PATIENTS' SAFETY AND FEASIBILITY OF INTRAVENOUS URAPIDIL IN THE PRETREATMENT OF PHEOCHROMOCYTOMA PATIENTS IN A NORMAL WARD SETTING – AN ANALYSIS OF 20 CONSECUTIVE CASES

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Abstract

Context. The intravenously administered selective α_1 antagonist urapidil represents an alternative to phenoxybenzamine in the preoperative treatment of pheochromocytoma patients.

Objective. The aim of the study was to investigate the blood pressure changes in pheochromocytoma patients with urapidil pretreatment with special regards to the need for interventions in order to estimate the safety of this treatment in a normal ward setting.

Design. The medical records of all patients who underwent adrenalectomy for PCC were reviewed retrospectively. Systolic blood pressure values $>180\text{mmHg}$ were defined as hypertensive episodes and systolic blood pressure values $< 50\text{mmHg}$ as hypotensive episodes. Episodes of blood pressure instabilities were considered significant and recorded as intervention if they led to a direct action.

Results. Twenty consecutive patients who received urapidil pretreatment were enrolled in this retrospective study. Preoperatively, a median of 9 blood pressure measurements per day have been performed on the ward. A total of 2 episodes of hypertension occurred, and 1 episode of hypotension has been recorded. In the period from 25-72 hours postoperatively the median number of blood pressure measurements was 5 per 24 hours. The blood pressure deviations led to a total of 3 interventions for hypertension in 1 (5%) patients and 5 interventions for hypotension in 3 (15%) patients. All interventions could be managed on the normal ward, without the need to transfer the patient to an ICU.

Conclusions. Intravenous urapidil can safely be administered on a normal ward without putting patients at risk. Intensive monitoring beyond 24 hours postoperatively was not necessary, the blood pressure measurements during the shift on a normal ward were sufficient for maintaining patients' safety.

Key words: Pheochromocytoma, Urapidil, Adrenalectomy, Pretreatment, patient safety.

INTRODUCTION

Patients' safety during surgical procedures has emerged from the edges of interest to a major issue which cannot be neglected by any surgeon worldwide. Besides large scale political programs, small steps in the everyday life in the operation room have been taken to lower complication rates and improve patients' outcome (1). These measurements range from analyzing the negative impact of private communication during an operation, comparing different draping regimes to reduce surgical side infections or addressing the issue of resident participation, all of them in the backdrop of rising economic pressure on the health care systems (2-4).

One example for the reduction of complication rates due to optimal pretreatment are adrenalectomies for pheochromocytoma (PCC). After introduction of α -Blockers, the complication rate dropped from 40% to below 3% (5, 6). Phenoxybenzamine is a noncompetitive inhibitor, which binds covalently to α_1 and α_2 receptors. Pharmacokinetic effects and the need for de novo synthesis of α -receptors lead to a hypotensive effect of phenoxybenzamine up to 48 hours (7).

The selective α_1 antagonist urapidil represents an alternative to phenoxybenzamine. The advantages are a close relationship between plasma concentration and antihypertensive effect and a shorter elimination half-life of 2-4.8 hours. Several series describe its use in pretreatment of PCC (8-10). Although urapidil is administered intravenously, the significant shorter pretreatment period results in shorter hospital stays and better cost effectiveness (10). The perioperative blood pressure changes in patients with urapidil are widely unknown, especially from a patients' safety point of view, as the feasibility of the intravenous administration of this potent medication on a normal ward can be

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questioned. The aim of the study was to investigate the blood pressure changes in pheochromocytoma patients with urapidil pretreatment with special regards to adverse effects and need for interventions in order to estimate the safety of this treatment in a normal ward setting.

