

RESEARCH

Preoperative blood pressure targets and effect on hemodynamics in pheochromocytoma and paraganglioma

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Abstract

Patients with pheochromocytoma and paraganglioma (PPGL) are treated with α -adrenoceptor antagonists to improve perioperative hemodynamics. However, preoperative blood pressure targets differ between institutions. We retrospectively compared per- and postoperative hemodynamics in 30 patients with PPGL that were pretreated with phenoxybenzamine aiming at different blood pressure targets at two separate endocrine departments. All patients were subsequently undergoing laparoscopic surgery at Department of Urology, Herlev University hospital. Fourteen patients were treated targeting to symptomatic and significant orthostatic hypotension and 16 patients to a seated blood pressure below 130/80 mmHg. As a control group, we included 34 patients undergoing laparoscopic adrenalectomy for other reasons. The group titrated to orthostatic hypotension required a higher dose of phenoxybenzamine to achieve the blood pressure target. This group had less intraoperative systolic and diastolic blood pressure fluctuation (Mann–Whitney *U* test; $P < 0.05$) and less periods with heart rate above 100 b.p.m. (Mann–Whitney *U* test; $P = 0.04$) as compared to the group with a preoperative blood pressure target below 130/80 mmHg. Perioperative use of intravenous fluids were similar between the two groups, but postoperatively more intravenous fluids were administered in the group with a target of orthostatism. Overall, the control group was more hemodynamic stable as compared to either group treated for PPGL. We conclude that phenoxybenzamine pretreatment targeting orthostatic hypotension may improve perioperative hemodynamic stability but causes a higher postoperative requirement for intravenous fluids. Overall, PPGL surgery is related to greater hemodynamic instability compared to adrenalectomy for other reasons.

Key Words

- ▶ blood pressure target
- ▶ hemodynamics
- ▶ pheochromocytoma
- ▶ phenoxybenzamine

Endocrine Connections
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Introduction

Surgery of pheochromocytoma and paraganglioma (PPGL) carries a risk of hemodynamic instability during induction of anesthesia and manipulation of the tumor (1, 2). Previously, the mortality related to surgical resection was high. However, with the improvement in pharmacological agents available and advances in surgical and anesthetic practice,

mortality has significantly reduced within the last decades (1, 3, 4, 5). The mainstay in preoperative pharmacological therapy is an alpha-adrenergic blockade to reduce the effect of catecholamines released during anesthesia and surgery and to optimize circumstances for hemodynamic stability (1). Recently, the efficacy of the alpha-receptor antagonists

phenoxybenzamine (PBZ) and doxazosin was compared in a randomized design showing improved hemodynamic stability in the PBZ group using a composite score but no difference between groups in maintaining blood pressure within target range (6). However, there is no evidence from randomized controlled studies to determine the optimal target blood pressure prior to surgery. Hence, guidelines are based on retrospective studies and expert opinion, and clinical practice varies between centers. Furthermore, progress in surgical and anesthetic practice within the last decades is speculated to have a greater impact on perioperative outcome than pretreatment with alpha-receptor blockers (4, 7). As pretreatment is time consuming, related to significant side-effects and carries a risk of postoperative hypotension it has been speculated to be redundant and a preoperative risk stratification of patients may be useful (8, 9). Others concur with international guidelines recommending preoperative treatment with an alpha-receptor blocker regardless the PPGL phenotype (3, 10, 11, 12).

We present a comparison of clinical practice between two centers in Denmark and retrospectively compare the per- and postoperative hemodynamics in patients with PPGL pretreated with PBZ titrated to different blood pressure targets. Secondly, hemodynamic parameters found in patients with PPGL is compared to a control group undergoing the same type of surgery but not having PPGL.

Materials and methods

This retrospective comparison of practice between two departments was approved by the Danish health authority (journal no. 3-3013-1029/1) and the Danish data protection agency (journal no. 2014-41-3220).

