Surgery and Anesthesia for Pheochromocytoma - A Series of 40 Operations

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Abstract

Pheochromocytoma is a catecholamine-producing tumor which can be life-threatening. A series of 40 operations in 39 pheochromocytoma patients at a tertiary hospital in Thailand from 1976 to 1997 was reported. The patients were 30 females and 9 males; aged 7-73 years. One man had 2 operations 5 years apart. The most common symptoms and signs were palpitation, headache and hypertension. Preoperative management consisted of control of blood pressure and restoration of intravascular volume by using prazosin, an alpha adrenergic blocker. New imaging techniques have improved the ability to localize the tumors; 20 were found in the right adrenal glands, 14 in the left, 1 patient had bilateral tumors, 4 in Organs of Zuckerkandl and 1 patient had metastatic liver nodules. The operative procedures were 39 laparotomies and 1 laparoscopic surgery. The surgical and anaesthetic procedures were presented, and nitroprusside was used to control intra-operative blood pressure. Removal of tumors was successful in all cases except for 1 mortality due to injury of the liver and massive blood loss. Other complications were postoperative pulmonary edema and renal vein thrombosis. One patient had MEN type 2 and five cases were malignant. Pheochromocytoma can be cured by surgery, but cooperation among surgeons, anesthesiologists and internists is very important.

Key word : Pheochromocytoma, Adrenalectomy, Surgery, Anesthesia

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Pheochromocytoma is a catecholamine-producing tumor that arises from chromaffin cells of the sympathoadrenal system. Ninety per cent of all cases arise from the adrenal medulla. Paraganglioma (or extraadrenal pheochromocytoma) is found along the sympathetic chain or from the organs of Zuckerkandl, with one per cent arising in the wall of the urinary bladder.

Although Pheochromocytoma occurs in only 0.1 per cent to 1 per cent of hypertensive persons[1], the surgical management can cure the patient and adrenalectomy remains the treatment of choice for this tumor. Since localization, preoperative preparation, anesthesia and surgical techniques have changed over time due to new technologies, we reported a series of 39 patients with pheochromocytomas who underwent 40 operations at the Department of Surgery, Faculty of Medicine, Siriraj Hospital in Bangkok, Thailand.

MATERIAL AND METHOD

Special files have been kept for 39 patients with pheochromocytomas who were operated on at the Department of Surgery between 1976 and 1997. Patients were consulted cases from the Department of Medicine or referred to the Department of Surgery from other hospitals.

RESULTS

Patients, diagnosis, and localization

Age and sex of the 39 patients are shown in Table 1. Ages ranged from 7 to 73 years. The most common presenting symptoms were palpitation, headache and perspiration. These and their duration before admission are shown in Table 2. The symptoms may be persistent or paroxysmal. Blood pressure on the day the patients sought medical care was abnormally high, especially for their age group. Systolic blood pressure was around 200 mmHg in all cases except two patients who presented with shock, and one patient who was thought to have a non-functioning tumor. The patients also presented with abdominal mass, abdominal pain, pulmonary edema and syncope.

Measurements of urinary catecholamines and their metabolite, vanillyl mandelic acid (VMA) were carried out in all cases. Investigations used to localize the tumors and the sites found are shown in Table 3. Plasma catecholamines were sometimes determined but this was not recommended due to the fluctuation of the serum level.

Table 1. Age and sex distribution of 39 cases (40 operations).

Age (year)	Females	Males
< 10	0	1
11 - 20	4	1
21 - 30	9	0
31 - 40	10	3
41 - 50	2	3
51 - 60	4	1 (2 operations)
> = 61	1	0
	30	9 (10 operations)

Table 2. Clinical presentation to the hospital (may have more than 1) and duration of symptoms.

Symptoms & signs	Number of patients
Palpitation, headache, hypertension	37
Abdominal mass	4
Abdominal pain	3
Shock	2
Angina with pulmonary edema	2
Syncope	1
Duration of symptoms	**Number of patients**
<1 month	5
1 – 12 months	21
1 – 6 years	13
> 6 years	1

Table 3. Localization of phaeochromocytomas and sites of tumors.

Localization technique	Number of patients
Blood sampling of catecholamine	2
Angiography	11
Ultrasonography	9
CT scan (since 1979)	32
MRI	2
MIBG (since 1994)	10
Site of tumor	**Number of patients**
Right adrenal gland	20
Left adrenal gland	14
Bilateral	1
Organ of Zuckerkandl	4
Liver	1

In the early 70's perinephric air insufflation and angiography (with or without blood sampling of catecholamine) were used to localize the suspected tumor. Ultrasonography was performed subsequently with a better yield and less suffering. Since 1979, computerized tomography (CT) scan has been the most common and informative radiological investigation. Magnetic resonance image (MRI) has been used but not in all cases because of its high cost. The MRI yields both cross-sectional and longitudinal images and is helpful in extra-adrenal mass and in pregnancy. CT and MRI improve the ability to plan the surgical maneuver before operation. Scintigraphy with the use of I^{131} meta iodobenzyl guanidine (MIBG) has been available since 1994 and is now in routine use. MIBG is concentrated in adrenergic vesicles and if there are several tumors in the patient, condensed image can be seen at the tumor site(s).

