

Effect of High or Low Dose Phenoxybenzamine on Per-Operative Hemodynamics in Pheochromocytoma

Randi Ugleholdt (✉ randi.kjaersgaard.ugleholdt@regionh.dk)

Copenhagen University Hospital <https://orcid.org/0000-0002-6656-0137>

Åse Krogh Rasmussen

Copenhagen University hospital

Pernille Agnete Heldager Haderslev

Copenhagen University Hospital

Bjarne Kromann-Andersen

Copenhagen University Hospital

Claus Larsen Feltoft

Copenhagen University Hospital

Research article

Keywords: Hemodynamics, pheochromocytoma, phenoxybenzamine, postoperative blood pressure, preoperative treatment

Posted Date: October 7th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-78802/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Effect of high or low dose phenoxybenzamine on per-operative hemodynamics in pheochromocytoma

Randi Ugleholdt[#] (1), Åse Krogh Rasmussen (2), Pernille A.H. Haderslev (3), Bjarne Kromann-Andersen (4), Claus Larsen Feltoft (1)

(1) Department of Endocrinology, Copenhagen University hospital, Herlev, Borgmester Ib Juuls Vej 1, Herlev DK-2730, Denmark. (2) Department of Medical Endocrinology, Copenhagen University hospital, Rigshospitalet, Blegdamsvej 9, Copenhagen DK-2100, Denmark. (3) Department of Anaesthesiology, Copenhagen University Hospital, Herlev, Borgmester Ib Juuls Vej 1, Herlev DK-2730, Denmark. (4) Department of Urology, Copenhagen University hospital, Herlev, Borgmester Ib Juuls Vej 1, Herlev DK-2730, Denmark.

[#]Corresponding author

Abstract

Background. Alpha-receptor blockade is the mainstay in preoperative treatment of patients with pheochromocytoma and paraganglioma (PPGL). However, evidence regarding optimal dosage regimen is lacking. This study compares the per- and postoperative hemodynamics in patients pre-treated with a high or low dose of phenoxybenzamine.

Methods. 30 consecutive patients with PPGL undergoing laparoscopic adrenalectomy were identified retrospectively. All were pretreated with phenoxybenzamine but at two separate endocrine departments aiming at different blood pressure target. End-dosage of phenoxybenzamine differed significantly between departments with 14 patients receiving a high dose regimen and 16 a low dose regimen. As a control group, we included 42 patients undergoing laparoscopic adrenalectomy for other reasons. Primary purpose was to compare per- and postoperative hemodynamics in the high and low dose groups. Secondly, to compare these endpoints to the control group.

Results. Baseline characteristics did not differ between the phenoxybenzamine treated groups. The high dose group had less intra-operative systolic and diastolic blood pressure fluctuation ($p = 0.03$) and less periods with heart rate above 100 bpm ($p = 0.04$) as compared to the low dose group. Use of intravenous fluids were similar between the two groups. However, postoperatively, more intravenous fluids were administered in the high dose group. Overall, the control group was more hemodynamic stable as compared to either group treated for PPGL.

Conclusions. High dose phenoxybenzamine improves per-operative 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.

Keywords.

Hemodynamics, pheochromocytoma, phenoxybenzamine, postoperative blood pressure, preoperative treatment

Introduction

Surgery of pheochromocytoma and paraganglioma (PPGL) carries a risk of hemodynamic instability during induction of anaesthesia 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 anaesthetic practice, mortality has significantly reduced within the last decades [1, 3–5]. The mainstay in preoperative pharmacological therapy is alpha-adrenergic blockade to reduce effect of catecholamines released during anaesthesia 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]. No other randomized trial data is available to support decision making prior to PPGL surgery. Hence, guidelines regarding alpha-blockade dosage strategies are primarily based on retrospective studies and expert opinion, and clinical practice vary between centers. Furthermore, progress in surgical and anaesthetic practice within the last decades are speculated to have greater impact on per-operative outcome than pretreatment with alpha-receptor blockers [4, 7]. As pretreatment is time consuming, related with 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 alpha-receptor blocker regardless the PPGL phenotype [3, 10, 11].