METHODS

The medical records of all patients who underwent adrenalectomy for PCC at University Hospital and Clinics Frankfurt between July 2007 and July 2014 were reviewed retrospectively. Preoperative diagnosis of pheochromocytoma was formulated in patients with elevated catecholamine levels (adrenaline, noradrenaline) in serum, elevated degraded catecholamine levels in urine (metanephrine, normetanephrine) in combination with an adrenal tumor in the preoperative imaging. A confirmation of PCC in the final pathology report was a mandatory requirement for the enrollment. The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) was used to predict malignant potential in patients operated after 2011(11).

All patients were pretreated with continuously i.v. administered urapidil, 5 mg/h on day 1, increased to 15 mg/h on day 3, as previously described (9,10). Blood pressure was measured several times per shift using the classic manual Riva-Rocci method performed by a nurse.

Parameters that were analysed included demographic and clinical data, laboratory results, imaging and histology results. Amplitude of systolic and diastolic blood pressure as well as the maximum blood pressure deviation in each patient was recorded.

Blood pressure changes and the need for intervention for hypertension or hypotension were analyzed during the pretreatment and intraoperative course. Same parameters were analyzed during the first 24 hours and first three days after operation. Systolic blood pressure values >180mmHg were defined as hypertensive episodes and systolic blood pressure values < 50mmHg as hypotensive episodes, irrespective of the fact that they led to a direct action. Episodes of hemodynamic instabilities (HDI) were considered significant and recorded as intervention if they led to a direct action (e.g. drug or colloid administration) or to a consequence on the further course (e.g. unplanned transfer to intensive care unit – ICU). If a continuous infusion of vasoactive drugs was necessary after transfer to PACU or ICU, this was rated as intervention due to hypo- or hypertension during the 24 h postoperative course. Intraoperative increase or decrease of a continuously administered vasoactive drug > 5% was rated as intervention due to hypertension

Blood pressure was monitored with an arterial catheter intraoperatively and for 24 hours postoperatively, later on via noninvasive blood pressure measurement as mentioned above.

All patients were admitted for postoperative monitoring to a postoperative care unit (PACU) for 24 hours. Laparoscopic transperitoneal (partial-) adrenalectomy was treatment of first choice in both groups, open approach was chosen in patients with large (>5 cm) or infiltrating tumors, extensive previous operations in the region of interest or patients preference.

Statistical analysis was performed using SPSS Statistics Version 22 (IBM, New York, USA).

The study was approved by the Internal Review

Table 1. Patients' characteristics and preoperative details

Variables*	All cases (n=20)
Age (y) (range)	54.5 (31-77)
BMI (kg/m ²) (range)	26 (21-36)
Male: female ratio	7:13
Preoperative stay (days) (range)	3 (3-7)
Total length of stay (days) (range)	11 (5-18)
Elevated Metanephrine (>90pg/mL) (n)	15
Elevated Normetanephrine (>180pg/mL) (n)	16
Elevated metanephrine or normetanephrine	20
Preoperative CT (n)	13
Preoperative MRI (n)	10
Preoperative MiBG	18
Preoperative contrast PET-CT	1
Preoperative contrast enhanced ultrasound	1
Patients with two independent imaging techniques	20

* Data presented as median

Table 2. Surgical procedures and characteristics

Variables*	All cases (n=20)
Laparoscopic resections	12
Open resections	8
Conversions	1
Left : right	11:8
Extraadrenal	1
Tumor diameter (cm) (range)	4.5 (1-12)
Operative time (min) (range)	139.5 (48-231)
PASS	2 (0-7)

* Data presented as median; PASS, Pheochromocytoma of the Adrenal Gland Scaled Score

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medullary thyroid carcinoma during the initial stay which prolonged the hospitalization.

RESULTS

Patients' characteristics

In total, 20 consecutive patients (7 male: 13 female) received urapidil pretreatment between 2007-2014 and were enrolled in this retrospective study. All patients presented with hypertension and had elevated catecholamines or degraded catecholamines levels in blood and/or urine. Every patient had an adrenal tumor visualized in two independent imaging procedures. Median age at operation was 54.5 years (range: 31-77 years) with a median BMI of 26 (range 21-37). Median preoperative physical status according to the American Society of Anesthesiologists (ASA) was 2.5 (range: 2-4). Final histology reports revealed a median tumor diameter of 4.5 cm (1-12cm). Preoperative treatment could be completed according to protocol in all patients.