Preoperative preparation

After pheochromocytoma is diagnosed and localized, the vascular bed of the patient is expanded by using alpha- adrenergic blocker. Phenoxybenzamine has been used elsewhere but this drug is not registered in Thailand. Labetalol was used in a few cases but it blocked the beta adrenergic receptor more than alpha adrenergic receptor. Nowadays prazosin, a selective alpha 1 adrenergic antagonist, is most commonly used. Beta-blocker, e.g. propranolol, was given only in those whose heart rate exceeded 120 bpm after treatment with prazosin. Calcium channel blocker was given when high dose prazosin could not control blood pressure (BP). Sodium nitroprusside was given in those who had hypertensive crisis.

The pharmacological treatment was evaluated from BP and heart rate, symptoms and signs of sympathetic activities also disappeared, while hematocrit came down as the intravascular volume expanded. Blood volume study was done with subsequent replacement of blood component that was lacking. The change in electrocardiography (ECG) was followed and, since 1995, echocardiography has been performed to evaluate cardiac function.

Surgery

The appropriate time for surgery was the co-decision of the surgeon, anesthesiologist and internist. We followed Roizon's guidelines: the systolic BP should not be higher than 165/90 mmHg for at least 48 hours; orthostatic hypotension should be present, but not lower than 80/45 mmHg; no change in ST and T waves of ECG for at least 2 weeks; if PVC was present, there should not be more than 1 in 5 minutes. The nature and risk of the disease and operation were explained to the patients. Abdominal palpation was prohibited and soap sud enema was not ordered preoperatively.

All patients lay in the supine position (except one in the kidney position) for bilateral subcostal incision. The use of large self-retaining retractors gave a much better exposure for exploratory laparotomy. Palpation of the urinary bladder, organ of Zuckerkandl and para-aortic area was performed and blood pressure checked in order to find an extra adrenal tumor. Then the opposite gland was palpated to rule out the chance of bilateral tumors. Surgical dissection and manipulation of the gland had to be meticulous and very gentle because these might cause catecholamine release and result in vasoconstriction and malignant hypertension. Communication between the surgeon and anesthesiologist was very important throughout the operation, e.g., bleeding, approaching the mass, etc.

Early control of the adrenal vein is the key of a successful and safe operation. The right adrenal vein could be identified by dissection along the inferior vena cava. The left adrenal gland could also be identified easily by dissection along the left renal vein. After the adrenal vein was clamped and transected, the fluctuation of blood pressure decreased. If the blood pressure remained high, there was a possibility of multifocal tumors. By using continuous invasive monitoring, reduction of the systemic peripheral vascular resistance was also another clue of total removal of the tumor.

Intraoperative complications included hypertension, hypotension, massive blood loss and massive transfusion. Tumor removal was successful in all cases except one patient who had massive blood loss from a liver injury (and resulted in one operative mortality in this series), and another patient who had malignant tumor. Tumor of the right adrenal had a higher risk of injury and bleeding of the liver. Tachycardia and arrhythmia were also found but not life-threatening. Hypothermia resulted from heat loss during the long operation and transfusion of a large quantity of cool blood and crystalloids. There were two postoperative complications. One patient developed acute pulmonary edema from overtransfusion and another patient had

renal vein thrombosis after intraoperative injury and repair.

There were no morphologic markers of malignancy. Four cases were considered malignant because of the presence of direct invasion of surrounding structures and one case because of distant metastasis. One malignant case had pheochromocytoma nodules in the liver removed in the second operation 5 years later. In another malignant case only partial resection of tumor could be done because the tumor involved the blood vessel and the patient had to have radiotherapy after operation.

Anesthesia

Intramuscular pethidine and scopolamine, and oral benzodiazepine were given for premedication, together with the morning dose of prazosin and other antihypertensive drugs. The technique of anesthesia was balanced general anesthesia with tracheal intubation and controlled positive pressure ventilation. Monitoring before induction included intra-arterial BP, ECG (modified V5) and pulse oximetry. With sodium nitroprusside (SNP) 0.012 per cent (25 mg in 200 ml water) ready to be given if needed, thiopentone and nondepolarizing muscle relaxant were given. Intravenous lidocaine 50 mg can be given to obtund the coughing. The patient was gently ventilated with oxygen, nitrous oxide and inhalation agent for three minutes before the trachea was intubated by an experienced anesthesiologist. Cases in the early years of the series received pethidine, halothane, diazepam, and pancuronium. Nowadays the drugs given are fentanyl, isoflurane, midazolam, and vecuronium.

