Controversies about the systematic preoperative pharmacological treatment before pheochromocytoma or paraganglioma surgery

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Abstract

The question of systematic use of a pharmacological treatment before surgery in patients diagnosed with pheochromocytoma and paraganglioma (PPGL) remains highly controversial. While recent guidelines suggest that this should be used in all patients, some experienced teams consider it unnecessary in some cases, provided the surgery is performed in a dedicated center that has expert endocrinologists, cardiologists, surgeons, and anesthetists. This controversy is aimed at shedding light on the potential benefits and risks of such a treatment, focusing specifically on alpha blockers which are considered as the first-line medical treatments in patients with PPGL. After discussing the rationale for alpha blockers, hemodynamic instability, tolerance, and acute cardiac complications will then be discussed in the first part of the manuscript, defending a systematic use. The second section will focus on blood pressure control, tolerance of alpha blockers, and also the management of normotensive PPGL, examining the daily risks of PPGL and arguing against the systematic use of a preoperative pharmacological treatment before surgery. Finally, we will discuss the concept of expert centers and define the patients in whom the risk/benefit profile would favor the use of this preoperative treatment.

Introduction

While unstable hypertension should be controlled in patients with pheochromocytoma and paraganglioma (PPGL), the systematic use of preoperative pharmacological treatment, especially alpha receptor blockers, before surgery remains a matter for debate. In this manuscript, we will mainly address the need to treat all patients systematically with alpha receptor blockers before surgery. This is a major point of controversy, as shown by Luiz et al. in their multicentric retrospective study, where the authors reported that only 69% of 381 patients operated for PPGL were managed according to US Endocrine Society Clinical Practice Guidelines (1, 2). Furthermore, the majority of the remaining patients were not treated with any drug or were treated with beta blockers (which are contra-indicated due to a risk of severe hypertensive crisis either before or concomitantly with alpha blockers) (3). In the US guidelines (1), as in the recent guidelines on the management of PPGL in the Journal of Hypertension (4), it was however stated...
that ‘Presurgical medical preparation using an α-adrenergic receptor blocker remains the mainstay for preventing life-threatening peri-operative cardiovascular complications’. Therefore, does the published data support the systematic use of alpha blockers prior to surgery?

FOR: There is a need for a systematic use of a pharmacological treatment

Alpha adrenergic receptor blockers: a pathophysiological basis

Surgery for PPGL is regarded as high risk, with a historical mortality rate exceeding 40% in some case series. However, the mortality rate is currently closer to 1%. The excess mortality was linked to the tumor size and the vascularization of the tumor, while specific risks were linked to epinephrine and norepinephrine hypersecretion. Indeed, norepinephrine stimulates both subtypes of α receptors, and β1 receptors, but has little activity on β2 receptors. Epinephrine stimulates both α and β adrenoreceptors. However, receptor activation is dose-dependent; β receptors are more sensitive and can be activated at lower concentrations, whereas α-activation requires higher levels of epinephrine. The stimulation of α-1 receptor by predominantly norepinephrine and/or epinephrine induces peripheral vasoconstriction and increases peripheral vascular resistance, leading to a marked increase in blood pressure. In PPGL, the hypersecretion of epinephrine and norepinephrine has two specific features. It can induce a massive catecholamine release into the circulation. Additionally, the specific nature of PPGL relies on the continuous or episodic release of epinephrine and norepinephrine. In this context, the use of alpha blockade has a clear pathophysiological basis.