In the eastern part of Denmark, all laparoscopic resections of PPGL have been performed at the University Hospital Herlev since 2011 in order to achieve optimal surgical and anesthetic experience and expertise. However, pretreatment using the alpha-receptor blocker PBZ is managed in endocrinological departments at two different University Hospitals (Herlev Hospital and Rigshospitalet) solely based on the municipality of the patient. Clinical approach for titration of PBZ has traditionally differed between the two departments. Retrospectively, we identified 30 consecutive patients with a histological diagnosis of pheochromocytoma ($n = 29$) or paraganglioma ($n = 1$) and pretreated with PBZ in one of the two endocrinological departments from 2011 to 2015. The patient with paraganglioma had a variation in the *SDHB* gene. Patients with a histological diagnosis of pheochromocytoma or

paraganglioma but not pretreated with PBZ were excluded from the dataset. In addition, we included 34 control subjects who underwent laparoscopic adrenalectomy during 2011–2015 at the same surgical and anesthesiological facility but did not have PPGL and were not treated with PBZ ahead of surgery. Indications for adrenalectomy in the control group were non-functioning incidentalomas or incidentalomas with autonomous cortisol secretion, unilateral primary hyperaldosteronism or Cushing disease with the finding of adrenocorticotrophic hormone-independent cortisol secretion and an adrenal adenoma. Histological pathologies were adrenocortical adenoma, adrenocortical adenoma with nodular hyperplasia, diffuse nodular hyperplasia, adrenocortical neoplasia, adrenal cyst, hematoma in the adrenal gland, ganglioneuroma or myelolipoma.

Patient electronic health records were reviewed for demographics (age, sex, tumor size by CT, comorbidity using American Society of Anesthesiologists classification, level of plasma metanephrines, blood pressure before and after treatment with PBZ, end dose of PBZ, duration of PBZ treatment and treatment with beta-blocker). Anesthesiological records were studied for operation and anesthesia time, total fluid administration, blood transfusion, highest and lowest systolic and diastolic blood pressure recorded during surgery, use of vasoactive substances, heart rate and perioperative complications. From postoperative registrations observation time, volume fluid administration, episodes with a mean arterial blood pressure (MAP) below 70 mmHg and use of vasoactive substances were extracted. Furthermore, length of stay, readmission within 30 days and postoperative complications were recorded.

Anesthesia and surgery

Patients with PPGL had an intra-arterial line inserted prior to induction of anesthesia for continuous monitoring of blood pressure and heart rate and a central venous catheter was placed for infusion of vasoactive drugs. General anesthesia was induced by propofol, fentanyl and rocuronium. Before tracheal intubation, an intravenous bolus of magnesium sulfate was administered and adenosine was connected to one lumen of the central venous catheter ready for rapid titration. Anesthesia was maintained with sevoflurane and remifentanyl infusion. Fentanyl was supplied at the discretion of the anesthesiologist. Intraoperative target blood pressure was MAP within 20–25% range of the preoperative MAP. Adenosine, sodium nitroprusside and magnesium sulphate were administered individually according to blood

pressure to prevent hypertensive episodes. Hypotensive episodes were primarily treated with intravenous fluid and norepinephrine as needed.

Control subjects had blood pressure and heart rate monitored non-invasively. General anesthesia was induced with propofol, fentanyl and rocuronium and maintained with sevoflurane or propofol/remifentanyl infusion.

Laparoscopic surgery was performed using a standard transperitoneal approach. The patients were placed in the left or right lateral decubitus position. Operative time was considered as the period from skin incision to wound dressing. Antithrombotic prophylactic therapy was administered in all cases. Cortical sparing adrenal surgery was not performed in any case, all surgery was unilateral and none were converted to open surgery.

After laparoscopic resections of PPGL, the patients were monitored at the post-anesthesia or intensive care unit.

Statistics

Data are reported as median and range and as the frequency for categorical variables. Group values were compared using a non-parametric Kruskal–Wallis rank-sum test with Dunn's multiple comparison analysis, Mann–Whitney *U* test or Fisher's exact test as appropriate. A two-tailed *P* value <0.05 was considered statistically significant.

