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**Paraganglioma &
Pheochromocytoma**

Pena-Shokeir syndrome

orphan**a**nesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 15 | 2017

OrphanAnesthesia –

ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patienten mit seltenen Erkrankungen. Damit will Orphan Anesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesisten damit keine Erfahrungen gesammelt haben, so dass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

OrphanAnesthesia –

a common project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommendations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

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A survey of until now in A&I published guidelines can be found on:

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orphananesthesia

Anaesthesia recommendations for patients suffering
from

Paraganglioma & Pheochromocytoma

Disease name: Paraganglioma & Pheochromocytoma

ICD 10: D35.00 benign phaeochromocytoma; C74.1 malignant phaeochromocytoma; D44.7 paraganglioma

Synonyms: Chromaffinoma, Chromaffin paraganglioma, Chromaffin tumor, intra-medullary paraganglioma, Chromaffin cell tumor

Paraganglioma and Pheochromocytoma are catecholamine-producing tumors (predominantly norepinephrine, epinephrine, and dopamine alone or in combination) that can lead to life-threatening complications including myocardial infarction, heart failure, stroke, and death. Pheochromocytomas are tumors of the adrenal medulla, while paragangliomas originate from the chromaffin tissue in the extra-adrenal autonomic ganglia [1]. The tumor is usually unilateral, and in some cases is associated to syndromes such as multiple-endocrine neoplasia II, neurofibromatosis, and Von Hippel-Lindau disease [2]. Germline mutations of susceptibility genes associated with this disease have been recently discovered, particularly in the genes responsible for the succinate dehydrogenase complex, SDHB, SDHC, SDHD, SDHA and SDHAF2, as well as mutations in TMEM127, MAX, KIF1B β , EGLN1/PHD2, and HIF2A [1,2]. Less than 5% are malignant tumors, and surgical removal often offers a definite cure.

Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

► **Citation:** Schumann R, Moreno-Duarte I, Groeben HT: Paraganglioma & Pheochromocytoma. Anästh Intensivmed 2017;58:S619-S627. DOI: 10.19224/ai2017.S619

Disease summary

The perioperative morbidity and mortality of pheochromocytoma surgery has decreased dramatically to a rate of about 1% or less since 1960. Many factors including improvements in surgery, diagnostics, and the development of new anaesthetic techniques and perioperative monitoring capabilities have contributed to this positive development. Often this improvement has been attributed to the adoption of perioperative blockade of alpha-adrenergic receptors with long acting agents such as phenoxybenzamine. Scientific proof of this concept is not available.

For the past 20 years, the surgical approach chosen for adrenalectomy has been minimally invasive rather than open procedures. Surgical manipulations of the tumor can lead to an uncontrolled release of catecholamines with subsequent multi-system complications intraoperatively, especially cardiovascular. Hypertensive episodes, which can occur during surgery despite alpha-receptor blockade, are treated with short and fast acting agents such as sodium nitroprusside, clevidipine, nicardipine and esmolol to name a few. These agents may also be employed perioperatively as needed.

Because approximately 25-30% of these tumors are inherited, genetic testing and a follow-up for recurrent tumors as well as family screening are advisable. To avoid a bilateral adrenalectomy in case of bilateral disease or a recurrence on the contralateral side, partial resections of the adrenal gland are increasingly common when feasible.

Typical surgery

For an adrenalectomy, transabdominal, laparoscopic or retroperitoneoscopic surgery has become the standard procedure even for tumors larger than 6 cm in diameter, although some references recommend open surgery [1,4]. Compared to open surgery, the minimally invasive procedure offers a lower mean operative time, shorter hospital stays, decreased need for intensive care, less blood loss, and a lower pain medication requirement. However, an open approach might be chosen for malignant disease.

The surgical strategy for paraganglioma removal is based on the localization of the tumor and the surgeons' preference either with an endoscopic or an open approach [5]. In the case of carotid body and neck paragangliomas, consideration should be given to the possibility of cerebral ischemia from compression of the carotid artery and subsequent decrease in blood flow to the brain. Preventive strategies in selected patients that may include placement of a carotid artery stent may be useful.

In patients with small tumors and inherited disease, a cortical sparing adrenalectomy is favourable when feasible to avoid the effects of a bilateral adrenalectomy, should a contralateral tumor arise at a later stage [5,6].

