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ORIGINAL ARTICLE

Selective α_1-adrenoceptor antagonist (controlled release tablets) in preoperative management of pheochromocytoma

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Abstract The objective of this article is to evaluate the efficacy of Doxazosin Mesylate Controlled Release Tablets for preoperative treatment of patients with pheochromocytoma. Between 2003 and 2008, 67 patients with confirmed diagnoses of pheochromocytoma were enrolled in this study. According to the drug used in preoperative management, patients were divided into two groups: Doxazosin Mesylate pretreatment group ($n = 36$) and Phenoxybenzamine pretreatment group ($n = 31$). Surgery was performed only in patients who met the optimal preoperative condition. The hematocrit decreased significantly ($P < 0.001$) after antiadrenergic therapy in patients pretreated with phenoxybenzamine or doxazosin. There was no significant difference between the fluid intakes during operation in both groups. The systolic arterial pressures both before and after induction of anesthesia were all significantly higher in the doxazosin patients than in the phenoxybenzamine group ($P < 0.05$). After tumor removed, the lowest systolic arterial pressure was significantly higher in doxazosin group than in phenoxybenzamine group ($P < 0.05$). The fluctuation of systolic arterial pressure during operation was more stable in doxazosin group than in phenoxybenzamine group ($P < 0.05$). Doxazosin mesylate controlled release tablet was as effective as phenoxybenzamine in preoperative volume expansion. Although phenoxybenzamine provided better arterial pressure control, patients pretreated with DOX experienced more stable perioperative hemodynamic changes, shorter preoperative management periods and more simple medication.

Keywords Pheochromocytoma · α-Adrenoceptor antagonist · Preoperative management

Introduction

Pheochromocytomas are pharmacologically volatile, potentially lethal neuroendocrine tumors that arise from the chromaffin tissue within the adrenal medulla and extra-adrenal sites. Because of excess secretion of the hormones epinephrine, norepinephrine, and dopamine, patients affected by pheochromocytomas present with a variable symptoms such as hypertension, palpitation, tachycardia, and dizziness [1]. To date, surgical resection remains the treatment of choice for curing the disease. However, the surgery has great potential for intra-operative and post-operative complications. The release of catecholamines during surgical manipulation of the tumor can result in hypertensive crisis, cardiac arrhythmias, cerebral vascular accident, myocardial infarction or ischemia, pulmonary edema, and multiorgan failure, while the sudden decrease in catecholamine levels after removal of the tumor may cause the severe hypotension. Therefore, adequate preoperative medical preparation is necessary to reduce the risk for perioperative complications. It is recommended that all patients with pheochromocytoma should receive appropriate preoperative pharmacological management to limit

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organ damage associated with excessive catecholamine secreting [2].

Phenoxybenzamine (PXB) is a non-selective adrenoceptor antagonist, which can blocks α-adrenergic receptors non-competitively and makes it difficult for released catecholamines to have a physiologic effect. PXB has been introduced as preoperative therapy in patients with pheochromocytoma since the early 1950s, which markedly decreased the perioperative mortality rate, and PXB has been regarded as the drug of choice in preoperative management. However, it has many adverse side effects such as orthostatic hypotension, fatigue, nasal stiffness, tachycardia, etc. [3, 4]. With the development of pharmaceutical technology, Miura et al. [5] first applied doxazosin (DOX) in the preoperative medical treatment of 24 patients with pheochromocytoma in 1988. The results indicated that DOX provided safe, efficacious control of arterial pressure, and the overall efficacy rate was 83.3%. In 2002, Prys-Roberts et al. also reported the safety and efficacy of DOX for the preoperative management of patients with pheochromocytoma [6]. DOX controlled release tablet (Cardura®) was introduced to China in October 2002. Since then, some studies have been conducted to compare the efficacy of PXB with that of DOX, and some trials with small sample sizes also evaluated the role of DOX in the preoperative management of patients with pheochromocytoma [7, 8]. Nowadays, PXB and DOX are the two most commonly used α-adrenoceptor antagonists in the preoperative management. In the present study, we analyzed the hemodynamic changes during operation and evaluated efficacy and safety of DOX and PXB in the preoperative management in patients with pheochromocytoma.

