Comparison of phenoxybenzamine and doxazosin in perioperative management of patients with pheochromocytoma

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Abstract

Background: Adrenalectomy with preoperative pharmacological preparation is strongly recommended in patients diagnosed with pheochromocytoma, in order to prevent perioperative complications.

Aim: To compare phenoxybenzamine (PhB) and doxazosin (DOX) in terms of perioperative haemodynamic status in patients with pheochromocytoma, who have been prepared for adrenalectomy.

Methods: Retrospective analysis of 44 patients with pheochromocytoma (aged 16–80 years, 29 females) who underwent adrenalectomy. Patients were divided into two groups: 35 patients on DOX and nine patients on PhB.

Results: Mean time of preparation for surgery was 38.8 days in the DOX group and 18.3 days in the PhB group (p = 0.04). No statistically significant differences between the DOX and PhB groups in intraoperative blood pressure (BP) fluctuations were found: < 170/100 mm Hg (34% vs. 44%, respectively, p = 0.42), ≥200/110 mm Hg (40% vs. 22%, respectively, p = 0.28). Mean greatest intraoperative systolic BP (195 ± 53 vs. 166 ± 42 mm Hg, p = 0.21) and diastolic BP (98 ± 20 vs. 89 ± 46 mm Hg, p = 0.21), and mean lowest intraoperative systolic BP (87 ± 13 vs. 79 ± 17 mm Hg, p = 0.25) and diastolic BP (49 ± 8 vs. 46 ± 12 mm Hg, p = 0.25) were not different between the DOX and PhB groups, respectively. Sodium nitroprusside was administrated in 30% DOX vs. 11% PhB patients (p = 0.25). Laparoscopic surgery was conducted in 97% DOX vs. 89% PhB patients (p = 0.64). Postoperative BP drop below 90/60 mm Hg was noted in 48% of the DOX vs. 43% of the PhB group (p = 0.56). Negative correlation was found between the length of DOX administration with maximal intraoperative systolic BP (r = –0.45, p = 0.006) and diastolic BP (r = –0.39, p = 0.019).

Conclusions: There are no clinically relevant differences between patients with pheochromocytoma, who have been prepared for adrenalectomy with DOX or PhB.

Key words: pheochromocytoma, blood pressure, adrenalectomy, doxazosin, phenoxybenzamine, alpha-adrenolytics

INTRODUCTION

Pheochromocytoma is a rare catecholamine-producing neuroendocrine tumour associated with high haemodynamic risk and mortality when left untreated [1]. Its management may lead to setbacks due to cardiovascular complications, e.g. hypertension, tachycardia, dysrhythmias, hyperglycaemia, intravascular volume depletion, and others [2]. Patients treated surgically are at increased cardiac risk, especially during the intraoperative period [3]. The approach to diagnosis and surgical treatment is well described, while preoperative...
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management is still controversial [4]. Recommendations strongly suggest preoperative blockade to prevent perioperative cardiovascular complications by using alpha-adrenergic receptor blockers (A-adrenolytics) as the first choice and calcium channel blockers as the second for 7–14 days prior to surgery, with or without beta-adrenergic blocking agents (B-adrenolytics) [5–7]. Alpha-blockade may be accomplished using drugs such as phenoxybenzamine (PhB) or doxazosin (DOX), each with its own pros and cons [8]. PhB blocks alpha-adrenergic receptors non-selectively, in contrast to DOX, which is a specific alpha-1 inhibitor [9]. PhB has some adverse side effects such as orthostatic hypotension, fatigue, nasal stuffiness, and tachycardia. DOX, on the other hand, does not cause baroreceptor reflex because it does not block the presynaptic alpha-2 receptors, which regulate noradrenalin release at adrenergic nerve endings [10]. PhB is the drug of choice for treating pheochromocytoma in many medical centres. In Poland, however, the availability of the drug is limited. This is why DOX has become the first-line medication in preoperative preparation of patients with pheochromocytoma. The aim of this study was to compare the results of preoperative preparation for pheochromocytoma resection between patients with DOX vs. PhB administration in terms of perioperative blood pressure (BP) stability.