Type of anaesthesia

For minimally invasive procedures, a balanced anaesthetic employing either a volatile or total intravenous anaesthetic technique can be recommended. Sevoflurane, isoflurane, and enflurane are reasonable and safe choices for volatile anaesthetics, although the latter is used rarely in modern anaesthesia practice [1]. Although it has been used without detriment, desflurane may best be avoided due to its propensity for sympathetic activation, and halothane is not recommended because of its myocardial sensitization to catecholamines.

Additionally, if etomidate is used as part of the anaesthetic, clinicians should be mindful of the potential detrimental effects of etomidate regarding the suppression of cortisol synthesis. This may be of particular concern in ACTH and cortisol producing tumors. For open surgery (via laparotomy) an epidural catheter for intra- and postoperative pain management can be considered, but careful attention to haemodynamic perturbations in patients on alpha-receptor blocking medications is necessary (postoperative hypotension) [7,8].

Necessary additional diagnostic procedures (preoperative)

For many patients the time to the final diagnosis may exceed one year. Therefore, secondary cardiovascular disturbances are not uncommon due to repeated episodes of hypertensive crises and/or sustained arterial hypertension. For this reason, a cardiac work up that includes an ECG, a trans-thoracic echocardiogram (TTE) and laboratory determination of pro-BNP can be recommended to investigate the presence of a catecholamine induced cardiomyopathy [7]. Electrolyte abnormalities such as hypercalcemia and metabolic derangements such as hyperglycaemia should be assessed and corrected. Hyperglycaemia should be evaluated with a fasting glucose, an oral glucose tolerance test, and/or a haemoglobin A1c. In the presence of an epinephrine secreting tumor, a history of reactive airway disease and asthma should be actively sought, as the cessation of the potent β^2 -adrenoceptor-mediated dilation of airways during surgery may unmask unexpected airway obstruction.

Traditionally, the preoperative management goals for these patients aimed at blood pressure control and volume expansion in hypertensive patients to reduce intraoperative hypertensive crises and surgical risk. Some authors recommend a preoperative salt-rich diet to facilitate intravascular volume expansion [5]. Many institutions have established pathways for preoperative medical management of these patients. Such management plans often include non-competitive or competitive α -blockade before the potential use of β -blockers for fear of unopposed α – agonism if the latter are used prior to the former [9]. Alpha blockade may typically be initiated 7 – 14 days before surgery to allow adequate time for blood pressure normalization and heart rate and to expand the contracted blood volume. The literature is unclear about α -agent selection, dose, and exact duration of preoperative therapy and has remained vague about therapeutic goals and hence these treatment plans are often individualized and institution specific. Although plausible, the concept of unopposed α -agonism when β -blockade is employed prior to β -blockade has not been systematically studied. Oral agents such as labetalol or carvedilol may not be ideal choices in the preoperative preparation because of the fixed ratio of the combined α and β antagonistic activity.

Metyrosine (250 mg/day divided in 3-4 doses), a catecholamine synthesis inhibitor that blocks tyrosine hydroxylase is an additional option when α -blockade is not sufficient (widespread disease with continued symptoms despite antihypertensive regimen), but often limited by its side effects [1]. Some practitioners consider calcium channel blockers and ACEI's or ARBs for situations of α -blocker intolerance and β -adrenergic stimulated renin secretion respectively.

Some researchers have questioned the need for extended preoperative medical treatment when anaesthetic expertise in the intraoperative management of these patients is available and close intraoperative monitoring is employed [10].

However, until more robust literature becomes available, management according to institutionally established pathways that may include preoperative medical treatment remains the recommended standard of care.

Particular preparation for airway management

None, unless clinically indicated independent of the diagnosis of a catecholamine producing tumor.

Particular preparation for transfusion or administration of blood products

Major bleeding is rare, but when present, blood loss can be rapid and massive. A type and screen is advisable, and blood products should be available.

Particular preparation for anticoagulation

None, unless otherwise medically indicated.

Particular precautions for positioning, transport or mobilisation

For the retroperitoneal approach, patients may be either in a lateral posterior or modified jack-knife prone position [11]. Such positioning may affect the choice of vascular access [8], as in the latter position subclavian venous and femoral arterial access is suboptimal and should not be first choices.

Probable interaction between anaesthetic agents and patient's long-term medication

There are no specific reports regarding any interactions between the preoperative pheochromocytoma/paraganglioma medication regimen and anaesthetic agents.

