that larger, more secretory tumours are more likely to “escape” with intra-operative

hypertension. This was also noted in the multivariable analysis of the PRESCRIPT trial, which highlighted the relevance of tumour size and catecholamine level to HDI (2). It is therefore incumbent upon the pheochromocytoma team to differentiate the management required for a large, highly-secretory pheochromocytoma from a small pheochromocytoma that may, as yet, not have led to an elevation of the metanephrines outside the normal range.

Conclusion III

Conclusion III: The risk of post-operative hypotension may be reduced by limiting the use of pre-operative beta-blockade therapy.

We feel that the effect of beta-blockade is highly dependent on, and inseparable from, the use of alpha-blockade, and do not feel there are sufficient data presented to attribute causation of post-operative HDI to beta-blockers. There was a change in practice at the centre from routine use of beta-blockade to selective use of beta-blockade. Additionally, three patients had neither alpha- or beta-blockade and two patients underwent surgery with unopposed beta-blockade. We believe that the patients with unopposed beta-blockade and patients with no blockade at all (due to levels of metanephrines within the normal range) should have been excluded from analysis. One would expect more HDI with unopposed beta-blockade and less HDI when catecholamine secretion is minimal, leading to an apparent increase in the association of beta-blockers with HDI. We agree that the change in practice from routine beta-blockade to more clinically guided blockade is entirely appropriate and reflects the current practice at most major pheochromocytoma centres (1). Where, historically, beta-blockers were used routinely but were potentially unnecessary, this will also likely lead to an increased association with HDI. We would go further and suggest that it is more likely that beta-blockers would be used when the tumours are any combination of large, highly secretory, or co-secretory—features that are also likely to predict HDI.

We think it helpful to consider the haemodynamic effects of introducing alpha-blockade and the physiological and non-physiological tachycardia that this may induce. A patient presenting with an untreated secretory pheochromocytoma is in a clinically volume-deplete state and will often have postural symptoms with tachycardia. Treatment with alpha-blockade will cause vasodilatation, which exacerbates these symptoms initially. Therefore, in order to achieve an adequate dose of alpha-blockade,

it is essential to ensure sufficient salt and water loading to fill the circulation before a further increase in dose. The tachycardia in this clinical context is an appropriate physiological response to vasodilatation such that introduction of beta-blockade, in the absence of complete alpha-blockade and re-filling of the circulation, will make the clinical situation worse, potentiating HDI.

Many factors can influence the choice of alpha-receptor antagonist, not just non-selective versus selective, but also outpatient management of the initial expected postural hypotension, and access to adequate supplies of medication. The recent prospective study, PRESCRIPT, addresses both the question of choice of alpha-blockade (doxazosin versus phenoxybenzamine) and the doses required to meet strict peri-operative criteria (2). Buitenwerf *et al.* for the PRESCRIPT Investigators found that achievement of pre-operative blood pressure <130/80 mmHg was negatively associated with intra-operative HDI, i.e., confirmation that good pre-operative control confers intra-operative stability. They reported median doses of alpha-adrenergic blockade as 120 mg of phenoxybenzamine or 40 mg of doxazosin, after a median duration of 14 days prior to surgery. Even at high dose, there was no finding of significant post-operative hypotension. Since discontinuation of the intravenous preparation of phenoxybenzamine, which our centre used in the immediate pre-operative period as an adjunct to oral phenoxybenzamine, we now aim to achieve much higher doses of oral alpha-blockade (typically phenoxybenzamine at 80–160 mg/day). We believe that lower doses may lead to inadequate blockade and thereby exacerbate negative effects of beta-blockade. The doses of doxazosin from the Thompson *et al.* cohort were substantially lower than the median 40 mg dose in the PRESCRIPT trial, as they used a cut-off of 8 mg doxazosin to define low or high-dose blockade, and nearly half the patients taking doxazosin received a low dose. As sparse data describing the pre-operative blood pressure and pulse control are presented, we are unable to assess the adequacy of alpha-receptor blockade achieved but, as presented, it seems likely that some patients in this report were incompletely alpha-blocked and, therefore, experienced relatively unopposed beta-blockade.

Where adequate alpha-blockade has been achieved and circulating volume restored, tachycardia can still cause a symptomatic or clinical concern, perhaps more so when there is significant secretion of adrenaline. This tachycardia is probably a combination of reflex tachycardia due to alpha₂-receptor blockade and what is now unopposed action

of the catecholamines at beta₁-receptors. When clinically indicated, this is where the introduction of beta-blockade can be beneficial. Interestingly, pre-operative beta-blockade was not found to affect intra-operative blood pressure variation or the HDI score used by Buitenwerf *et al.*

Conclusion IV

Conclusion IV: Routine intensive care monitoring may not be necessary in low risk patients.

At a time when critical care beds are particularly scarce and precious, Thompson *et al.* have demonstrated that a strict rule for post-operative intensive care need not be applied to all PPGL surgeries. This is logical considering the considerable heterogeneity of PPGL manifestation as discussed above and brings us back to the initial conclusions that it is the large and very secretory PPGLs that need particular care and attention.

This paper focuses on the difficult and controversial clinical management of a rare tumour and highlights the need for large, prospective multi-centre studies to try to demonstrate which peri-operative interventions are most important for achieving the best outcomes. Based on the limited current evidence, we advocate the use of high dose alpha-blockade as the principal tool to minimise peri-operative HDI as demonstrated by the PRESCRIPT trial and believe that beta-blockers, when used judiciously, provide an essential part of the management of selected PPGLs.

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Footnote

Conflicts of Interest: Both authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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