METHODS

Patients
A retrospective analysis was conducted using the data of 44 patients diagnosed with pheochromocytoma, who had undergone adrenalectomy in the period 2010 to 2016 at the Department of General and Endocrine Surgery, Medical University of Warsaw. Patients were qualified to the study based on histopathology report. Enrolled patients were divided into two groups: with administration of DOX (n = 35) and PhB (n = 9). A study flowchart is presented in Figure 1.

Study design

Collected data included preoperative patient characteristics (age, sex, body mass index, clinical manifestations), tumour characteristics (laterality, maximal dimension), two samples of 24-h urine metanephrines (24-HUM), preoperative treatment (drug administration with BP control), intraoperative characteristics (surgery technique of adrenalectomy, BP control, sodium nitroprusside requirement), and postoperative BP control. The characteristics of the study groups are shown in Table 1.

Biochemical measurements

Urine metanephrine measurement was done by the spectrophotometric method [11]. The medication interfering with the measurements, e.g. sotalol-, labetalol-, and catecholamine-containing drugs, were withdrawn before urine collection.

Preoperative interventions

The patients were prepared for surgery with increasing doses of DOX or PhB. The maximal doses per day were 1 mg to 12 mg of DOX and 10 mg to 60 mg of PhB. The doses were increased according to BP and heart rate (HR) control. The target BP and HR measurements while seated were below 130/80 mm Hg and 70–80 bpm, respectively. If required, the patients continued the treatment with other hypertensive drugs such as angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers or calcium channel blockers.

All patients were given antihypertensive treatment in the evening one day before surgery. In the morning of the operation day the patients were left without antihypertensive medication.

All patients were prepared for surgery with intravenous (IV) 0.9% saline infusion 1–2 L in the evening before surgery and in the morning of the surgery day. B-adrenolytics were given in case of tachycardia > 80–90 bpm.

Intraoperative interventions

Intra-arterial beat-to-beat BP measurements were done. Data were obtained by averaging for 30-s readings. The mean intraoperative BP was calculated from the induction of general anaesthesia until the end of stitching the wound after surgery. The greatest intraoperative BP was the maximal measurement of BP between the induction of general anaesthesia until the end of stitching the wound after surgery. The lowest intraoperative BP was the minimal measurement of BP between the induction of general anaesthesia until the end of stitching the wound after surgery.

Hypotension was defined as sudden BP drop below 90/60 mm Hg and was managed with IV 0.9% saline infusion. According to institutional procedures, sodium nitroprusside was administered when a sudden BP increase by at least 30% of baseline was observed. B-adrenolytics were administered in cases of sudden HR increase.

Figure 1. Study flowchart
Table 1. Demographic characteristic of the groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DOX (n = 35)</th>
<th>PhB (n = 9)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 14</td>
<td>50 ± 16</td>
<td>0.68</td>
</tr>
<tr>
<td>Males</td>
<td>12 (34%)</td>
<td>3 (33%)</td>
<td>0.64</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>27 ± 6</td>
<td>24 ± 2</td>
<td>0.47</td>
</tr>
<tr>
<td>Left-side tumour</td>
<td>11 (35%)</td>
<td>5 (56%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Maximal tumour dimension [cm]</td>
<td>4.2 ± 1.8</td>
<td>4.8 ± 2.4</td>
<td>0.62</td>
</tr>
<tr>
<td>Time of alpha-adrenolytics administration before adrenalectomy [days]</td>
<td>38.8 ± 25.7</td>
<td>18.3 ± 10.5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Beta-adrenolytics:
- before operation: 16 (46%) vs. 2 (22%) (p = 0.19)
- after operation: 11 (31%) vs. 1 (11%) (p = 0.22)

ACEI/ARB:
- before operation: 3 (9%) vs. 2 (22%) (p = 0.24)
- after operation: 1 (3%) vs. 1 (11%) (p = 0.28)

Amlodipine:
- before operation: 3 (9%) vs. 2 (22%) (p = 0.24)
- after operation: 1 (3%) vs. 0 (0%) (p = 0.61)

Laparoscopy:
- 34 (97%) vs. 8 (89%) (p = 0.64)