Results

Preoperative characteristics

In the period 2011–2015, 30 patients underwent laparoscopic surgery after treatment with PBZ. All had histological-verified PPGL and a biochemical secretory profile with elevated p-methoxyadrenaline and/or p-methoxynoradrenaline. Characteristics are shown in [Table 1](#). Fourteen patients had PBZ titrated at Copenhagen University Hospital, Rigshospitalet to a target defined as a significant drop in orthostatic blood pressure in combination with symptoms of orthostatic hypotension (PBZ-1). The other 16 patients had PBZ titrated to a target blood pressure below 130/80 mmHg in the seated position during regular visits at the outpatient endocrinological clinic at Copenhagen University Hospital Herlev (PBZ-2). The different approaches for titration resulted in significantly different end doses of PBZ ($P=0.0007$, [Table 1](#)). As control group, data from 34 patients undergoing laparoscopic adrenalectomy from 2011 to 2015 were analyzed. No patients in the control group had histological-verified PPGL or received PBZ prior to operation. All patients (PPGL and controls) underwent an operation at the same surgical and anesthesiological

unit. The PBZ groups were similar regarding to age and sex. However, a tendency for more comorbidity (diabetes mellitus and coronary artery disease) in PBZ-2 vs PBZ-1 was noted. The two groups with PPGL did not differ statistically regarding tumor size, plasma level and biochemical profile of metanephrines prior to surgery and MAP prior to the alpha-receptor blockade. Mean MAP was significantly reduced in both PPGL groups after titration of PBZ and MAP measured preoperatively did not significantly differ between PBZ groups ($P < 0.13$, [Table 1](#)) although a trend toward lower MAP in PBZ-1 was present. MAP registered for patients in the control group was similar to the two PPGL groups before pretreatment and significantly higher than preoperative MAP in PBZ-1 ($P < 0.001$, Kruskal–Wallis test) but not PBZ-2.

Perioperative hemodynamics

Perioperative characteristics and hemodynamics are shown in [Table 2](#). Groups did not differ regarding anesthesia and operation time. Two patients in PBZ-2 received a blood transfusion during surgery but overall blood loss was similar between the PBZ groups and significantly less in the control group. In accordance, both PBZ groups received more intravenous fluids compared to controls whereas a similar amount of intravenous fluids was administered in the two PBZ-treated groups. The difference between the highest and lowest systolic or diastolic blood pressure recorded during surgery was calculated for all groups as an indicator of hemodynamic stability. As expected, the control group had less intraoperative systolic blood pressure fluctuations as compared to both PBZ groups. In agreement with other studies ([11](#), [13](#)) we could demonstrate a relation between total level of metanephrines and the difference between highest and lowest systolic blood pressure measured during surgery (Spearman $r=0.58$, $P=0.0008$, data not shown). The difference between the highest and lowest systolic or diastolic blood pressure recorded during surgery was less in PBZ-1 indicating improved hemodynamic stability when titrating PBZ to a preoperative blood pressure target of orthostatic hypotension. It was not possible to quantify the use of vasopressor and -dilators used due to limitations in the anaesthesiological documentation. However, noradrenaline and adenosine were widely used preoperatively in all PBZ-treated patients. Furthermore, four patients in the PBZ-2 received nitrates in addition to adenosine whereas only one in PBZ-1 received additional nitrate infusion.

Postoperative hemodynamics and complications

Patients undergoing surgery for PPGL had longer stay at the postoperative observation unit and experienced longer

Table 1 Baseline characteristics. Control group consisted of patients undergoing laparoscopic adrenalectomy for other reasons than pheochromocytoma. PBZ-1 consisted of patients treated with PBZ titrated to significant orthostatic hypotension accompanied by symptoms of orthostatism. PBZ-2 consisted of patients treated with PBZ titrated to a seated blood pressure below 130/80 mmHg.