Use of alpha blockers to prevent hemodynamic instability (HDI) during surgery

The main goal of preoperative management of PPGL is to normalize blood pressure and heart rate, restore effective circulating blood volume, improve metabolic condition, and prevent a catecholamine storm and HDI in patients during surgery (5). As these conditions are due predominantly to the release of norepinephrine, the use of alpha blockers seems obvious from a pathophysiological viewpoint as previously discussed. The use of alpha blockers prior to resection of a PPGL was first introduced in 1949 (6). Later, in 1999, Goldstein published a retrospective study of 108 patients operated for PPGL and showed that patients who did not receive alpha blockers had a higher rate of complications (69% vs 3%) than those who did (7). Since then, it has become part of routine clinical care for the management of patients with PPGL and is recommended in both International and European guidelines: ‘We recommend that all patients with a hormonally functional PPGL should undergo preoperative blockade to prevent perioperative cardiovascular complications. We suggest α-adrenergic receptor blockers as the first choice’. (1). More recently, ‘Presurgical administration of α-adrenergic receptor blockers is considered as the treatment of first choice’ (4), and ‘All patients with PPGL (even those with apparent normal levels of catecholamines) should receive appropriate preoperative medical management to block the effects of released catecholamines’. Phenoxycbenzamine, an α-adrenoceptor blocker, is most commonly used for preoperative control of blood pressure’ (8). Usually, preoperative treatment with alpha blockers is initiated 7–14 days before surgery. Treatment should be introduced using a gradual increase in dose depending on blood pressure. The goal is to block alpha adrenergic receptors to limit HDI and to help reduce blood pressure. Evidence from randomized, controlled clinical studies regarding the effectiveness of alpha blockers is unavailable. There are no placebo-controlled, randomized studies on this topic, and analysis of the literature shows conflicting results (9). All previous studies on the type of α-adrenergic receptor blocker were retrospective in design and suffered from several biases, including the use of historical controls and the lack of a well-defined perioperative management protocol. Many studies reported a decrease in preoperative blood pressure, a lower rate of reactive tachycardia, and better postoperative recovery (5, 10, 11, 12). A recently published meta-analysis, based on only four studies, showed that mortality, perioperative cardiovascular complications, mean maximal intraoperative systolic and diastolic blood pressure, and mean maximal intraoperative heart rate did not differ between patients with or without alpha blocker administration (13). However, this is probably due to the low risk of events in these studies. In addition, these four studies were conducted in expert centers, in which surgeons and anesthetists are trained to manage the blood pressure fluctuations that may occur during surgery, which could explain the low number of events in these series. Additionally, among these four studies, one concerned only normotensive patients (14) and the three others had selection bias (see below). At the end of the meta-analysis, the authors concluded that ‘The level of evidence is too low to conclude that the practice of
preoperative α-blockade can safely be abandoned’ (13) and that randomized studies should be performed to generate the required evidence on this subject. One monocentric, pilot, open-label, randomized-controlled trial with the objective of comparing the efficacy of calcium channel blockers (CCB) and α-blockers on intraoperative HDI has been recently published. However, the results did not reach statistical significance as the authors initially decided to include 26 patients ‘based on feasibility’ and finally, only included 23 patients and analyzed the data from 20 patients (15). Moreover, the study protocol cannot be found in the clinicaltrials.gov database. In this context, without knowing the power, sample size determination, or hypothesis, the interpretation of the results of this pilot study appears impossible. Since all these studies were retrospective, there are multiple biases, the first being patient selection. Indeed, the decision of whether to initiate alpha adrenergic receptor blockade is likely to be affected by the severity of symptoms, the patient’s age and general condition, and the level of hypersecretion. Additionally, in most of the studies, the dose of alpha blockers was not specified and was likely too low to achieve efficacy, and the blood pressure target was not defined (16). For example, in the study by Groeben et al., the average daily dose of doxazosin was 11 mg (17), compared to an average dose of 40 mg/day in the only randomized study (18). Indeed, there is only one published randomized study and it compared phenoxybenzamine (non-selective and non-competitive α₁- and α₂-adrenergic receptor blocker) to doxazosin (selective and competitive α₁- and α₂-adrenergic receptor blocker). This study provides no information regarding the indication of alpha blockade vs another antihypertensive drug (or no antihypertensive drug). However, in this randomized study, which included 134 patients, the median cumulative time outside target blood pressure was approximately 11–12% during surgery, which is much lower than the time outside target blood pressure reported in other studies without alpha blockade. The median duration of pretreatment was 14 days, a CCB was administered in 40% of the patients, and 77% of the patients received metoprolol. During surgery, 50–70% of patients had a hypertensive peak with a systolic blood pressure > 160 mmHg. The duration of blood pressure outside the target range during the resection of a PPGL was not different after preoperative treatment with either phenoxybenzamine or doxazosin. Phenoxybenzamine was more effective in preventing intraoperative HDI, but it could not be established whether this was associated with a better clinical outcome. Phenoxybenzamine is also unavailable in some European countries.