In the eastern part of Denmark pretreatment using the alpha-receptor blocker PBZ is managed in endocrinological departments at 2 different University Hospitals. However, all laparoscopic resections of PPGL are performed at the same University Hospital in order to achieve optimal surgical and anaesthetic experience and expertise. The two endocrinological departments up-titrate PBZ regarding to a different target blood pressure resulting in significantly different PZB end dosage. Hence, the primary aim was retrospectively to examine the effect of a high or low dose regimen of PBZ on per-operative hemodynamic stability during similar anaesthetic and surgical conditions. Secondly, to relate these hemodynamic

parameters found in these two groups of patients with PPGL to a control group undergoing same type of surgery but not having PPGL.

Methods:

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).

In 2009 laparoscopic surgery in patients with PPGL was in eastern Denmark centralised to one urological and anaesthesiological department at Herlev University Hospital. Treatment with alpha-receptor blockade prior to surgery was administered at the endocrinological departments at Herlev hospital or Rigshospitalet (Copenhagen University Hospitals). Medical records for patients undergoing surgery at the urological department between 2009-2015 were examined for histological diagnosis of PPGL. We identified 43 patients with histological diagnosis of pheochromocytoma and 2 with paraganglioma. However, referral from both endocrinological departments was not in practice effectuated until 2011. Hence, to reduce possible selection bias we only included patients from 2011-2015 and identified 30 consecutive patients with a histological diagnosis of pheochromocytoma (n=29) or paraganglioma (n=1) pretreated with PBZ in one of the two endocrinological departments. Clinical approach for up-titration of PBZ has traditionally differed between the two departments resulting in significantly different end dose of PBZ. At Rigshospitalet PBZ was up-titrated during admission to a preoperative blood pressure target defined as a significant fall in orthostatic blood pressure and subjective symptoms of orthostatism. At Herlev hospital PBZ was up-titrated to a target blood pressure below 130/80 mmHg in the seated position at regular visits in the outpatient clinic. In addition, we included 42 control subjects who underwent laparoscopic adrenalectomy during 2009-2015 at the same surgical and anaesthesiological facility but did not have PPGL and were not treated with PBZ ahead of surgery. The control group was comprised of various pathologies including adenoma, neoplasia, ganglioneuroma, myelolipoma and hyperplasia.

Patients electronic health records were abstracted for demographics (age, sex, tumor size by computed tomography, comorbidity using ASA physical status classification, level of plasma metanephrines, blood pressure before and after treatment with PBZ, end dose of PBZ, duration of PBZ treatment, treatment with

beta-blocker). Anaesthesiological records were reviewed for operation and anaesthesia 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 with 30 days and postoperative complications were recorded.

Anaesthesia 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 were placed for infusion of vasoactive drugs. General anaesthesia was induced by propofol, fentanyl and rocuronium. Before tracheal intubation an i.v. bolus of magnesium sulfate was administered and adenosine was connected to one lumen of the central venous catheter ready for rapid titration. Anaesthesia 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 i.v. 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.

All laparoscopic adrenalectomies were 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. An antithrombotic prophylactic therapy was administered in all cases. Cortical sparing adrenal surgery was not performed in any case, all surgery was unilateral and non were converted to open surgery.

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

Statistics

Data are reported as median and range unless noted otherwise, as mean +/- sem for continuous variables and as frequency for categorical variables. Group values were compared using one-way ANOVA with non-parametric Kruskal Wallis test and Dunns multiple comparison analysis, Mann-Whitney test or Fischers exact test as appropriate. For normal distributed data one-way ANOVA with Dunnets multiple correction or Students t test were used. A two-tailed P value ≤ 0.05 was considered statistically significant.