Laparoscopy converted to open surgery:
- 1 (3%) vs. 1 (11%) (p = 0.37)

Hypertension:
- 24 (69%) vs. 5 (56%) (p = 0.63)

Diabetes:
- 8 (23%) vs. 1 (11%) (p = 0.42)

Hyperlipidaemia:
- 15 (43%) vs. 5 (56%) (p = 0.38)

Values are presented as mean ± standard deviation or number (%); ACEI — angiotensin converting enzyme inhibitors; ARB — angiotensin receptor blockers; BMI — body mass index; DOX — group with doxazosin administration; PhB — group with phenoxybenzamine administration

Postoperative interventions
All patients after surgery were monitored within an intensive care unit (ICU) for 12 h after surgery. BP and HR were measured every 30 min. The mean values were calculated from the whole period of ICU observation. All patients were administered IV 0.9% saline infusions.

Postoperatively, DOX or PhB were withdrawn. Other hypertensive drugs were given according to the patient’s requirements.

Outcome analyses
- The comparison between the DOX and PhB groups in terms of clinical characteristics and laboratory evaluation.
- The analysis of correlations between maximal and minimal intraoperative and minimal postoperative BP values with length of drug administration, maximal A-adrenolytics doses, maximal tumour dimension, and 24-HUM measurements in both groups.
- The intraoperative analysis of BP fluctuations assessed according to systolic BP (SBP)/diastolic BP (DBP) in three groups: < 170/100 mm Hg, 170/100–199/109 mm Hg, and ≥ 200/110 mm Hg.

Statistical analyses
Statistica software package v.12 (StatSoft, Tulsa, OK) was used for statistical analysis. The quantitative data results were expressed as mean ± standard deviation. To quantify differences between both groups, the Mann-Whitney U test and Fisher’s exact test were used. Spearman’s rank test was used for correlations of ranked, quantitative variables. P < 0.05 was chosen as statistically significant.

RESULTS

Preoperative evaluation and interventions
Demographic characteristics of the groups are demonstrated in Table 1. Differences in presented parameters between DOX and PhB groups were not statistically significant except for longer time of A-adrenolytic administration before adrenalectomy in DOX group than in PhB. Tumour-associated symptoms were observed in 37% and 56% in the DOX and PhB groups, respectively, without statistical difference between groups (Table 2).

The doses of drugs in both groups are presented in Table 3. The maximal DOX dose was 12 mg, while PhB was 60 mg. Among our patients 34% of the DOX group reached
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No statistically significant differences between groups were found in terms of intraoperative BP fluctuations: highest and lowest intraoperative BP, analysis in subgroups: <170/100 mm Hg, 170/100–199/109 mm Hg, and ≥200/110 mm Hg. No difference was also detected between mean SBP and DBP between groups (Table 5).

We found in the DOX group significant correlations between the length of DOX administration with intraoperative maximal SBP (r = –0.45, p = 0.006) and maximal intraoperative DBP (r = –0.39, p = 0.019) — the shorter the time of preparation the higher the BP.

A negative correlation was also detected between mean postoperative SBP and length of DOX administration (r = – 0.35, p = 0.04).

We did not find any correlations between the maximal dose of either drug and other analysed parameters.

Among PhB patients no statistically significant correlations were found between maximal and minimal intraoperative and minimal postoperative BP values and length of drug administration, maximal tumour dimension, or 24-HUM measurements.

Postoperative evaluation and interventions

The data are described in Table 6. There was no difference between groups in the minimal and maximal SBP noted in 12-h postoperative BP control and in postoperative BP drop below 90/60 mm Hg as well as mean SBP and DBP. None of the patients required BP-increasing drugs after surgery, apart from 0.9% saline infusion.