However, concerns for interactions of certain intraoperative drugs with the physiology of the catecholamine producing tumor exist. Indirect sympathomimetic agents and drugs known to be associated with histamine release including morphine and droperidol should be avoided as they could potentially contribute to uncontrollable catecholamine release from the tumor. For the treatment of intraoperative hypotension, direct sympathomimetics or alpha-adrenergic agents are preferable and may have to be dosed higher than expected when an alpha receptor blockade has been initiated [12].

Anaesthesiologic procedure

Balanced anaesthesia as described above with invasive monitoring is the most common technique for these procedures. Adequate depth of anaesthesia prior to laryngoscopy is recommended. Propofol, etomidate and thiopental have been used safely for induction, whereas the response to ketamine can be unpredictable [1]. Due to the cortisol inhibitory effect of etomidate, perioperative steroid use in patients with a pheochromocytoma-associated Cushing's syndrome should be carefully considered. In such patients, steroid use may trigger a hypertensive crisis while stress dose steroids may be required following tumor removal. Rocuronium, vecuronium and atracurium have been used successfully for

neuromuscular blockade [1]. Pancuromium is not recommended because of its vagolytic properties and long duration of action.

Intraoperative periods that require particular attention from the anaesthesiologist due to potential haemodynamic perturbations are the time of laryngoscopy, direct tumor manipulation, ligation of the tumor's venous effluent, tumor extraction and the period following tumor removal. Steroid replacement is indicated if bilateral adrenalectomy is performed.

Intraoperative fluid management is aimed at maintenance of euolemia with balanced salt solutions as indicated by haemodynamic monitoring indices.

Treatment of intraoperative hypertensive episodes is recommended if the systolic blood pressure exceeds 160 mmHg. Multiple drug choices with a fast onset and offset are available and at the discretion of the anaesthesiologist including but not limited to sodium nitroprusside (0.5-3.0 mcg/kg/min), nitroglycerin (0.5-10 mcg/kg/min), esmolol (50-300 mcg/kg/min), urapidil, clevidipine (1-2 mg/hr), nicardipine (5-15 mg/hr), phentolamine (1-5 mg boluses) and magnesium [1,7,13,14,15,16,17]. Each agent has its own advantages, disadvantages and cost, and although there are suggestions in the literature for first vs second line intraoperative antihypertensive choices, the evidence in support of one agent over another is weak. During severe hypertension, a combination of agents with different mechanisms of action may be indicated. Clinicians should use their best clinical judgment for the choice of these agents.

Intraoperative hypotension (usually after tumor removal) should be treated first by ensuring euolemia, giving fluid boluses as guided by haemodynamic monitoring parameters. Depending on the technology used, these may include stroke volume and pulse pressure variation, central venous pressure, mixed venous oxygen saturation, cardiac output assessment, pulmonary artery pressures, transoesophageal echocardiography (TEE) and urine output. However, in the absence of significant co-morbidities that would indicate use of advanced haemodynamic monitoring, clinicians may often rely on routine techniques including pulse pressure variation, central venous pressures and urine output. Following exclusion of hypovolemia, intraoperative hypotension should be treated with vasopressors such as norepinephrine, phenylephrine and vasopressin [7].

Aiming to extubate the awake patient at the end of the procedure is routine for most cases of pheochromocytoma or paraganglioma resection unless determined otherwise by an unusual intraoperative course and patient status at the end of the procedure or the patient's comorbidities.

Particular or additional monitoring

As even asymptomatic patients can develop hypertensive episodes during surgical manipulations, placement of an arterial line prior to induction of anaesthesia for close perioperative blood pressure and volume status monitoring and to facilitate frequent blood draws for metabolic assessment is routine. Some authors recommend using the axillary or the femoral arteries to estimate "central" arterial pressures more accurately, depending on the planned surgical approach.

Prior to or immediately following induction of anaesthesia, some clinicians recommend placement of a central line for intravenous access, to secure rapid administration of vasoactive medications into the central circulation and to provide advanced haemodynamic monitoring. Outcome evidence for the latter two concepts is not well established in the

literature. In the presence of large bore peripheral IV access the decision for central line placement can be more selective, and central access may be a lesser concern in asymptomatic patients with a small tumor diagnosed by family screening. Analgesic and sedative administration prior to line placement should be considered.

Advanced intraoperative cardiac monitoring with modalities such as TEE or a pulmonary artery catheter is usually reserved for patients with significant cardiac co-morbidity and dysfunction at the discretion and experience of the anaesthesiologist, and may be helpful when there is evidence of catecholamine-induced cardiomyopathy or congestive heart failure [7,12].