Results:

Preoperative characteristics

In the period 2011–2015 thirty patients underwent laparoscopic surgery after treatment with PBZ. All had histological verified PPGL. Characteristics are shown in table 1. 14 patients were up-titrated in PBZ during hospitalization at the endocrinological department (Copenhagen University hospital Rigshospitalet) to a significant fall in orthostatic blood pressure in combination with symptoms of orthostatism. 16 patients were up-titrated in PBZ to a target blood pressure below 130/80 mmHg in the seated position at regular visits at the outpatient endocrinological clinic (Copenhagen University hospital Herlev). The different approaches for up titration resulted in significantly different end doses of PBZ ($p < 0.0007$, table 1) allowing us to refer to the first approach as “High dose PBZ” and the other approach as “Low dose PBZ”. Similar proportions of PPGL patients received beta blockade before surgery. As control group data from 42 patients undergoing laparoscopic adrenalectomy from 2009-2015 were analyzed. No patients in the control group had histological verified PPGL or received PBZ prior to operation. All patients (PPGL and controls) underwent operation at the same surgical and anaesthesiological unit. The PBZ groups were similar regarding to age and sex. However, a tendency to more comorbidity in the Low dose vs High dose group was noted. The two PPGL groups did not differ statistically regarding to tumor size, plasma level of metanephrines prior to surgery and MAP prior to alpha-receptor blockade. Mean MAP was significantly reduced in both PPGL groups after up-titration of PZB and MAP measured preoperatively did not significantly differ between PZB groups ($p < 0.09$, table 1) although a trend towards lower MAP in the high-dose group was present. MAP

registered for patients in the control group were similar to the two PPGL groups before pretreatment and significantly higher than both PPGL groups just preoperatively ($p < 0.0001$, ANOVA).

Perioperative hemodynamics

Perioperative characteristics and hemodynamics are shown in table 2. Groups did not differ regarding to anaesthesia and operation time. Two patients in the Low dose group received 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 iv fluids compared to controls. No difference in iv fluids administered in the Low dose PBZ and the High dose PBZ groups was seen. The difference between the highest and lowest systolic or diastolic blood pressure recorded during surgery was calculated for all groups as an indicator for hemodynamic stability. As expected, the control group had less intraoperative systolic blood pressure fluctuations as compared to the Low and High dose PBZ groups. The difference between the highest and lowest systolic or diastolic blood pressure recorded during surgery was less in the High dose group indicating improved hemodynamic stability when using a high dose PBZ pretreatment regime. It was not possible to quantify the use of vasopressor and –dilators used. However, noradrenaline and adenosine were widely used peroperatively in all PBZ-treated patients. Furthermore, four patients in the Low dose PBZ group received nitrates in addition to adenosine whereas only one in the High dose PBZ received additional nitrate infusion.

Postoperative hemodynamic and complications

Patients undergoing surgery for PPGL had longer stay at the postoperative observation unit and experienced longer time periods with MAP below 70 mmHg than control subjects (table 3). The High dose PBZ group required more intravenous fluids compared to the Low dose PBZ groups to maintain a similar MAP. However, the similar number of patients received noradrenaline infusion, but one patient pretreated with high dose PBZ was transferred to the intensive care unit because of a continuous need for noradrenaline infusion after 23 hours at the observation unit. Another patient in the High dose PBZ 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, on average total length of stay and all course readmission within 30 days was similar between groups. Overall, no major complications were reported. Postoperative complications were dysregulated diabetes, hypoglycemia, fever, infections, nausea, hypotension, hypertension and pain. Causes of readmission was hypertension, shortness of breath, infection, minor bleedings and hemorrhage, gastric ulcer, adrenal insufficiency and dehydration.

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, 12]. Increasing dose of PBZ used over 2 decades has previously been related to improved hemodynamic stability [5]. However, direct comparison of dosage regimens for pretreatment with PBZ have not been investigated, and randomized studies are difficult to perform because of the rare nature of the disease. Hence, guidelines regarding preoperative blood pressure targets are based mainly on expert opinion and institutional experience.