Surgical procedures

Laparoscopic adrenalectomy was performed in 12 patients, whereas 8 patients underwent open adrenalectomy due to the size of the tumor. One patient required conversion to an open procedure. Two patients underwent a bilateral adrenalectomy, one of them with an open approach due to tumor size. Two tumors required extensive resections due to infiltration of surrounding tissue and the inferior vena cava. The median operative time was 139.5 min (range: 48-231 min).

Severe intraoperative complications occurred in 2 patients with injuries of the diaphragm and a significant bleeding while 3 minor complications (Dindo-Clavien I & II) have been recorded. None of these complications was related to blood pressure deviations. These two patients were admitted to the ICU due to the intraoperative complications. The median total hospital stay was 11 days (range 5-18 days). One patient with MEN IIa underwent a thyroidectomy for

Blood pressure characteristics

In the preoperative pretreatment setting, a median of 9 blood pressure measurements (range: 6-15) per day have been performed on the normal ward. A total of 2 episodes of hypertension occurred, and 1 episode of hypotension has been recorded. The median maximum systolic blood pressure was 148 mmHg (range: 120-184 mmHg) with a median minimum systolic blood pressure of 104.5 mmHg (range: 86-140 mmHg). The median maximum diastolic blood pressure was 89 mmHg (range: 68-106 mmHg) with a median minimum diastolic blood pressure of 62 mmHg (50-82 mmHg). The individual systolic and diastolic blood pressure deviations were 41 mmHg (19-70 mmHg) and 25.5 mmHg (5-56 mmHg), respectively. The blood pressure deviations led to a total of 3 interventions for hypertension in 2 (10%) patients and 5 interventions for hypotension in 3 (15%) patients, all performed on a normal ward. These interventions consisted of orally administered antihypertensive drugs (nitrendipine) for hypertensions and i.v. fluid for hypotension. As a result, none of the patients was transferred to an ICU or needed invasive monitoring in the preoperative setting. Intraoperatively, the median maximum systolic blood pressure was 170 mmHg (range: 120-200 mmHg) with a median minimum systolic blood pressure of 87.5 mmHg (range: 40-110 mmHg). The median maximum diastolic blood pressure was 90 mmHg (range: 60-120 mmHg) with a median minimum diastolic blood pressure of 50 mmHg (20-80 mmHg). The individual systolic and diastolic blood pressure deviations were 80 mmHg (30-120 mmHg) and 45 mmHg (20-80 mmHg), respectively. The number of interventions for hypertension (n=43) and hypotension (n=36) differed substantially to the preoperative period.

During the first 24 hours after adrenalectomy, the median maximum and minimum systolic blood

Table 3. Blood pressure characteristics*

	EHype ¹	EHypo ¹	sBP max. ²	sBP min. ²	dBp max. ²	dBp min. ²	iBPD (syst) ³	iBPD (diast) ³
Preoperative	2 (0-1)	1 (0-1)	148 (120-184)	104.5 (86-140)	89 (68-106)	62 (50-85)	41 (19-70)	25.5 (5-56)
Intraoperative	37 (0-5)	34 (0-4)	170 (120-200)	87.5 (404-110)	90 (60-120)	50 (204-80)	80 (30-120)	45 (20-80)
0-24 h post OP	8 (0-2)	11 (0-3)	150 (110-195)	110 (70-140)	80 (60-100)	47.5 (30-74)	50 (20-95) ⁴	29.5 (16-60)
25-72 h post OP	3 (0-3)	5 (0-2)	140 (108-180)	110 (78-140)	88 (40-80)	60 (50-85)	30 (10-75)	25 (0-50)

* Data presented as median. EHype, hypertensive episodes (sBP $\geq$ 180 mmHg); EHypo, hypotensive episodes (sBP $<$ 50 mmHg); sBP, systolic blood pressure; dBp, diastolic blood pressure; iBPD individual blood pressure deviation (in one patient). 1n; per patient; 2median, (min./max.)[mmHg]; 3median (max) [mmHg]; 4one patient with intraoperative hemorrhage and shock.

