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# Perioperative α-receptor blockade in phaeochromocytoma surgery: an observational case series†

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## Abstract

**Background.** Mortality associated with surgery for phaeochromocytoma has dramatically decreased over the last decades. Many factors contributed to the dramatic decline of the mortality rate, and the influence of an α-receptor blockade is unclear and has never been tested in a randomized trial. We evaluated intraoperative haemodynamic conditions and the incidence of complications in patients with and without α-receptor blockade undergoing surgery for catecholamine producing tumours.

**Methods.** Haemodynamic conditions and perioperative complications were assessed in 110 patients with (B) and 166 without (N) α-receptor blockade. Data were analysed as a consecutive case series of 303 cases and subsequently via propensity score matching, and presented as mean and confidence interval (CI).

**Results.** No difference in maximal intraoperative systolic arterial pressures (B = 178 mm Hg (CI 169-187) *vs* N = 185 mm Hg (CI 177-193; $P = 0.2542$) and hypertensive episodes above 250 mm Hg were found ($P = 0.7474$) for the closed case series. No major complications occurred. Propensity score matching (75 pairs) revealed a significant difference of 17 mm Hg in maximal intraoperative systolic bp for these selected pairs ($P = 0.024$).

**Conclusions.** Only a slight difference in mean maximal systolic arterial pressure was detected between patients with or without an α-receptor blockade. There was no difference in the incidence of excessive hypertensive episodes between groups and no major complications occurred. The basis for the general recommendation of perioperative α-receptor blockade for phaeochromocytoma surgery demands further study.

**Key words:** doxazosin; paraganglioma; phaeochromocytoma; phenoxybenzamine

Phaeochromocytoma and extra-adrenal paraganglioma are catecholamine-producing tumours, which without treatment can lead to cardiovascular decompensation and death. Surgical removal offers a definitive cure.[1–3] However, unavoidable intraoperative manipulation of the tumour can cause release of catecholamines and hypertensive crisis. Therefore, adrenalectomy for phaeochromocytoma is regarded as high risk surgery with a historical mortality rate exceeding 40% in some case series.[1–3]

During the second half of the 20th century the mortality rate decreased dramatically to a rate of 1.0 to 3.0%, which has often been credited to the introduction of perioperative α-receptor blockade.[1–10] However, this development can also be explained

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**Editor's key points**

- Perioperative pharmacological blockade of α-receptors is routinely used in preparation for surgery for phaeochromocytoma, but its clinical impact has not been conclusively established.
- Arterial pressure and complications were analysed in a consecutive case series of 303 cases of surgery for phaeochromocytoma removal with or without perioperative α-receptor blockade.
- There was only a small difference in maximal systolic arterial pressure and no difference in complications with or without α-receptor blockade.

by significant improvements in diagnostics, surgery, and anaesthesia. Improvement in diagnostic techniques led to earlier diagnosis and more precise localization of tumours,[5 11 12] while surgical techniques developed from extensive abdominal to minimally invasive endoscopic procedures.[5 11 12–20] Moreover, development of invasive haemodynamic monitoring and improved management including the use of sodium-nitroprusside allowed better handling of acute hypertensive episodes intraoperatively.

The clinical impact of these factors has never been properly investigated.[1–3 21] Although pre-treatment with an α-receptor blocker has never been tested in a controlled randomized trial, this treatment is considered obligatory according to international guidelines.[1–3 7 10 12] However, many case series report intraoperative hypertensive episodes exceeding 200 mm Hg systolic arterial pressure despite use of an α-receptor blocker, which is not without side-effects.[7–10 17 22–23] In contrast, phaeochromocytoma surgery without α-receptor blockade has been successfully performed in selected patients without increased perioperative complications.[8 24 25]

To explore the need for and effectiveness of perioperative α-receptor blockade, we performed an observational study and evaluated perioperative bp in 303 consecutive procedures in patients undergoing excision of chromaffin tumours with or without α-receptor blockade.