The purpose of this study was to examine effect of a high or low preoperative dose of PBZ under similar surgical and anaesthetic conditions. This study indicates that pre-treatment with a high dose of the non-selective alpha-receptor blocker PBZ improves per-operative hemodynamic stability. However, an increased demand for intravenous fluid administration and tendency to longer observation time postoperatively, indicates that the high dose regimen increases risk of postoperative hypotension. In a recent prospective study blood pressure targets in the seated and postural position was evaluated, indicating that postural systolic blood pressure below 90 mmHg was associated with increased per-operative hemodynamic instability [6, 13]. A similar association was reported in a retrospective design [14]. In this study postural blood pressures were not systematically reported. However, the same association does not seem to apply. In spite of the dose regimen chosen, anaesthesia and surgery of PPGL was associated with greater fluctuations in blood pressure as compared to the control group undergoing same type of surgery but not having PPGL, without increasing operation and anaesthesia time or 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

outcome and highlighting the anaesthesiological expertise for successful management [4, 7, 15]. Speculation on avoiding alpha-receptor pretreatment in certain groups of patients with PPGL has been raised [4, 8, 16–18]. However, reliable predictors of hemodynamic instability are not well characterized [11, 14, 19–21]. This study does not have power to examine risk factors for per-operative hemodynamic instability but favours high dose PBZ pretreatment for minimizing perioperative hemodynamic variability.

The current study has several limitations. The retrospective design is limited by the quality and inconsistency of data in the medical records. Hemodynamic parameters were obtained from handwritten anaesthesiological reports updated every 5 min. Certain data could not reliably be extracted from the available records, including quantifying the use of vasoactive substances. Since preoperative blood pressure targets were not predefined as in a prospective design, approach to up-titration of PBZ within each endocrinological department were vulnerable to variation dependent on the clinician involved in the treatment and changes over time. Traditionally, only a few clinicians at both endocrinological departments have been involved in the preoperative treatment of this rare disease. We ended inclusion for this study in 2015 as a clinical approach to administer higher PBZ dosage were introduced at this time at the facility traditionally using a low dose PBZ regime based on 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 per-operative blood pressure range were observed within each PBZ treated group and lack of power cannot be excluded. As a strength we attempt to eliminate surgical and anaesthetic 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 level of catecholamine as a predictor of hemodynamic instability [11, 14, 22]. Preoperative metanephrine levels did not significantly differ between the two PBZ groups although we did see a trend to higher metanephrine levels in the low dose PBZ group in spite of similar tumour sizes. In this relatively small data set we could also demonstrate a relation between 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). But, in agreement with a previous study [11], substantial variation of 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 does not alone predict hemodynamic control during operation.

In conclusion, this study indicates a dose related positive effect of PBZ on per-operative hemodynamic stability but with a postoperative increased need for intravenous fluid administration. However, PPGL surgery is still associated with substantial hemodynamic instability independent of the preoperative PBZ dose used but without significantly increasing operation and anaesthesia time or length of stay compared to adrenal non-PPGL surgery.

List of abbreviations

PPGL: pheochromocytoma and paraganglioma

PBZ: phenoxybenzamine

ASA: American Society of Anesthesiologists

MAP: mean arterial blood pressure

iv.: intra venous

Declarations

Ethics approval and consent to participate:

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).

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

This work was supported solely by departmental sources.

Authors' contributions:

RU contributed to the design and planning of the study, data collection and analysis and preparing the manuscript. CLF contributed to the design and planning of the study, data collection and analysis. BKA contributed to design of the study and preparing the manuscript. ÅKR contributed to data collection and preparing of the manuscript. PAHH contributed to preparing the manuscript. All authors have contributed in interpretation of data and have read and approved the final manuscript.