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**Table 2. Clinical manifestations; p = not significant**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>DOX</th>
<th>PhB</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more</td>
<td>13 (37%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Sweats</td>
<td>13 (37%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>15 (44%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Tremor</td>
<td>3 (9%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (31%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (11%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Pallor</td>
<td>7 (20%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Agitation</td>
<td>8 (23%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

Values are presented as number (%); DOX — group with doxazosin administration; PhB — group with phenoxybenzamine administration

**Table 3. Alpha adrenolytics administration**

<table>
<thead>
<tr>
<th>Maximal doses [mg]</th>
<th>DOX</th>
<th>PhB</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4</td>
<td>12 (34.3%)</td>
<td>10 (11.1%)</td>
</tr>
<tr>
<td>5–9</td>
<td>19 (54.3%)</td>
<td>20 (77.8%)</td>
</tr>
<tr>
<td>≥10</td>
<td>4 (11.4%)</td>
<td>60 (11.1%)</td>
</tr>
</tbody>
</table>

Values are presented as number (%); DOX — group with doxazosin administration; PhB — group with phenoxybenzamine administration

**Table 4. 24-hour urine metanephrines measurements**

<table>
<thead>
<tr>
<th></th>
<th>DOX (n = 35)</th>
<th>PhB (n = 9)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 HUM 1 [µg/24 h]</td>
<td>2344 ± 1897</td>
<td>1250 ± 356</td>
<td>NS</td>
</tr>
<tr>
<td>24 HUM 2 [µg/24 h]</td>
<td>2067 ± 1988</td>
<td>2350 ± 1021</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation; 24-HUM 1 — 24-h urine metanephrines 1st measurement; 24-HUM 2 — 24-h urine metanephrines 2nd measurement; 24-h urine metanephrines measured by spectrophotometry (normal range 100–1000 µg/24 h); DOX — group with doxazosin administration; NS — not significant; PhB — group with phenoxybenzamine administration;

the target BP value with ≤4 mg/day and only 11% required a dose ≥10 mg. In the PhB group the highest dose of 60 mg required 11% of patients to properly control BP before surgery.

The measurements of 24-HUM showed no statistically significant differences between groups (Table 4).

**Intraoperative evaluation and interventions**

The main method of adrenalectomy in this study group was laparoscopic surgery in 97% vs. 89% of patients in the DOX and PhB groups, respectively. One patient from each group had the operation converted from laparoscopic to open surgery due to tumour removal difficulty. Usage of sodium nitroprusside was without statistical difference between groups (Table 5).
DISCUSSION

Surgical excision is the recommended method of pheochromocytoma treatment [12–14]. However, patients are at risk of haemodynamic instability before, during, and after surgery [12]. Therefore, appropriate perioperative management is warranted to prevent unnecessary complications [13]. We compared the effects of DOX and PhB in preparation for surgery. No differences were found in terms of intraoperative BP fluctuations or in postoperative BP control.

There are few studies that compare DOX and PhB in preparation pheochromocytoma for surgery, but data are equivocal. Prys-Roberts and Farndon [9] carried out a retrospective analysis on the safety and efficacy of DOX vs. PhB in operated pheochromocytoma patients and found that a lower diastolic arterial BP accompanied the administration of DOX preoperatively and intraoperatively. Weingarten et al. [15] analysed results of studies in two large United States medical centres comparing preoperative medical management strategies for pheochromocytoma resection. At the Mayo Clinic, PhB was more likely to be used (98%), while Cleveland Clinic patients were treated more frequently with selective alpha-1 blockade (65%; doxazosin, terazosin, or prazosin). According to BP fluctuations, Cleveland Clinic patients had a greater maximal SBP intraoperatively (209 vs. 187 mm Hg, p = 0.01). However, phenylephrine was administered more often at the Mayo Clinic (56 vs. 27%, p = 0.01), which could have helped maintain intraoperative BP. During postoperative observations in both studies, no significant differences were found. Weingarten et al. [15] showed that management with PhB can lead to better results in the control of intraoperative BP; however, the use of PhB was associated with longer-lasting intraoperative hypotension. The mean minimal SBP we noted in 12-h postoperative BP control showed no difference between DOX and PhB patients. In another study, Agrawal et al. [16] prospectively compared the results of preoperative preparation for adrenalectomy with administration of PhB vs. prazosin and showed no significant differences in postoperative hypotensive episodes. The

CONCLUSIONS

Patients with pheochromocytoma can be successfully prepared to adrenalectomy with DOX and PhB without any difference in intraoperative and postoperative BP control and additional pharmacological interventions.