	Control (<i>n</i> = 34)	Pheochromocytoma/paraganglioma		P value (PBZ-1 vs PBZ-2)
		PBZ-1 (<i>n</i> = 14)	PBZ-2 (<i>n</i> = 16)	
Sex (F/M)	22/12	8/6	9/7	
Age (median, range)	51 (32–80)	57 (34–82)	54 (39–72)	
ASA class (<i>n</i>) ^c				
1–2	25	14	12	
3	6	0	4	
4	0	0	0	
Co-morbidities (<i>n</i>)				
Diabetes mellitus	4	1	3	
Coronary artery disease	1	0	4	
Previous stroke	4	1	1	
Pretreatment				
Days before surgery (days) ^a	ns	20 (14–41)	34.5 (16–96)	0.001
End dose phenoxybenzamine (mg/kg/day) ^a	ns	2.04 (0.53–3.2)	0.58 (0.17–1.3)	0.0004
End dose phenoxybenzamine (mg/day) ^a	ns	130 (30–270)	40 (10–100)	0.0007
Beta-blockade, <i>n</i> (%)	ns	10 (71)	7 (44)	0.16
Tumor size (mm) ^a	31.0 (0–70)	31.5 (12–80)	32.5 (20–95)	0.6
P-metanephrines (level above upper limit)				
P-methoxyadrenaline (MA) ^a	ns	2.3 (0.3–23.0)	3.4 (0.4–45.7)	0.33
P-methoxynoradrenaline (MNA) ^a	ns	2.2 (0.3–14.5)	4.2 (0.6–69.0)	0.18
Biochemical profile				
MA as % of MA + MNA ^a	ns	62.8 (7.5–92.9)	54.5 (0.63–95.3)	0.82
Preblockade MAP (mmHg) ^a	ns	101.7 (79.3–150.3)	109.3 (74–135.7)	0.7
Preoperative MAP (mmHg) ^a	109.8 (77.3–137.7)	90.8 (65–111.7) ^b	100.0 (81.3–114.7)	0.13

^aMedian, range; ^b*P* < 0.001: Kruskal–Wallis rank-sum test, Dunn's multiple comparison test, control vs PBZ-1 or PBZ-2; ^cASA was not classified for 3 in the control group.

ASA, American Society of Anesthesiologists, MAP, mean arterial pressure; ns, not significant; PBZ, phenoxybenzamine.

time periods with MAP below 70 mmHg than the control subjects (Table 3). Patients in the PBZ-1 group required more intravenous fluids compared to the PBZ-2 to maintain a similar MAP. However, a similar number of patients received noradrenaline infusion, although one patient in PBZ-1 was transferred to the intensive care unit because of a continuous need for noradrenaline infusion after 23 h at the observation unit. Another patient in the PBZ-1 group was transferred to the internal medical department 14 days after surgery for further treatment of pneumonia and exacerbation of chronic obstructive lung disease. Nevertheless, the median total length of stay was 2 days in all groups. In total nine patients were readmitted within 30 days, but it should be considered that seven out of nine readmissions were within 6 days of discharge and all course readmission within 30 days was similar between groups. Overall, no major peroperative complications were reported. Postoperative complications were dysregulated diabetes, hypoglycemia, fever, infection, nausea, hypotension, hypertension and pain. Causes of readmission were hypertension, shortness of breath, infection, minor bleedings, hemorrhage and gastric ulcer.

Discussion

The introduction of preoperative alpha-receptor blockade in PPGL surgical treatment has been considered to contribute substantially to the decrease in perioperative mortality (5, 14). Increasing the dose of PBZ used over two decades has previously been related to improved hemodynamic stability (5). However, there are no randomized studies to determine the optimal blood pressure targets, and guidelines are based mainly on expert opinion and institutional experience.

In this comparison of clinical practice, we examine the per- and postoperative hemodynamics in patients pretreated with PBZ titrated to either significant orthostatic hypotension or a seated blood pressure below 130/80 mmHg. From this review of patient files, we find it likely that titration of PBZ to a target of orthostatic hypotension improves peroperative hemodynamic stability accompanied by a postoperative increased use of intravenous fluids and a tendency to longer observation time after surgery. This likely reflects that a target of

Table 2 Perioperative characteristics and hemodynamics. Control group consisted of patients undergoing laparoscopic adrenalectomy for other reasons than pheochromocytoma. PBZ-1 consisted of patients treated with PBZ titrated to significant orthostatic hypotension accompanied by symptoms of orthostatism. PBZ-2 consisted of patients treated with PBZ titrated to a seated blood pressure below 130/80 mmHg. (Max SBP) – (min SBP) is defined as the highest SBP subtracted the lowest SBP during surgery. Similar defines the (max DBP)–(min DBP).