Acknowledgements:

Not applicable

List of references

1. Lenders JWM, Eisenhofer G. Update on modern management of pheochromocytoma and paraganglioma. *Endocrinol Metab.* 2017;32:152–61.
2. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. In: *Lancet.* 2005. p. 665–75.
3. Lenders JWM, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SKG, Murad MH, et al. Pheochromocytoma and paraganglioma: An endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism.* 2014;99:1915–42.
4. Challis BG, Casey RT, Simpson HL, Gurnell M. Is there an optimal preoperative management strategy for phaeochromocytoma/paraganglioma? *Clin Endocrinol (Oxf).* 2017;86:163–7.
5. Livingstone M, Duttchen K, Thompson J, Sunderani Z, Hawboldt G, Sarah Rose M, et al. Hemodynamic Stability During Pheochromocytoma Resection: Lessons Learned Over the Last Two Decades. *Ann Surg*

Oncol. 2015;22:4175–80.

6. Buitenwerf E, Osinga TE, Timmers HJLM, Lenders JWM, Feelders RA, Eekhoff EMW, et al. Efficacy of α -Blockers on Hemodynamic Control during Pheochromocytoma Resection: A Randomized Controlled Trial. *J Clin Endocrinol Metab.* 2020;105:1–11.

7. Groeben H, Nottebaum BJ, Alesina PF, Traut A, Neumann HP, Walz MK. Perioperative α -receptor blockade in phaeochromocytoma surgery: An observational case series. *Br J Anaesth.* 2017;118:182–9.

8. Shao Y, Chen R, Shen ZJ, Teng Y, Huang P, Rui W Bin, et al. Preoperative alpha blockade for normotensive pheochromocytoma: Is it necessary? *J Hypertens.* 2011;29:2429–32.

9. Lentschener C, Gaujoux S, Tesniere A, Dousset B. Point of controversy: Perioperative care of patients undergoing pheochromocytoma removal-time for a reappraisal? *European Journal of Endocrinology.* 2011;165:365–73.

10. Isaacs M, Lee P. Preoperative alpha-blockade in phaeochromocytoma and paraganglioma: is it always necessary? *Clin Endocrinol (Oxf).* 2017;86:309–14.

11. Weingarten TN, Welch TL, Moore TL, Walters GF, Whipple JL, Cavalcante A, et al. Preoperative Levels of Catecholamines and Metanephrines and Intraoperative Hemodynamics of Patients Undergoing Pheochromocytoma and Paraganglioma Resection. *Oncology.* 2017;100:131–8.

12. Goldstein RE, O'Neill JA, Holcomb GW, Morgan WM, Neblett WW, Oates JA, et al. Clinical experience over 48 years with pheochromocytoma. In: *Annals of Surgery.* 1999. p. 755–66.

13. Edward Buitenwerf, Tamara E Osinga, Henri JLM Timmers, Jacques WM Lenders RA, Feelders, Elisabeth MW Eekhoff, Harm R Haak, Eleonora PM Corssmit PHB, Gerlof D Valk, Ronald GrooteVeldman, Robin PF Dullaart, Thera P Links, Magiel F Voogd G, JKG Wietasch MNK. Efficacy of phenoxybenzamine versus doxazosin on hemodynamic control during pheochromocytoma resection - a randomized controlled trial. 2019. doi:10.1017/CBO9781107415324.004.

14. Bruynzeel H, Feelders RA, Groenland THN, Van Den Meiracker AH, Van Eijck CHJ, Lange JF, et al. Risk factors for hemodynamic instability during surgery for pheochromocytoma. *J Clin Endocrinol Metab.* 2010;95:678–85.

15. Lentschener C, Gaujoux S, Thillois JM, Duboc D, Bertherat J, Ozier Y, et al. Increased arterial pressure

is not predictive of haemodynamic instability in patients undergoing adrenalectomy for pheochromocytoma. *Acta Anaesthesiol Scand.* 2009;53:522–7.

16. Groeben H, Walz MK, Nottebaum BJ, Alesina PF, Greenwald A, Schumann R, et al. International multicentre review of perioperative management and outcome for catecholamine-producing tumours. *Acad Med Cent Amsterdam.* 2020;18:170–8.