Table 4. Interventions for hemodynamic instabilities

Variables	Total
Preoperative BPM per day (range)	9 (6-15)
Postoperative BPM per day (range)	5 (4-8)
Preoperative interventions for hypertension	3
Preoperative interventions for hypotension	5
Intraoperative interventions for hypertension	43 (0-5)*
Intraoperative interventions for hypotension	36 (0-4)*
Interventions for hypertension 0-24 h post OP	9
Interventions for hypotension 0-24 h post OP	17
Interventions for hypertension 25-72 h post OP	3
Interventions for hypotension 25-72 h post OP	5

BPM, blood pressure measurements (on the normal ward); * per single patient.

pressures with 150 mmHg (range 110-195 mmHg) and 110 mmHg (range: 70-140) revealed a tendency towards the preoperative blood pressure values. Still, the total number of required interventions for hypertension (n=9) and for hypotension (n=17) were substantially, but not significantly higher compared to the preoperative period and lower than during the operation.

The period from 25-72 hours postoperatively resembled the preoperative period regarding the blood pressure values. The median number of blood pressure measurements was 5 (range: 4-8) per 24 hours. The median maximum systolic blood pressure was 140 mmHg (range: 108-180 mmHg) with a median minimum systolic blood pressure of 110 mmHg (range: 78-140 mmHg). In this period, the blood pressure deviations led to a total of 3 interventions for hypertension in 1 (5%) patient and 5 interventions for hypotension in 3 (15%) patients. These interventions could be managed on the normal ward, without the need to transfer the patient to an ICU.

All blood pressure data are shown in Tables 3 and 4.

DISCUSSION

This study reveals for the first time that the potent α 1 antagonist urapidil might safely be administered intravenously on a normal ward for the pretreatment of PCC patients. Furthermore, the surveillance needed can be guaranteed with a reasonable amount of blood pressure measurements performed by nurses during their regular shift. The rare events of hemodynamic instabilities can be handled on the normal ward, which leads to an optimized preoperative management of PCC patients that saves expensive resources without impairing patients' safety.

After several decades in which surgery for PCC developed from a high risk procedure to a safe operation optimized by guidelines, the time has now come to further optimize the pre- and postoperative monitoring and treatment algorithms to save resources without harming the patients (12, 13). Several issues have been addressed regarding PCC surgery. One topic that is periodically discussed is which pretreatment scheme should be employed to minimize hemodynamic instabilities. Recently, Brunaud and colleagues demonstrated that preoperative calcium channel blockade (i.e. nicardipine) is equally safe compared to the "standard" phenoxybenzamine pretreatment, but revealed less and shorter severe hypotensive episodes and significantly less need for intraoperative vasoactive drugs. Furthermore, calcium channel blockers lead to lower treatment costs and are available in every pharmacy (14). In a large randomized study, Li and coworkers observed more adverse reactions in patients pretreated with phenoxybenzamine compared to doxazosin. However, the vast majority of the described adverse reactions are clearly linked to the antihypertensive effect of the drugs (e. g. dizziness, orthostatic hypotension) (15). Though, in his study patients treated with phenoxybenzamine are more likely to experience

gastrointestinal discomfort as a side effect (1.17% doxazosin vs. 5.7% phenoxybenzamine). Interestingly, these 2 studies did not mention the blood pressure course during the pretreatment phase. Burnaud described the length of the oral pretreatment as a minimum of 10 days in the phenoxybenzamine group and 8 days to 3 weeks for the nicardipine group. Li and coworkers do not present any data regarding this at all. Furthermore, these 2 studies lack the blood pressure course and HDI for the period beyond 24 hours after the operation.