End tidal carbondioxide, urine output and core temperature were also monitored. In order to follow the cardiac performance, a balloon-tipped, flow-guided catheter was placed to measure central venous pressure, pulmonary capillary wedge pressure and cardiac output. We found this helpful during the operation in SNP titration and resuscitation of intravascular volume. The increase in systemic vascular resistance index (SVRI) pointed to the need of more SNP. When the catecholamine-producing mass was successfully removed, cardiac index increased and SVRI dramatically decreased.

SNP was used to control the BP which, even with preoperative alpha-adrenergic blockade, still increased sharply to around 200 mmHg when the surgeon manipulated the mass. If SNP could not bring the pressure down, the surgeon was asked to stop manipulating. Blood loss and insensible loss were replaced as soon as it occurred. If this was not done, when the adrenal vein was clamped and the catecholamine from the tumor did not reach the circulation, the patient could have profound hypotension from vasodilation and hypovolemia. We treated paroxysmal ventricular contraction with intravenous lidocaine.

Postoperative care

We did not extubate the patients at the end of surgery but preferred to ventilate them in the intensive care unit. This gave time for intravascular volume to adjust to the change in catecholamines and the patients to receive adequate pain relief. Four patients developed postoperative hypoglycemia in the intensive care unit which was promptly detected and treated.

DISCUSSION

C.H. Mayo of the Mayo Clinic successfully removed pheochromocytoma in 1926 and reported "paroxysmal hypertension with tumor of retroperitoneal nerve" in 1927[2]. From that time until now, the strife to diagnose the disease, to localize the tumor, to control the manifestation and prepare the patient for surgery have received much attention from biochemists, radiologists and internists[3-5]. Although biochemical tests have high sensitivity and specificity, there are situations and drugs that interfere with biochemical diagnoses of pheochromocytoma[6].The investigation and medical treatment of thirty-four patients had been reported by our internist colleagues[7]. Surgeons and anesthesiologists play important roles in the care of these patients[8]. Even with the best preoperative management, the operation can be dangerous and demanding. When proper preoperative medication is lacking, severe cardiovascular complication could occur, resulting in mortality.

Most patients were first admitted to treat hypertension in general hospitals but when their BP could not be controlled or when the CT scan showed a suprarenal mass, they were then referred to a tertiary care, teaching hospital that is better equipped to manage pheochromocytoma.

In our series there were 30 females to 9 males, a ratio of more than 3:1. In Samaan's series there were 21 females to 20 males[1]. The other case series in Thailand reported 14 females to 10 males[9]. Pheochromocytoma in a child is rarer

than in an adult[10]. Extraadrenal pheochromocytomas occurred in 10 per cent of this series but represented at least 15 per cent of adults in another review[11].

Preoperative alpha-blocker treatment is very important[12-14]. Prazosin helps dilate the vasculature to bring the BP down and allows gradual expansion of the retracted blood volume. Methyltyrosine, which is safe and effective, is used in many countries[15] but is not yet available in Thailand. Echocardiography is now requested because these patients could have left ventricular hypertrophy and cardiomyopathy from longstanding hypertension[16]. Roizen's criteria[17] aim to decrease hypertension but maintain orthostatic hypotension to make sure that the vascular system was dilated but not too dilated.

It is important to give heavy premedication so that invasive monitoring can be started before the induction of anesthesia. An arterial line allows the change in BP to be instantaneously followed. Even with heavy premedication, BP usually rises very rapidly during induction and intubation. Only experienced personnel should intubate these patients and the position of the tracheal tube has to be perfect. Every step has to be carefully executed. In our series, high BP was successfully controlled by SNP and by asking the surgeon to stop manipulating. No complication of SNP, e.g., cyanide poisoning, occurred and no neurological complications were found even though the marked BP fluctuations were quite frightening. During anesthesia all drugs with potential release of histamine (tubocurarine and atracurium[18] and catecholamine (pancuronium) should be avoided[19]. Vecuronium is now the muscle relaxant of choice because of its cardiac stability[20,21]. Isoflurane and newer inhalation agents have less induction effect on the heart to have arrhythmia when exposed to catecholamine. Intraoperative tachycardia could be treated with esmolol. Hypoglycemia could occur because the level of catecholamine, which used to inhibit insulin, decreased[22].

In this series, two patients were pregnant when pheochromocytomas were diagnosed. Another 4 female patients gave histories of marked hypertension at various weeks of pregnancy. They had received treatment at other hospitals but pheochromocytomas were not diagnosed. Two of these pregnancies resulted in stillbirths. After delivery, because of the persistently high blood pressure, they were transferred to this hospital, were investigated and pheochromocytomas were diagnosed and removed.