17. Buisset C, Guerin C, Cungi PJ, Gardette M, Paladino NC, Taïeb D, et al. Pheochromocytoma surgery without systematic preoperative pharmacological preparation: insights from a referral tertiary center experience. *Surg Endosc.* 2020;1:3.

18. Schimmack S, Kaiser J, Probst P, Kalkum E, Diener MK, Strobel O. Meta-analysis of α -blockade versus no blockade before adrenalectomy for pheochromocytoma. *Br J Surg.* 2020;107:e102–8.

19. Kiernan CM, Du L, Chen X, Broome JT, Shi C, Peters MF, et al. Predictors of Hemodynamic Instability During Surgery for Pheochromocytoma. *Ann Surg Oncol.* 2014;21:3865–71.

20. Jiang M, Ding H, Liang Y, Tang J, Lin Y, Xiang K, et al. Preoperative risk factors for haemodynamic instability during pheochromocytoma surgery in Chinese patients. *Clin Endocrinol (Oxf).* 2018;88:498–505.

21. Lafont M, Fagour C, Haissaguerre M, Darancette G, Wagner T, Corcuff JB, et al. Per-operative hemodynamic instability in normotensive patients with incidentally discovered pheochromocytomas. *J Clin Endocrinol Metab.* 2015;100:417–21.

22. Liu H, Li B, Yu X, Huang Y. Perioperative management during laparoscopic resection of large pheochromocytomas: A single-institution retrospective study. *J Surg Oncol.* 2018;118:709–15.

Tables

TABLE 1. Baseline Characteristics

	Control n=42	Pheochromocytoma/Paraganglioma		P value HD vs LD
		High dose PBZ (HD) n=14	Low dose PBZ (LD) n=16	
Sex (F/M)	24/18	8/6	9/7	
Age (mean, range)	55 (32-80)	56 (34-82)	56 (39-72)	
ASA class (n)				
1-2	34	14	12	
3	8	0	4	
4	0	0	0	
Co-morbidities (n)				
Diabetes Mellitus	5	1	3	
Coronary Artery Disease	2	0	4	
Previous Stroke	5	1	1	
Pretreatment				
Days before surgery (days) [#]	//	20 (14-41)	34.5 (16-96)	<i>P</i> = 0.001
Phenoxybenzamine (mg/kg/day) [#]	//	2.04 (0.53-3.2)	0.58 (0.17-1.3)	<i>P</i> = 0.0004
Phenoxybenzamine (mg/day) [#]	//	130 (30-270)	40 (10-100)	<i>P</i> = 0.0007
Beta-blockade, n (%)	//	10 (71 %)	7 (44 %)	<i>P</i> = 0.16
Tumor size (mm) [#]	31.0 (0-91)	31.5 (12-80)	32.5 (20-95)	<i>P</i> = 0.6
p-metanephrines (level above upper limit)				
p-methoxyadrenaline (MA) [#]	//	2.3 (0.3-23.0)	3.4 (0.4-45.7)	<i>P</i> = 0.33
p-methoxynoradrenaline (MNA) [#]	//	2.2 (0.3-14.5)	4.2 (0.6-69.0)	<i>P</i> = 0.18
MA + MNA [#]	//	5.7 (1.8-29.3)	9.6 (3.2-101.4)	<i>P</i> = 0.08
Preblockade MAP (mmHg) ^{&}	109.2 (± 2.3)	106.1 (± 5.0)	108.0 (± 4.6)	<i>P</i> = 0.80
Preoperative MAP (mmHg) ^{&}	111.4 (± 2.4)	90.4 (± 4.1) [§]	98.9 (± 2.7) [§]	<i>P</i> = 0.09

Control group consisted of patients undergoing laparoscopic adrenalectomy for other reasons than pheochromocytoma

median, range

& mean ± SEM

§ *p* < 0.05: One-way ANOVA, Dunnett's multiple correction, vs. control group

// not relevant

ASA: American Society of Anesthesiologists, PBZ: Phenoxybenzamine, MAP: mean arterial pressure