The specific case of normotensive patients

Patients with hypersecretion of epinephrine/norepinephrine may have either permanent hypertension or acute elevations of blood pressure. First, the discussion among ‘normotensive patients with PPGL’ should exist only among patients who underwent an ambulatory blood pressure measurement (4). Besides, some studies have shown that patients with normotensive PPGL have the same per-operative HDI risk as hypertensive patients with PPGL (19). In this context, they should receive the same preparation for surgery as hypertensive patients. One can consider that prevalence of side effects would be higher among normotensive patients, but this has not been evaluated and additionally, patients would not receive this treatment over a long period. To conclude, analysis of the literature regarding the benefit of alpha blockade to prevent HDI shows conflicting results. The current literature thus does not help us to decide whether alpha blockers should be used or not. All published studies conclude that the only way to reach a decision would be to conduct a randomized study comparing preoperative treatment with alpha blockers to preoperative treatment with placebo, but such a study appears to be impossible to perform as it would need to include thousands of patients with a rate of mortality of surgery of PPGL of 1% (9). Studies based on morbidity might be more feasible, but it would need clinical events as a primary endpoint and it would still require a lot of patients.

Prevention of acute cardiac complications?

It must be kept in mind that the main goal in the management of PPGL is to prevent catecholamine storm, and for this reason, all guidelines recommend surgical resection of a secreting PPGL. We could therefore question whether alpha blockers prevent adrenergic storms. Considering their mode of action, α-adrenergic receptor blockers should reduce the risk of cardiovascular complications during the waiting period prior to surgery (20). To our knowledge, no study has evaluated the benefit of alpha blockers in reducing the risk of acute complications of PPGL, and this would be very difficult to evaluate since most patients will undergo surgery. However, it is generally accepted that patients with metastatic PPGL, in whom surgical removal of all secreting tumors is not possible, should have long-term medical treatment with alpha blockers (21, 22). In addition, several studies have shown that approximately 11% of PPGL patients will experience acute complications, particularly Takotsubo
cardiomyopathy (23, 24, 25, 26). In all of these studies reporting acute stress cardiomyopathy, it occurs before the diagnosis of PPGL, even in those patients who have already shown symptoms of catecholamine excess (hypertension, sweating, etc.) (24, 25, 27). The fact that most patients with metastatic PPGL do not develop acute cardiovascular manifestations (28) could be explained by the use of alpha blockers. Additionally, alpha blockade is also useful to protect from the risk of adrenergic storm linked to beta blockers because of unopposed alpha receptor stimulation—adrenergic stimulation (29), in a context where beta blockers are useful for treating tachycardia.

Tolerance of alpha blockers

The potential side effects of alpha blockade have led to questioning of the routine preoperative use of alpha blockade. Indeed, patients may experience side effects, mainly orthostatic hypotension. Moreover, the use of these drugs is likely associated with a higher risk of intraoperative hypotension. These side effects are probably increased by hypovolemia; therefore, it is important to hydrate patients and recommend a high-salt diet before surgery. In some centers, saline solution is infused for 24 h before surgery to decrease the risk of intra- and postoperative hypotension (29). Besides, dosing alpha blockers regarding BP level and dose escalation with a BP target might increase the tolerance of alpha blockers, as shown in the randomized study; no hypotension was reported after surgery, with appropriate perioperative management (18). Other studies have shown that phenoxybenzamine has a longer duration of action and causes more reflex tachycardia when compared to selective alpha blockers (16). However, the potential benefits of alpha blockers in reducing the catastrophic effects of severe intraoperative hypertension and controlling the risk of acute stress cardiomyopathy outweigh the risk of side effects. In addition, the tolerance of alpha blockade is much better, with a lower rate of hypotension, when patients were hydrated prior to commencing alpha blockade.

Conclusions

Even though the current guidelines acknowledge the lack of solid evidence, the potential benefits of alpha blockers, in reducing the catastrophic effects of severe intraoperative hypertension and controlling the risk of acute stress cardiomyopathy, outweigh the risk of side effects. This explains why the guidelines recommend the use of alpha adrenergic receptor blockers in view of the long-standing clinical experience with these drugs, their targeted mode of action, and the various methodological shortcomings of the studies that have suggested that they could be safely omitted.