Patients and methods

Criteria for selection of cases

From March 2003 to June 2008, a total of 142 patients with pheochromocytoma were prepared medically for subsequent surgery in our institute. Diagnosis evaluation of pheochromocytoma consisted of a thorough history taking, physical examination, routine laboratory studies, biochemical evaluation (including 24-h urinary catecholamines and metanephrines, plasma metanephrines), imaging examinations. Tumors were localized by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and when necessary, by radiotracer-labeled meta-iodobenzyl-guanidine (^{131}I-MIBG) scanning.

Following approval from institutional ethics review board, the complete medical records of these patients were reviewed from our database. The inclusion criteria of this study included: (1) patients had symptoms of pheochromocytoma; (2) pheochromocytoma was confirmed both biochemically and by CT or MRI; (3) tumor was localized in the unilateral adrenal gland; (4) tumor largest diameter was no more than 6 cm; (5) patients without concomitant hypertensive encephalopathy and severe injury in the heart, lung, or kidney; (6) operation was performed through retroperitoneal 11th intercostal incision. The design of inclusion criteria aimed to control the difficulty of the operation and exclude the difference in the surgery, anesthesia and skills of surgeons. According to the inclusion criteria, a total of 67 patients were enrolled in the present study. All patients were pathologically confirmed to be pheochromocytoma. Preoperative variables for all 67 patients were obtained by reviewing these records, including baseline and peak value for blood pressure before preoperative treatment, results of biochemical evaluation, imaging tests and preoperative treatment (dose and duration). Intraoperative variables reviewed included total operative time, estimated blood loss, and hemodynamic changes. Between March 2003 and November 2005, 31 patients received PXB as preoperative medical treatment, while 36 patients received DOX from December 2005 to June 2008. Based on the difference in the preoperative management, the patients were divided into DOX group and PXB group.

Preoperative management

In DOX group, 36 patients received doxazosin mesylate controlled release tablets (4 mg, Cardura®) as the preoperative management. The initial dose of DOX was 4 mg by mouth daily. Dose of 4 mg daily was generally adequate but it was increased for blood pressure control of up to 16 mg/day. The dose was increased by 4-mg increments every 3–5 days until stabilization of arterial pressure and reduction in symptoms achieved.

In PXB group, 31 patients received PXB as the preoperative treatment. The initial dose of PXB was 5–10 mg by mouth twice daily, combined with non-invasive monitoring of arterial pressure in the supine and standing positions. The dose was adjusted according to the blood pressure and elevated gradually every 2–3 days with an increase of 10–20 mg once. The maximal dose of PXB was 60 mg/day.

If the blood pressure cannot be controlled at the expected levels (usually no more than 160/100 mmHg) under the monotherapy with a maximal dose, other antihypertensive drugs (calcium antagonist and angiotensin-converting enzyme inhibitor) are employed. β-Blockers were administered to patients to control tachycardia and supraventricular arrhythmia. The following criteria for optimal preoperative condition are used in our institute: (1) blood pressure reading should ≤160/100 mmHg for at least 24 h before surgery; (2) heart rate should ≤100 bpm and the electrocardiogram should be free of ST-T changes for

at least 1 week; (3) the patient should have no more than one premature ventricular contraction every 5 min; and (4) hematocrit should >0.045. The operation was performed only in patients who meet these criteria. The last PXB/DOX dose was usually administered at 8 pm on the night before surgery.

Anesthesia and surgery

Adrenalectomy was performed through retroperitoneal 11th intercostal incision by two experienced surgeons under general anesthesia. Anesthesia was inducted by intravenous administration of propofol and was maintained with inhalation agent sevoflurane. Acute hypervolemic hemodilution was performed in all patients underwent operation. Before induction of anesthesia, an intra-arterial catheter was appropriate for continuous systolic and diastolic arterial pressure monitoring. The heart rate and central venous pressure (CVP) was also measured continuously using electrocardiogram monitor. The blood pressures were measured before and after stable anesthesia, during manipulation of the tumor, immediately after removal of the tumor and postoperatively. The fluctuation of systolic (ΔSAP) and diastolic arterial pressure (ΔDAP) represents the difference between the minimum and maximum systolic and diastolic arterial pressure values during the operation, respectively. In addition, the total operative time, estimated blood loss, and fluid intake were accurately recorded.

Statistical analysis

Statistical analyses were performed using the SPSS statistical software version 11.5. The quantitative data results were expressed as Mean ± SD. Paired t test was used for comparisons within groups and unpaired t test for comparisons between groups (PXB and DOX groups). The χ^2 test was used to compare categorical variables such as supplementary anti-hypertension medication, β-adrenoceptor antagonists medication, and inter-operative blood transfusion between patients pretreated with PXB and DOX. The level of statistical significance was chosen as $P < 0.05$.