Urapidil has been used for the treatment of PCC patients for almost 30 years. Since the initial data raised by Miura for antihypertensive therapy of PCC patients with urapidil 1988 it took 16 years until Tauzin-Finn described its use in the pretreatment scheme of 18 PCC patients prior to adrenalectomy (16, 17). In this study, Tauzin-Finn described the safety of urapidil in the pretreatment of PCC patients regarding intraoperative HDI. It is noteworthy to mention that all of these 18 patients received oral α - and β - blockers for 15 days prior to the intravenous urapidil pretreatment. Again, it remains unclear how the patients have been monitored in this 72 hours period, and no data on the blood pressure and interventions have been presented. Additionally, the blood pressure course beyond 24 hours postoperatively has not been demonstrated in this study.

The advantages of the urapidil pretreatment compared to the standard phenoxybenzamine treatment has recently been demonstrated by our group.¹⁰ The use of urapidil led to a significantly shorter preoperative and overall hospital stay, saving resources and costs without any differences regarding intraoperative HDI.

Several publications addressed the issue of risk factors for postoperative HDI and the necessity for extended monitoring of PCC patients after adrenalectomy.

In a study presented by Namekawa and coworkers on 73 patients undergoing adrenalectomy for PCC, tumor size above 60mm, urinary epinephrine level $>200\mu\text{g/day}$ and urinary norepinephrine level $>600\mu\text{g/day}$ emerged as a risk factor for prolonged postresection hypotension with subsequent catecholamine support. The pretreatment in this study was performed using α -blockers for a period of 2 weeks prior to the operation (18). Additionally, postresection hypoglycemia was associated with an elevated need for postoperative intensive care monitoring as demonstrated by Chen and his group analyzing 213 patients with PCC (19). Taken together, several factors can be analyzed to preoperatively assess the patients' need for postoperative intensive care monitoring

and therapy which will be helpful in the operational planning process regarding the rare and expensive resources of intensive care units. In our study presented here, we did not analyze the aforementioned factors, as we focused on the preoperative blood pressure and the period beyond 24 hours post-surgery.

In an approach to further save valuable monitoring resources without impairing the safety of the patients, Benay and colleagues identified risk factors for postoperative HDI in order to select patients who do not require intensive monitoring postoperatively (20). Only 14 of the analyzed 41 PCC patients (34%) developed HDI beyond 6 hours postoperatively and required intensive monitoring. Preoperative mean arterial pressure (MAP) $>100\text{ mm Hg}$, norepinephrine/normetanephrine levels $>3\times$ normal and resection of another solid organ emerged as risk factors for HDI. The costs that could be saved by avoiding unnecessary monitoring were estimated as CAD 37,917, which was a calculated saving of 34%. All patients in this study received different pretreatment schemes consisting of α -and/or β -blockers or calcium channel inhibitors, but no data regarding the influence of the pretreatment on the incidence of HDI were presented. In our study, none of the patients required intensive monitoring due to HDI beyond 24 hours postoperatively.

Our study is limited by the small sample number and its retrospective character. Still, the case load of 3 cases per year in our department matches those in the studies discussed here, and treating 20 patients consecutively with the same scheme has led to an experience that we use the 3 day pretreatment scheme routinely on a normal ward.

In conclusion, intravenous urapidil might safely be administered on a normal ward without putting patients at risk due to a lack of monitoring. Intensive monitoring beyond 24 hours postoperatively was not necessary, the "normal" blood pressure measurements during the shift on the normal ward were sufficient for maintaining patients' safety. The optimized pretreatment scheme using intravenous urapidil on a normal ward in combination with the detection of risk factors for HDI and optimized and shorter postoperative monitoring will help surgery for PCC to emerge from a long-planned, intensive monitoring requiring procedure to a resource-preserving, timely accomplishable but still safe operation.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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