AGAINST: There is no need for systematic use of a pharmacological treatment

Uncertainty concerning the systematic use of alpha blockers vs other hypertensive drugs is highlighted by one of the sentences in the most recent guidelines on the management of PPGL (4): 'Even though the evidence underpinning these recommendations for optimal presurgical treatment is almost entirely based on observational studies and expert opinion, the published studies that question this approach do not provide sufficient solid evidence that surgery without appropriate presurgical preparation is safe and feasible', showing that evidence is lacking from both the pro and con sides of the discussion. Indeed, the available literature lacks a prospective randomized, controlled study comparing alpha blockers vs placebo to ascertain the benefits of alpha blockers. Such a trial would be difficult to perform due to the rarity of the disease, and it would also imply no drug being used to treat hypertension in half of the patients. For this reason, the majority of studies have used a retrospective approach to analyze patient treatment, frequently in a historical perspective, and likely leading to a number of biases. For example, in some studies which included cases from the last 30 years, the decrease in mortality rates observed (from 40 to 0–3%) was ascribed to higher use of alpha blockers (16). However, this conclusion needs to be tempered in view of the major improvements in preoperative characterization of the tumors, as well as improvements in anesthetic and surgical techniques over the same time. Surgery for PPGL is considered high risk due to the possible massive release of catecholamines during intubation and during mobilization of the adrenal mass. Moreover, HDI (usually defined by high > 160 mmHg or low < 60 mmHg blood pressure level peaks and nadirs) is frequently observed during PPGL surgery. However, alpha blockers are not clearly superior to CCB for improving these parameters. Indeed, Brunaud et al. reported that in 155 patients pretreated with either alpha blockers (n = 41) or CCB (n = ), while mean maximal systolic blood pressure was lower with alpha blockers, the number of episodes of low blood pressure was increased with this treatment in comparison to CCB. Interestingly, one-third (n = 54) of patients had HDI, which was irrespective of the preoperative treatment (30). Groeben et al. evaluated hemodynamic
conditions and perioperative complications in 276 patients with PPGL, of whom 110 were treated with alpha blockers and 156 with other antihypertensive drugs or no treatment. While no difference in major hemodynamic parameters was observed between the two groups, a 17 mmHg difference in intraoperative maximal systolic blood pressure was observed, being lower in patients receiving alpha blockers. As no major complications occurred after surgery, the authors questioned the systematic use of alpha blockers vs antihypertensive drugs (17). In line with these results, we recently reported a low rate of HDI in 134 patients operated for PPGL in a center with extensive surgical and anesthesiological experience and non-systematic use of alpha blockers (29). Obviously, other publications (31, 32) have reported positive results with systematic use of alpha blockers, but all of these studies, both for and against alpha blockers, had the same methodological limits, these being retrospective series, lack of comparison, and retrospective analysis of patient outcomes.

**Side effects of alpha blockers**

The most important risk of alpha blocker use is hypotension, sometimes severe, which, per se, is a risk factor of HDI during the surgery, as shown by Bruynzeel et al. (33). In patients with PPGL, it might indeed be associated with more and longer hypertensive episodes during surgery, while immediately after surgery, the risk of alpha blocker use is a persistent alpha adrenergic receptor blockade leading to hypotension and requiring i.v. fluids. In the recent randomized, controlled trial comparing the efficacy of two different alpha receptor blockers, Buitenwerf et al. reported the side effects of these drugs based on 144 patients treated on a systematic basis: 80–92% of patients reported mild to moderate side effects on alpha receptor blockers (including two-thirds who reported at least two different side effects among dizziness, fatigue, headache, or palpitations). Unfortunately, preoperative hypotension was not reported in this study, but roughly 10% of the patients presented with cardiovascular complications despite being on alpha receptor blockers. As a comparison to a group without pretreatment was not performed, it is difficult to determine whether the severity of side effects might have differed in the patients without systematic pretreatment. These data, however, emphasize that alpha blockers should only be used by expert cardiologists/endocrinologists/internists, experienced in managing patients with PPGL (18). Finally, only one recently published study has reported the preliminary results of a monocentric, pilot, open-label, randomized-controlled trial comparing alpha blockers (prazosin, n = 9) and CCB (amlodipine, n = 11) in 20 patients presenting with secreting PPGL. Interestingly, in this study, the number of per-operative episodes of hypertension (systolic blood pressure > 160 mmHg) and hypotension (MAP < 60 mmHg) and the per-operative duration of HDI were higher in patients treated with alpha receptor blockers. Currently, CCB are recommended as a second-line treatment in patients on alpha receptor blockers and still presenting with hypertension, or in patients presenting with hypotension on alpha receptor blockers. Their use in patients with mild hypertension is still debated. Though only a limited number of patients were included, the authors concluded that CCB should be considered as an alternative to pre-surgical medical treatment in secreting PPGL (15).