Intraoperative metabolic monitoring should include frequent determination of blood glucose levels. Catecholamine-induced hyperglycaemia may turn into hypoglycaemia from sudden catecholamine withdrawal and relative hyperinsulinemia following tumor removal. Calcium determinations may also be helpful as hypercalcemia can be associated with some of these tumors.

Possible complications

Although rare, patients with catecholamine producing tumors are at risk for severe pre- and intra-operative hypertensive episodes with the potential for acute cardiac failure, haemorrhagic stroke and cardiogenic pulmonary oedema.

Loss of peripheral vasoconstriction after tumor removal, the effects of (irreversible) α -adrenergic blockade and relative hypovolemia can lead to serious hypotension intra- and postoperatively with a risk for ischemic cardiac or cerebral perfusion deficits, arrhythmias, acute kidney injury, and polycythemia.

Postoperative hypoglycemia that can be worsened by α -blockade should be monitored and treated [7,12].

Postoperative care

The possibility of postoperative haemodynamic changes requiring treatment mandate close postoperative patient observation for 24 – 48 hours, although most perturbations resolve within 24 hours. While such monitoring does not necessarily warrant admission to a critical care unit, particularly patients that received extensive preoperative (non-competitive) α -receptor blockade may experience sustained postoperative hypotension. These patients and those that displayed concerning intraoperative haemodynamic instability may be good candidates for a step-down or intensive care unit for at least the first 24 hours postoperatively [1].

Metabolic assessment should include blood glucose monitoring postoperatively. Some authors suggest serum glucose determination every 4-6 hours for the first 24 hours.

A multidisciplinary postoperative care plan should be instituted, involving the endocrine service as patients may need to be followed for longer periods of time. This is especially important in patients with residual hypertension, inherited tumors and those with metastatic disease.

Information about emergency-like situations / Differential diagnostics

caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the disease:

Induction of anaesthesia and intubation, establishment of pneumoperitoneum, tumor manipulation, and ligation of the venous effluent can cause intraoperative haemodynamic changes, including hyper- and hypotension and dysrhythmias. Open communication with the surgical team during the different stages of the procedure is essential to anticipate and treat periods of haemodynamic fluctuation.

Air embolism during endoscopic surgery is a differential diagnosis for cardiovascular decompensation and hypotension that the anaesthesia team should consider when appropriate.

Ambulatory anaesthesia

Up to now, surgery for catecholamine secreting tumors is not considered as an ambulatory procedure.

Obstetrical anaesthesia

Previously undiagnosed tumors may be uncovered during pregnancy. Diagnosis prior to delivery is important because of an increased risk in maternal and fetal mortality. Vaginal delivery is considered contraindicated because of the physiologic changes associated with the first and second stages of labor. Several case reports of pheochromocytoma and paraganglioma removal during pregnancy are available. However, the timing of tumor resection is controversial and depends on gestational age at the time of the diagnosis. A multidisciplinary approach including the maternal-fetal medicine and endocrine services is necessary.

The avoidance of phenoxybenzamine and sodium nitroprusside for these patients have been emphasized, as these drugs cross the placenta with potential detrimental effects to the fetus. Alternative medications to treat hypertension intraoperatively are nitroglycerine, hydralazine, and magnesium [15,18,19,20,21].

Regarding the choice of anaesthetic technique for cesarean section in the presence of a catecholamine producing tumor, either general or regional techniques can be considered, aiming at minimizing catecholamine surges [22].

Authors' note

These recommendations for the anaesthetic and surgical care of patients with paragangliomas and pheochromocytomas are based as much as possible on the available literature. For orphan diseases including paragangliomas and pheochromocytomas, the level of evidence for specific practices largely remains that of expert opinion, often published as guidelines, and some information based on retrospective studies rather than the highest evidence level derived from randomized controlled trials. These recommendations should be interpreted with this in mind.

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namen, Warenbezeichnungen usw. in
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besondere Kennzeichnung nicht zu der
Annahme, dass solche Namen im Sinne
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ren und daher von jedermann benutzt
werden dürften.

Wichtiger Hinweis

Für Angaben über Dosierungsanwei-
sungen und Applikationsformen kann
vom Verlag und den Herausgebern keine
Gewähr übernommen werden. Derartige
Angaben müssen vom jeweiligen An-
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prüft werden. Gleiches gilt für berufs-
und verbandspolitische Stellungnahmen
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Please do not hesitate to contact us. We will be glad to answer and provide further information to you at any time.

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I would like to participate in the project

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