Results

Preoperative management

According to the different drugs used in preoperative treatment, patients were divided into DOX group and PXB group (Table 1). DOX group included 36 patients, among which 21 cases achieved the optimal preoperative condition using DOX 4 mg as a single oral dose taken daily, while other 15 cases were treated with a relative high dose of DOX (12 received DOX 4 mg twice daily and 3 received DOX 8 mg twice daily). In these 15 patients, 14 received supplementary anti-hypertensive drugs to achieve the ideal blood pressure control (<160/100 mmHg): 7 patients received calcium antagonist, 4 patients received angiotensin-converting enzyme inhibitor (ACEI), and 3 patients (all of them received DOX 8 mg twice daily) were given calcium antagonist plus ACEI therapy. Of the 36 patients, 4 received β blocker to control tachycardia and arrhythmia related to epinephrine-secreting tumors.

The PXB group included 31 patients received PXB in final doses of 20–60 mg/day as the antiadrenergic therapy and the medications were administrated orally two or three times daily. Twenty-four patients received β-blocker due to tachycardia and arrhythmia and only three of them were epinephrine-secreting tumors. Five patients were given supplementary anti-hypertensive medications such as calcium antagonist and/or ACEI to achieve optimal blood pressure control.

There were no significant differences between age, body weight, baseline, and peak values for blood pressure before preoperative treatment in patients received PXB or DOX. No significant differences were observed in preoperative blood pressure, hematocrit level before and after medication between two groups (Tables 1, 2). The mean preoperative treatment period in DOX group was markedly shortened compared to that in PXB group (11 ± 3.6 vs. 25 ± 3.2, $P < 0.001$). Fourteen patients (38.9%) pretreated with DOX experienced supplementary anti-hypertension therapy, while only five patients (16.1%) in PXB group received supplementary anti-hypertension medication ($P < 0.05$). In addition, the proportion of patients received β-blocker treatment in DOX group was dramatically lower than that in PXB group (11.1 vs. 77.4%, $P < 0.05$). Furthermore, in both groups, the hematocrit markedly decreased after preoperative treatment (DOX: 0.41 ± 0.039 before treatment vs. 0.37 ± 0.040 after treatment; PXB: 0.39 ± 0.045 before treatment vs. 0.36 ± 0.044 after treatment; $P < 0.05$).

Intraoperative blood pressure

The systolic arterial pressure (SAP) before and after stable anesthesia were all significantly higher ($P < 0.01$) in DOX group patients than in PXB group. In the DOX group, the SAP value after removal of the tumor was 96 ± 10.8 mmHg, which was significantly higher than that in PXB group (74 ± 8.8 mmHg, $P < 0.01$). The ΔSBP value in DOX group was significantly lower than that in PXB group (73 ± 15.7 mmHg vs. 88 ± 10.4 mmHg, $P < 0.01$). However, there were no significant differences between the peak SAP during tumor manipulation, SAP after surgery and

Table 1 Patients and their diagnosis, preoperative drug therapy and survival

Parameters	Phenoxybenzamine	Doxazosin	*P* value
Patient characteristics			
Males	15	19	
Females	16	17	
Age (years), median and range	42.4 (18–77)	41.6 (15–79)	0.49
Weight (kg), median and range	65.5 (42–79)	69.4 (48–85)	0.57
Pheochromocytoma			
Right adrenal	18	20	
Left adrenal	13	16	
Tumor size (cm), mean ± SD	5.0 ± 0.7	5.0 ± 0.8	0.64
Preoperative drug therapy			
Phenoxybenzamine, daily dose (mg)	20–60	–	
20	2	–	
30	2	–	
40	16	–	
50	6	–	
60	5	–	
Doxazosin, daily dose (mg)			
4	–	21	
8	–	12	
16	–	3	
Preoperative period (days)	25 ± 3.2	11 ± 3.6	<0.001
Hematocrit			
Before drug therapy	0.41 ± 0.039	0.39 ± 0.045	0.29
After drug therapy	0.37 ± 0.040	0.36 ± 0.044	0.21
P value	<0.001	<0.001	
Operation data			
Estimated blood loss (ml), mean ± SD and range	270 ± 180.6 (100–800)	260 ± 188.2 (80–700)	0.15
Blood transfusion (ml), mean ± SD and range	282 ± 56.0 (200–600) ($n = 15$)	252 ± 50.7 (200–600) ($n = 12$)	0.23
Crystal solution infusion (ml), mean ± SD and range	2549 ± 279.2 (2000–3000)	2580 ± 260.3 (1500–3000)	0.72
Colloidal fluid infusion (ml), mean ± SD and range	2100 ± 247.3 (1500–2500)	2083 ± 253.6 (1500–2500)	0.69
Survival (no. alive/total)	31/31[a]	36/36	