**Normotensive patients with PPGL**

Is a systematic use of alpha receptor blockers mandatory in normotensive patients with PPGL, a situation reported in 10–40% of patients with PPGL (34, 35, 36). The recent guidelines on the management of PPGL state that ‘Normotensive patients with a PPGL should also receive presurgical medical treatment as they are also at increased risk of HDI’ (4). This is mainly based on the work of Lafont et al., in which the authors reported that HDI was similar between hypertensive patients (n = 24) and normotensive patients (n = 10) with PPGL and was more prevalent than in adrenal incidentalomas (n = 16). Interestingly, the majority of patients had been pre-treated with alpha receptor blockers or CCB (19). The authors concluded that patients with this profile required the standard of care for PPGL anesthesia. These results are in contrast with those reported by Shao et al., based on 59 patients, of whom 38 received the alpha blocker doxazosin and 21 did not receive an alpha blocker (no randomization was performed). Intraoperative hemodynamics were not significantly different between the two groups, and preoperative administration of alpha blockers did not improve the peak and nadir blood pressure during tumor resection. In contrast, the group treated with alpha blockers required more vasoactive drugs and colloid infusion. Unfortunately, preoperative catecholamine levels were not provided (14). In such patients, CCB, which inhibit noradrenaline-mediated calcium influx into vascular smooth muscle and present an optimal tolerance profile with a very low risk of hypotension, might be better suited (37). As these results clearly show that ‘silent’ PPGL should not be considered as non-secreting adrenal incidentalomas, their preoperative management should be individualized, weighing the risk of hypertension during surgery, and the

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Prevention of adrenergic storm

Wolf and coworkers defended the systematic use of alpha blockers because of the daily risk to life of catecholamine release in situations of psychological and physical stress (20). To our knowledge, this has never been specifically described in the literature; though it is logical to assume that patients with high levels of norepinephrine (i.e. three to five times above the upper limit of the normal range, leading to tachycardia and hypertension) would be at risk, as shown for peroperative HDI (33). Therefore, in our opinion, this justifies the need for an urgent and thorough examination of cardiac function and blood pressure (including ECG, echocardiography, and 24-h ambulatory blood pressure monitoring), as soon as the diagnosis is raised to determine the need for treatment to be prescribed, including alpha blockers or CCB. Moreover, a list of contra-indicated drugs should be systematically provided to the patient. Such patients should not have postponed surgery (as the time needed to obtain maximal efficacy of alpha blockers would be 7–14 days).

To our knowledge, there has not been any report of any adrenergic crisis in normotensive patients with PPGL. In such patients, adding alpha receptor blockers might lead to severe vertigo, malaise, headache, gastrointestinal distress, and hypotension.

Conclusions

Published data are difficult to interpret due to the lack of randomized studies. Additionally, patients with more severe preoperative profiles were more frequently treated using alpha blockers. Moreover, excellent morbidity and mortality results are reported by centers with extensive experience: this might suggest that alpha blockers could be necessary especially in less-experienced centers.

While a retrospective study identified the size of the tumor and epinephrine and norepinephrine levels as significant predictors of prolonged hypotension requiring postoperative catecholamine support after surgery (38), another study identified the same parameters as predictors of HDI (39). We thus advocate an individualized medicine approach for presurgical medical treatment, which should consider the cardiological evaluation, the characteristics and comorbidities of the patient and of the PPGL, and the experience of the anesthetist and the surgeon (Fig. 1). Systematic use of alpha blockers as a pre-treatment before surgery should be carefully considered via shared decision-making that includes the cardiologist/endocrinologist/anesthetist on a case-by-case basis. We now propose an algorithm to help decide whether alpha blockers should be considered, based on patient blood pressure and variability, past medical history, and the level of metanephrine (Fig. 1). The key to treatment remains based on preoperative cardiological and anesthetic assessments, short delay to surgery, and peri- and postoperative management of patient hemodynamic status sometimes with catecholamine support; this can only be performed in referral centers with trained physicians, anesthesiologists, and surgeons.

Declaration of interest
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