Pheochromocytomas in pregnant women need to be differentiated from toxemia of pregnancy, a much more common problem associated with pregnancy in developing countries. Even when adrenal tumor was suspected, the fear of radiological consequence to the fetus led to late diagnoses in these patients and only two out of six pregnancies were diagnosed before deliveries. When to operate and which anesthetic technique to use are also important issues to consider[23]. Because of the gravid uterus lying on the inferior vena cava and relative hypovolemia from chronic constriction of blood vessels, major regional anesthesia could lead to marked and life threatening hypotension. Rapid fall of BP led to the use of vasopressor which resulted in marked hypertension and pulmonary edema. If the anesthesiologist decides to use a conduction blockade, local anesthetic drug should be titrated very slowly via a continuous epidural technique. If pheochromocytoma is diagnosed during the first or second trimesters, the tumor should be removed. But if pheochromocytoma is diagnosed in the third trimester, the baby should be delivered by C/S; and then the tumor should be removed the same day or afterwards[24,25]. Magnesium has been advocated for pheochromocytoma in pregnancy[26].

In our 39 patients, 34 were benign and 5 were malignant (12.8%), which is similar to a previous report[27]. One patient had neurofibromatosis and cafe ole spot which have been associated with pheochromocytoma in the literature. One patient had bilateral tumors. There was a report that MEN type 2 occurred in patients who had bilateral tumors in more than 70 per cent of cases[28]. In this series, one patient developed medullary carcinoma of the thyroid after adrenalectomy for pheochromocytoma.

Our experience confirms that surgery and anesthesia for pheochromocytoma in Thailand have reached a level that most cases can be successfully treated, as in the experience of another country[29].

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การผ่าตัดและการระงับความรู้สึกผู้ป่วยฟีโอโครโมซัยโตมา: รายงานผู้ป่วย 40 ราย

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ฟีโอโครโมซัยโตมาเป็นก้อนเนื้องอกที่สร้าง catecholamine และอาจมีอันตรายถึงแก่ชีวิต ผู้ศึกษาทำการเก็บข้อมูลผู้ป่วย 39 รายซึ่งได้รับการผ่าตัด 40 ครั้งที่โรงพยาบาลระดับตติยภูมิในประเทศไทยระหว่างปี พ.ศ. 2519–2540 พบว่าผู้ป่วย 30 รายเป็นผู้หญิง, 9 รายเป็นผู้ชาย, อายุเฉลี่ย 7–73 ปี ผู้ป่วยชายรายหนึ่งได้รับการผ่าตัดสองครั้งห่างกัน 5 ปี อาการและอาการแสดงที่พบบ่อยที่สุดคือใจสั่น, ปวดศีรษะ, และความดันเลือดสูง การรักษาก่อนผ่าตัดได้แก่การใช้ยา prazosin ซึ่งเป็น alpha-adrenergic blocker ในการควบคุมความดันเลือดและทดแทนปริมาตรไหลเวียนเลือด เทคนิคการถ่ายภาพรังสีแบบใหม่ทำให้การหาตำแหน่งเนื้องอกแม่นยำขึ้น ผู้ป่วย 20 รายมีก้อนเนื้องอกที่ต่อมหมวกไตข้างขวา, 14 รายมีก้อนเนื้องอกที่ต่อมหมวกไตข้างซ้าย, 1 รายมีก้อนเนื้องอกที่ต่อมหมวกไตทั้งสองข้าง, 4 รายมีก้อนเนื้องอกที่ Organ of Zuckertkandl, ผู้ป่วย 1 รายมีเนื้องอกกระจายไปที่ตับ การผ่าตัดรักษาได้แก่ laparotomy 39 ครั้ง และ laparoscopic surgery 1 ครั้ง ผู้ศึกษารายงานวิธีการผ่าตัดและการระงับความรู้สึกซึ่งใช้โซเดียมไนโตรปรัสไซด์ในการควบคุมความดันเลือด การผ่าตัดเอาก้อนออกได้สำเร็จทุกครั้งยกเว้นมีผู้ป่วยถึงแก่กรรม 1 รายเนื่องจากมีการฉีกของตับและเสียเลือดมาก อาการแทรกซ้อนอื่นที่พบคือ acute pulmonary edema 1 รายและ renal vein thrombosis 1 ราย, ผู้ป่วย 1 รายมี MEN type 2, และ 5 รายเป็นเนื้องอกชนิดร้ายฟีโอโครโมซัยโตมาเป็นโรคซึ่งการผ่าตัดสามารถรักษาหายได้แต่ต้องอาศัยความร่วมมือระหว่างศัลยแพทย์ วิสัญญีแพทย์และอายุรแพทย์

คำสำคัญ : ฟีโอโครโมซัยโตมา, ผ่าตัดต่อมหมวกไต, การผ่าตัด, การให้ยาสลบ

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