[a] Coma occurred in one patient aged 77 years of the PXB group 5 days after surgery, and ischemic cerebral infarction was considered. Then, the patient was treated in the SICU and discharged 1 month later with right motor dysfunction

intra-operative DAP in patients pretreated with PXB or DOX (Table 2).

Intraoperative fluid intake

The estimated blood loss, volume of crystal solution infusion, and colloidal fluid infusion during operation in DOX and PXB groups were shown in Table 1, and no significant difference was observed in these intra-operative variables between two groups. Twelve patients (33.3%) in DOX group and 15 patients (48.4%) in PXB group received intra-operative blood transfusion. The proportion of patients who were given intra-operative blood transfusion in DOX group was slightly lower than in PXB group, but there was no statistical significance.

Discussion

PXB, a non-competitive, non-selective antagonist was first used in preoperative management of pheochromocytoma in the early 1950s, which magnificently reduced the perioperative mortality associated with pheochromocytoma resection. Nowadays PXB has become one of the most widely used drugs in preoperative medical treatment. However, because of non-competitive binding to α-adrenoceptors and resistance to displacement by endogenous catecholamines, the actions of the drug are longer lasting, which may contribute to persistent hypotension. As a non-selective α-adrenoceptor antagonist, PXB not only decreases the blood pressure, but blocks the α_2-adrenoceptor on the presynaptic membrane which causes the

Table 2 Changes in the systolic and diastolic arterial pressure

Parameters	Systolic arterial pressure			Diastolic arterial pressure		
	PXB ($n = 31$)	DOX ($n = 36$)	P value	PXB ($n = 31$)	DOX ($n = 36$)	P value
Baseline before preoperative treatment	135 ± 17.7	134 ± 18.4	ns	86 ± 9.2	85 ± 13.0	ns
Peak value before preoperative treatment	190 ± 25.2	189 ± 32.7	ns	105 ± 21.9	109 ± 20.0	ns
Pre-operation	125 ± 13.2	123 ± 15.9	ns	78 ± 11.5	77 ± 8.7	ns
Before anesthesia	132 ± 20.6	145 ± 16.3	<0.01	82 ± 12.3	86 ± 13.1	ns
After stable anesthesia	91 ± 16.2	110 ± 15.6	<0.01	65 ± 15.1	70 ± 14.0	ns
During manipulation of the tumor	162 ± 19.2	169 ± 24.7	ns	100 ± 15.1	98 ± 13.4	ns
Removal of the tumor	74 ± 8.8	96 ± 10.8	<0.01	52 ± 7.5	53 ± 6.3	ns
Immediately after surgery	111 ± 13.1	112 ± 14.1	ns	71 ± 10.0	72 ± 9.2	ns
ΔSAP/ΔDAP	88 ± 10.4	73 ± 15.7	<0.01	48 ± 12.2	47 ± 11.7	ns

increased release of norepinephrine by the cardiac sympathetic nerve endings [9] and increases incidence of tachycardia. Therefore, a majority of patients often require administration of β-blockers. Considering these side effects of PXB are caused by the blockage of the α_2-adrenoceptor, selective competitive α_1-adrenergic blockade with prazosin was once advocated. However, it did not be widely used because of a short elimination half-life (2–3 h) [10]. In 1986, researchers found that DOX, a selective α_1-adrenoceptor antagonist, had no effect on α_2-adrenoceptor on the presynaptic membrane and would not affect norepinephrine uptake or release [11, 12]. In 1988, Miura et al. used DOX preoperatively in 24 patients with pheochromocytoma and noted that DOX appeared to be an excellent agent for the management of hypertension associated with pheochromocytoma (the overall effective rate was 83.3%). DOX monotherapy was effective in 8 of 12 patients (66.7%), and combined therapy with a β-blocker was effective in 11 of 12 patients (91.7%). During the treatment, transient and minor adverse effects were occurred in only three patients [5]. DOX was used preoperatively by Prys-Roberts et al. in a series of 35 patients with pheochromocytoma from 1993 to 2001. Among them, 8 patients received PXB and 27 patients received DOX. They noted that DOX alone or in conjunction with a β-blocker therapy provided safe, efficacious preoperative control of blood pressure in patients with pheochromocytomas. In our study, only four patients in DOX group received β-blocker to control tachycardia related to a predominantly epinephrine-secreting tumor. The proportion was 11.11% which was significantly lower than that in PXB group (77.42%), which indicated that co-administration of β-adrenoceptor antagonists was unnecessary under DOX-based preoperative preparation except in patients with epinephrine-secreting tumors. The results were similar with those of previous studies.