Future studies should focus on confirming this observation in a larger prospective study.

Table 6. Postoperative blood pressure (BP) measurements

<table>
<thead>
<tr>
<th>BP</th>
<th>DOX</th>
<th>PhB</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal SBP [mm Hg]</td>
<td>125.5 ± 12.3</td>
<td>103.3 ± 16.6</td>
<td>0.47</td>
</tr>
<tr>
<td>Maximal SBP [mm Hg]</td>
<td>187.9 ± 16.6</td>
<td>209.0 ± 30.1</td>
<td>0.22</td>
</tr>
<tr>
<td>Postoperative BP drop</td>
<td>4 (42.9%)</td>
<td>2 (22%)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Values are presented as number (%) and mean ± standard deviation; DBP — diastolic blood pressure; DOX — group on doxazosin; SBP — systolic blood pressure; PhB — group on phenoxybenzamine.
Acknowledgements
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Conflict of interest: none declared

References

Porównanie doksazosyny i fenoksybenzaminy w przygotowaniu do leczenia operacyjnego guza chromochłonnego

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*Klaudia Małeć (pierwszy autor) i Piotr Miśkiewicz (drugi autor) mają równy udział w przygotowaniu niniejszej pracy.

Streszczenie

Wstęp: Główną trudnością w przygotowaniu pacjenta z guzem chromochłonnym do adrenalektomii jest stabilizacja układu sercowo-naczyniowego w trakcie oraz po operacji. Dlatego też farmakologiczne przygotowanie chorego stanowi nadal wyzwanie dla klinicystów. Odpowiednia podaż leków ma za zadanie zapobiec niepożądanych skutkom wzrostów i spadków ciśnień śród- oraz pooperacyjnych.

Cel: Celem pracy było porównanie skuteczności leczenia doksazosyną (DOX) i fenoksybenzaminą (PhB) w prewencji niestabilności hemodynamicznej u pacjentów przygotowywanych do operacji guza chromochłonnego.

Metody: Retrospektywną analizą objęto 44 chorych (16–80 lat, 29 kobiet) operowanych z powodu guza chromochłonnego, w tym 35 pacjentów leczonych DOX oraz 9 osób stosujących PhB.

Wyniki: Średni czas przygotowania farmakologicznego do operacji w grupie DOX wynosił 38,8 dnia vs. 18,3 dnia w grupie PhB (p = 0,04). Nie odnotowano istotnych statystycznie różnic między DOX i PhB w śródoperacyjnym pomiarze ciśnienia tętniczego w zakresach < 170/100 mm Hg (34% vs. 44%, p = 0,42) oraz ≥ 200/110 mm Hg (40% vs. 22%, p = 0,28); w zakresie średniego najwyższego skurczowego BP (195 ± 53 vs. 166 ± 42, p = 0,21) i rozkurczowego BP (98 ± 20 vs. 89 ± 46, p = 0,21); średniego najniższego skurczowego BP (87 ± 13 vs. 79 ± 17, p = 0,25) i rozkurczowego BP (49 ± 8 vs. 46 ± 12, p = 0,60). Z powodu wzrostu ciśnienia nitroprusydek sodu stosowano u 30% pacjentów z grupy DOX i u 11% osób z grupy PhB (p = 0,25). Adrenalektomię drogą laparoskopową wykonano u 97% chorych z grupy DOX i u 89% pacjentów z grupy PhB (p = 0,64). Odnotowano pooperacyjną hipotensję < 90/60 mm Hg u 48% chorych z grupy DOX i u 43% osób z grupy PhB (p = 0,56). Ujemną, statystycznie istotną korelacją stwierdzono między długością przyjmowania DOX a najwyższym śródoperacyjnym skurczowym BP (r = –0,45; p = 0,006) oraz rozkurczowym BP (r = –0,39; p = 0,019).

Wnioski: Nie zaobserwowano istotnych klinicznie różnic między wynikami chorych przygotowywanych do operacji za pomocą DOX oraz PhB.

Słowa kluczowe: guz chromochłonny, ciśnienie tętnicze, adrenalektomia, doksazosyna, fenoksybenzamina, alfa-adrenolityki

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