TABLE 2. Per-operative Characteristics and Hemodynamics

	Control n=42	Pheochromocytoma/Paraganglioma		P value HD vs LD
		High dose PBZ (HD) n=14	Low dose PBZ (LD) n=16	
Operation time, min [#]	88 (45-244)	96 (46-154)	105 (45-218)	ns
Anaesthesia time, min [#]	138 (75-325)	153 (90-225)	163 (90-300)	ns
Blood loss (ml) [#]	0 (0-500)	100 (0-330) [§]	100 (0-1400) [§]	ns
Nitrate, n (%)	0	1 (7 %)	5 (31 %)	ns
Adenosine, n (%)	0	12 (86 %)	16 (100 %)	ns
Noradrenaline, n (%)	0	14 (100 %)	14 (88 %)	ns
Hemodynamics				
(Max. SBP)-(min. SBP), mmHg [#]	40 (25-55)	57 (39-130) [§]	89 (20-164) [§]	P = 0.03
(Max. DBP)-(min. DBP), mmHg [#]	25 (5-55)	30 (5-65)	45 (15-98) [§]	P = 0.03
Heart rate > 100 bpm, episodes [#]	0 (0-2)	0 (0-3)	0.5 (0-3) [§]	P = 0.06
Heart rate > 100 bpm, min [#]	0 (0-35)	0 (0-30)	7.5 (0-45) [§]	P = 0.04
IV fluids (crystalloids + colloids), ml	900 (300-2500)	1575 (1000-2500) [§]	1650 (700-5750) [§]	ns
Blood transfusion, n (%)	0	0	2 (13 %)	ns

Control group consisted of patients undergoing laparoscopic adrenalectomy for other reasons than pheochromocytoma.

Range SBP or DBP defined as the highest SBP or DBP subtracted the lowest SBP or DBP during surgery.

median (min. - max)

& mean \pm SEM

§ p < 0.05: Kruskal Wallis rangsum test, Dunn's multiple comparison test, Control vs HD or LD

PBZ: Phenoxybenzamine, SBP: systolic blood pressure, DBP: diastolic blood pressure, ns: not significant

TABLE 3. Postoperative Characteristics

	Control n=42	Pheochromocytoma/Paraganglioma		<i>P</i> value HD vs LD
		High dose PBZ (HD) n=14	Low dose PBZ (LD) n=16	
Observation time, min [#]	226 (60-605)	372 (232-1380) [§]	324 (215-795) [§]	<i>P</i> = 0.09
Noradrenaline, n (%)	0	2 (14 %) ^α	3 (19 %)	ns
MAP < 70 mmHg (minutes) [£]	3.2 (0-105)	41.1 (0-240) [§]	56 (0-300) [§]	ns
MAP < 70 mmHg/observation time (%) [£]	1 (0-38)	5 (0-24) [§]	13.3 (0-74) [§]	ns
IV fluids (crystalloids + colloids), ml [#]	700 (100-3200)	1850 (600-4000) [§]	1400 (800-2700) [§]	<i>P</i> = 0.05
Blood transfusion, n (%)	0	0	1 (6 %)	ns
Length of stay, days [£]	2.0 (1-4)	3.4 (1-14) [*]	2 (1-6)	ns
All course readmission within 30 days, n	7 (17 %)	2 (14 %)	1 (6 %)	ns

Control group consisted of patients undergoing laparoscopic adrenalectomy for other reasons than pheochromocytoma

median (min. - max)

& mean ± SEM

§ *p* < 0.05: Kruskal Wallis rang sum test, Dunn's multiple comparison test, Control vs HD or LD

£ mean (min. - max)

α 1 patient was transferred from the post operation observation unit to the intensive care unit because of sustained need for vasopressor infusion

* 1 patient is transferred to local medical department 14 days postsurgery because of exacerbation of chronic obstructive lung disease and pneumonia

PBZ: Phenoxybenzamine, ns: not significant