## Methods

After approval by the local ethics committee (Board of Physicians Ärztekammer Nordrhein reg.no.: 2008126) 276 consecutive patients undergoing surgery between June 2008 and June 2016 gave informed written consent to have their data analysed in this observational study. Patients suffered from neurofibromatosis (n = 5), von Hippel-Lindau disease (VHL; n = 73), multiple endocrine neoplasia Type 2A (MEN 2A; n = 42), or sporadic phaeochromocytoma and not further described entities (n = 156). In 27 patients bilateral tumours were removed. In addition, 26 patients had extra-adrenal paraganglioma. There was no statistical difference ($P = 0.2488$) in the pattern of catecholamines produced by the tumours with regard to the use of α-receptor blockade or not. Epinephrine was secreted by 24, norepinephrine in 45, and both in 33 tumours of patients with α-receptor blockade. In patients without α-receptor blockade, tumours produced epinephrine in 23, norepinephrine in 81, and both in 43. In 19 patients of the patients with α-receptor blockade and 35 of the patients without blockade, no elevated catecholamine concentrations could be detected. In 4 patients the tumour was regarded as incidental and the diagnosis of a phaeochromocytoma was missed until the time of surgery, therefore no catecholamine concentrations were determined.

## Preoperative management

Whenever a physician or patient contacted our institution for referral of a patient with a catecholamine = producing tumour, they were asked not to initiate α-receptor blockade. Over the last four yr many physicians and patients contacted our institution explicitly because they did not want α-receptor blockade. In case α-receptor blockade had already been started, it was continued until the day of surgery (n = 121). 98 patients received phenoxybenzamine (1.1mg $kg^{-1}$ per day [CI 1.0-1.3 mg $kg^{-1}$ per day]) and 23 patients doxazosin (0.14 mg $kg^{-1}$ per day [CI 0.11 - 0.17 mg $kg^{-1}$ per day]). Usually, patients were admitted the day before surgery, and patients were hospitalized < 24 h until they underwent surgery. The number of antihypertensive drugs prescribed before surgery was assessed.

## Anaesthesia and surgery

On the day of surgery after patients arrived in the anaesthesia induction room, non-invasive monitoring was applied and an arterial line was placed under local anaesthesia. Subsequently, general anaesthesia was induced with propofol, remifentanil, and mivacurium. After tracheal intubation, a 3-lumen central venous catheter was placed in the right or left internal jugular vein. Depending on the surgical approach, patients were placed in prone or supine position. Sodium nitroprusside was connected to one lumen of the central venous catheter and run at a minimal dose (1mg per h) to have it ready for rapid titration as needed. Anaesthesia was maintained with isoflurane in an oxygen/air mixture and continuous i.v. administration of remifentanil.Baseline systolic, highest systolic, and lowest mean arterial pressure, number and duration of systolic arterial pressure episodes > 250 mm Hg and episodes of mean arterial pressure < 60 mm Hg were assessed. Intraoperatively, the dose of sodium nitroprusside was individually increased if systolic arterial pressure exceeded 160 mm Hg. Esmolol was administered at the discretion of the responsible anaesthetist (n = 21).

Two-hundred-ninety operations were performed by the retroperitoneoscopic approach, four by the laparoscopic route, and one thoracoscopically. Eight patients were initially or secondarily operated upon by an open procedure (part of a multivisceral open resection n = 5, conversion to open surgery n = 2, paraganglioma in the wall of the bladder n = 1). The surgical techniques of the retroperitoneoscopic and laparoscopic approach have been described in detail.[16 26]

The incidence of complications potentially related to arterial hypertension such as myocardial infarction, acute congestive heart failure, pulmonary oedema, and cerebral stroke as a result of haemorrhage was assessed. Testing (troponin concentrations and postoperative ECG) was initiated in case of clinically suspected myocardial ischaemia and in patients with a history of myocardial ischaemia. Testing was not performed in asymptomatic patients without a history of myocardial ischaemia or a history of cardiac decompensation.

## Data analysis

Data are presented as mean (95% confidence interval). The null hypothesis was no significant difference in maximal systolic arterial pressure between patients who received α-receptor