First-dose effect, which is characterized by orthostatic hypotension, is often occurred and is a major problem in the PXB treatment. However, this problem has been solved with the development of pharmacokinetics and the application of controlled release technology. The ideal drugs used in the preoperative management of patients with pheochromocytoma should meet the following criteria: (1) the effective concentration of drugs in plasma can be achieved rapidly and maintained stably; (2) the concentration of drugs in plasma should increase gradually and rapidly occurring maximal concentration should be avoided. Pfizer Pharmaceuticals applied the advanced Gastro-Intestinal Therapy System (GITS) to develop mesylate doxazosin controlled release tablet, an α_1-adrenoceptor antagonist, of which the absorption is performed at a constant rate and first-dose effect can be avoided, thus reducing the incidence of orthostatic hypotension. DOX was introduced to China in October 2002, and DOX has been widely used in our institute as the preoperative medical therapy in patients with pheochromocytoma since 2005. There was general agreement that preoperative treatment using α-adrenoceptor antagonists should last at least 10–14 days, doses should be patient-titrated [1]. In our study, it took about 11 days for patients received DOX to achieve the optimal preoperative condition, which was significantly shorter than that in PXB group (about 25 days). Furthermore, using DOX simplified the regimen on administration and dose escalation, thus increasing the patient compliance.

It has been found that the dose of DOX was positively related with 24-h urinary norepinephrine excretion and could be calculated according to the following formula: DOX dose (mg) = 1.48 + 0.00066 urinary norepinephrine (nmol/24 h) [6]. Previous studies found the effect of PXB on the blood pressure control was superior to that of DOX, which might be related with the property of PXB as a non-

competitive α-adrenoceptor antagonist [6, 13, 14]. In the present study, no significant difference in the preoperative blood pressure was observed between patients pretreated with PXB and DOX. However, 14 patients in DOX group experienced supplementary anti-hypertension therapy, while only 5 patients in PXB group received supplementary anti-hypertension medication, which indicated that PXB alone provided better blood pressure control compared to DOX monotherapy. In addition, the SAP before and after stable anesthesia in DOX group was higher than those in PXB group, which also demonstrated the efficacy of PXB in controlling perioperative blood pressure was superior to that of DOX.

The hematocrit dramatically decreased after preoperative medical treatment in both groups. No significant differences were observed in hematocrit level both before and after medication between two groups, which indicated that DOX was at least as well as PXB in preoperative volume expansion. Under the condition when the volume of estimated blood loss was similar, there was no significant difference in the volume of crystal solution infusion, colloidal fluid infusion, and blood transfusion during operation between two groups, suggesting similar preoperative volume expansion effect between PXB and DOX.

In our study, the ΔSBP value in DOX group was significantly lower than that in PXB group, while the SAP value after removal of the tumor was dramatically higher than that in PXB group, which indicated that DOX provided more stable perioperative hemodynamic changes compared to PXB. This effect of DOX is crucial for surgery because dramatic fluctuation in blood pressure may easily cause cerebrovascular accident, heart failure, and arrhythmia.

Conclusion

DOX was as effective as PXB in preoperative volume expansion. Although PXB provided better blood pressure control compared to DOX, patients pretreated with DOX experienced more stable perioperative hemodynamic changes and shorter preoperative management periods. Furthermore, the administration of DOX was simple, thus shortening the duration when patients were exposed to high level catecholamine. DOX has a long duration of action, allowing once daily dosing, and may have a near-ideal profile for the preoperative management of patients with pheochromocytoma.

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