	Control (<i>n</i> = 34)	Pheochromocytoma/paraganglioma		P value (PBZ-1 vs PBZ-2)
		PBZ-1 (<i>n</i> = 14)	PBZ-2 (<i>n</i> = 16)	
Operation time, min ^a	83 (45–180)	96 (46–154)	105 (45–218)	ns
Anesthesia time, min ^a	135 (75–265)	153 (90–225)	163 (90–300) ^b	ns
Blood loss (mL) ^a	0 (0–500)	100 (0–330) ^b	100 (0–1400) ^b	ns
Nitrate, <i>n</i> (%)	0	1 (7)	5 (31)	ns
Adenosine, <i>n</i> (%)	0	12 (86)	16 (100)	ns
Noradrenaline, <i>n</i> (%)	0	14 (100)	14 (88)	ns
Hemodynamics				
(max SBP)–(min SBP), mmHg ^a	38 (5–75)	57 (39–130) ^b	89 (20–164) ^b	0.03
(max DBP)–(min DBP), mmHg ^a	25 (5–55)	30 (5–65)	45 (15–98) ^b	0.05
Heart rate >100 b.p.m., episodes ^a	0 (0–1)	0 (0–3)	0.5 (0–3) ^b	0.06
Heart rate >100 b.p.m., min ^a	0 (0–35)	0 (0–30)	7.5 (0–45) ^b	0.04
IV fluids (crystalloids + colloids), mL	825 (300–2400)	1575 (1000–2500) ^b	1650 (700–5750) ^b	ns
Blood transfusion, <i>n</i> (%)	0	0	2 (13 %)	ns

^aMedian (min–max); ^b*P* < 0.05: Kruskal–Wallis rank-sum test, Dunn's multiple comparison test, control vs PBZ-1 or PBZ-2. DBP, diastolic blood pressure; ns, not significant; PBZ, phenoxybenzamine; SBP, systolic blood pressure.

orthostatism resulted in a significantly higher median end dosage of PBZ increasing the postoperative risk of hypotension as previously reported (7, 8, 15, 16). Due to the retrospective design, the PBZ groups are not matched and differ regarding the duration of medical pretreatment and some patients are treated longer than recommended in international guidelines (3, 12). Whether the duration of pretreatment influences per- and postoperative hemodynamics has not been tested in a prospective design. In a retrospective design duration of pretreatment with PBZ did not influence hemodynamics (17). Although, a longer duration of medical pretreatment with doxazocin

did seem to increase the risk for per- and postoperative hypotension (18).

In a recent prospective study, blood pressure targets in the seated and postural position were evaluated, indicating that postural systolic blood pressure below 90 mmHg was associated with increased perioperative hemodynamic instability (6). A similar association was reported in a retrospective design (13). In our dataset, postural blood pressures were not systematically reported.

Regardless of the preoperative blood pressure target, anesthesia and surgery of PPGL were associated with greater fluctuations in blood pressures and higher intravenous

Table 3 Postoperative characteristics. Control group consisted of patients undergoing laparoscopic adrenalectomy for other reasons than pheochromocytoma. PBZ-1 consisted of patients treated with PBZ titrated to significant orthostatic hypotension accompanied by symptoms of orthostatism. PBZ-2 consisted of patients treated with PBZ titrated to a seated blood pressure below 130/80 mmHg.

	Control (<i>n</i> = 34)	Pheochromocytoma/paraganglioma		P value (PBZ-1 vs PBZ-2)
		PBZ-1 (<i>n</i> = 14)	PBZ-2 (<i>n</i> = 16)	
Observation time, min ^a	226 (60–420)	372 (232–1380) ^b	324 (215–795) ^b	0.09
Noradrenaline, <i>n</i> (%)	0	2 (14) ^d	3 (19)	ns
MAP <70 mmHg (minutes) ^c	4.0 (0–105)	41.1 (0–240) ^b	56 (0–300) ^b	ns
IV fluids (crystalloids + colloids), mL ^a	700 (100–2200)	1850 (600–4000) ^b	1400 (800–2700) ^b	0.05
Blood transfusion, <i>n</i> (%)	0	0	1 (6)	ns
Length of stay, days ^a	2.0 (1–4)	2 (1–14) ^e	2 (1–6)	ns
All course readmission within 30 days, <i>n</i>	6 (18%)	2 (14%)	1 (6%)	ns

^aMedian (min–max); ^b*P* < 0.05: Kruskal–Wallis rank-sum test, Dunn's multiple comparison test, control vs PBZ-1 or PBZ-2; ^cMean (min–max.); ^dOne patient was transferred from the post operation observation unit to the intensive care unit because of sustained need for vasopressor infusion; ^eOne patient is transferred to local medical department 14 days postsurgery because of exacerbation of chronic obstructive lung disease and pneumonia. ns, not significant; PBZ, phenoxybenzamine.

fluid requirements both per- and postoperatively as compared to the control group undergoing the same type of surgery but not having PPGL. Nonetheless, this did not influence operation and anesthesia time or total length of stay. Furthermore, no major complications related to perioperative hypertensive episodes were reported. This is in agreement with the previous reports questioning the impact of alpha-receptor blockade prior to PPGL surgery for improving outcomes and highlighting the anesthesiological expertise for successful management (4, 7, 19). Speculation on avoiding medical pretreatment in certain groups of patients with PPGL has been raised (4, 8, 15, 20, 21). However, reliable predictors of hemodynamic instability are not well characterized (11, 13, 22, 23, 24). Our dataset does not have the power to examine risk factors for perioperative hemodynamic instability but while keeping this limitation in mind, it suggests that medical pretreatment with PBZ titrated to orthostatic hypotension reduces perioperative hemodynamic variability. On the other hand, a higher dose of PBZ may increase the risk of postoperative hypotension as reflected by the use of more intravenous fluids in PBZ-1.

This retrospective comparison of practice between two centers introduces a risk of bias that may not be apparent from the patient records and consequently has inherent limitations. The retrospective design is limited by the quality and inconsistency of data in the medical records. Hemodynamic parameters were obtained from handwritten anesthesiological reports updated every 5 min. Certain data could not reliably be extracted from the available records, including quantifying the use of vasoactive substances due to inconsistent documentation. Due to the retrospective design, blood pressure measurements and targets are based on local institutional guidelines and are vulnerable to variation dependent on the attending clinician and changes over time. Traditionally, only a few clinicians at both endocrinological departments have been involved in the preoperative treatment of this rare disease. However, we ended inclusion in 2015 as the institution traditionally aiming at a seated blood pressure below 130/80 mmHg started to administer higher PBZ dosage due to the introduction of a new national guideline. Only a total of 30 patients with PPGL could be included during the 4 years inclusion period. As expected, a substantial variation in perioperative blood pressure range was observed within each PBZ-treated group and lack of power cannot be excluded. As a strength, we attempt to eliminate surgical and anesthetic factors affecting hemodynamic control as all operations are performed at the same urological department during the same time period using the same surgical procedure.

Previous studies have found a level of catecholamine as a predictor of hemodynamic instability (11, 13, 25). Preoperative metanephrine levels or biochemical profile did not significantly differ between the two PBZ groups although we did see a trend to higher metanephrine levels in the PBZ-2 group in spite of similar tumor sizes. In this relatively small data set, we could also demonstrate a relation between the total level of metanephrines and the difference between highest and lowest systolic blood pressure measured during surgery. But, in agreement with a previous study (11), substantial variations in preoperative levels of metanephrines were seen and subjects with the highest perioperative systolic blood pressure variations had metanephrine levels below average, indicating that metanephrine levels alone do not predict hemodynamic control during operation.

In conclusion, this retrospective comparison of practice indicates improved operative hemodynamic stability when titrating PBZ to a target of orthostatic hypotension but with a postoperative increased need for intravenous fluid administration. However, PPGL surgery is associated with substantial hemodynamic instability independent of the preoperative blood pressure target but without significantly increasing operation and anesthesia time or length of stay as compared to adrenal non-PPGL surgery.

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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Ethics approval

The study was approved by the Danish health authority (journal no. 3-3013-1029/1) and the Danish data protection agency (journal no. 2014-41-3220).

Author contribution statement

R U contributed to the design and planning of the study, data collection and analysis and preparing the manuscript. C L F contributed to the design and planning of the study, data collection and analysis. B K A contributed to design of the study and preparing the manuscript. Å K R contributed to data collection and preparing of the manuscript. P A H H contributed to preparing the manuscript. All authors have contributed in interpretation of data and have read and approved the final manuscript.

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