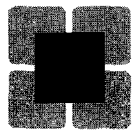

Perioperative management of 63 patients with pheochromocytoma

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■ During a 10-year period, 60 patients with confirmed diagnoses of pheochromocytoma underwent a total of 63 surgical procedures. To control extreme blood pressure elevations, 6 patients received phenoxybenzamine preoperatively and 28 patients received prazosin. The remaining 29 patients received neither drug. Intravenous sodium nitroprusside and nitroglycerin, alone or in combination, were used in all but 10 patients to control intraoperative hypertensive episodes. One patient died after surgery due to pre-existing intracranial malignant tumor. All other patients were discharged from the hospital with no clinical evidence of stroke or myocardial infarction. We conclude that pheochromocytoma patients can undergo successful surgery without preoperative profound and long-lasting alpha adrenergic blockade.

□ INDEX TERM: PHEOCHROMOCYTOMA □ CLEVE CLIN J MED 1990; 57:613–617

PHEOCHROMOCYTOMA is a rare disease that accounts for no more than 0.1% of all causes of hypertension.[1] It is nevertheless important because surgical removal of the tumor can achieve complete cure of hypertension.

The management of pheochromocytoma has been dominated by attempts to minimize the dramatic increases in blood pressure often encountered during surgery because of the sudden release of large quantities of catecholamines into the circulation.[2,3]. Phenoxybenzamine (POB), a long-acting, noncompetitive alpha-adrenergic blocking agent, has been the drug of choice. The use of prazosin, a short-acting, post-synaptic alpha-adrenergic blocker has also been advocated.[4,5]

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The criteria proposed[2] to ensure adequate preoperative preparation with these blockers were: (1) arterial pressure not greater than 160/90 mmHg for 48 hours, (2) orthostatic hypotension present but not exceeding 80/45 mmHg, (3) electrocardiogram (ECG) free of ST-segment and T-wave changes for at least 2 weeks and (4) no more than one premature ventricular contraction every 5 minutes. In this institution, no attempt was made to achieve alpha–adrenergic blockade as defined above by any drug.

We describe the perioperative management and report the outcome of anesthesia and surgery for a group of pheochromocytoma patients treated in this institution during a 10-year period beginning in 1978.

METHODS

This retrospective study includes all patients who underwent surgical removal of pheochromocytoma tumors or other surgical procedures following confirmed diagnosis of pheochromocytoma from January 1978

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through April 1988. Medical charts were reviewed by one of the authors (A.R.B.).

A computer registry was compiled containing details of preoperative status, investigative procedures, drug therapy, and intra- and postoperative management and events. Histologic diagnosis of pheochromocytoma was confirmed in all patients at The Cleveland Clinic Foundation. Autopsy findings were documented for the sole patient who died in the postoperative period. Follow-up information was considered valid if it was obtained during a subsequent examination of the patient at the Cleveland Clinic. Statistical methods used were paired and unpaired student *t* test and analysis of variance.

RESULTS

The patients treated included 29 males and 31 females whose average age was 48 years (range, 15 to 73). Average height was 167.8 cm (range, 147 to 193) and average weight was 70.8 kg (range 42.5 to 166).

Sixty-three surgical procedures were performed on 60 patients following confirmed diagnosis of pheochromocytoma.[5] The surgical procedures included 46 adrenalectomies: 21 left, 25 right (12 through thoracoabdominal surgical approach), and 5 bilateral. In 11 patients the pheochromocytoma was outside the adrenal glands (para-aortic, urinary bladder, diaphragm, and Zuckerkandl's organ). One patient, who had a pheochromocytoma in his left adrenal gland, underwent left ventricular myomectomy and triple coronary grafting and had the adrenalectomy performed at a later date. Included in the above count are two other patients who each had two separate procedures to remove recurrent pheochromocytoma at other sites.

Preoperative preparation

Preoperative evaluation and diagnostic procedures, such as the clonidine test, magnetic resonance imaging, and computed tomographic (CT) scanning, were mostly performed on an outpatient basis. Some patients were hospitalized for evaluation and then discharged and readmitted later for surgery. Others remained as inpatients until surgery was performed. The average length of stay during the admission immediately prior to surgery was 8.4 ± 4.5 days (mean ± SD) for 30 patients between 1978 and 1983 and 4.7 ± 4.0 days for 33 patients between 1984 and 1988, after new Medicare regulations were instituted. A t test analysis revealed significant difference ($P < 0.005$).

One of the authors (E.L.B.) was consulted on all patients by the primary service when pheochromocytoma was suspected. He recommended appropriate investigative procedures and the drugs and fluid therapies to be used. He also recommended the use of prazosin to control severe hypertensive episodes and the discontinuation of POB therapy if that drug had been started by the primary physician. However, the recommendations were not binding upon the primary service. As a result, on the basis of the preference of some primary physicians, six patients received POB in the week prior to surgery. The total doses given were 50 mg, 60 mg (three patients), 90 mg, and 310 mg. The average preoperative peak systolic pressure in this group of patients was 198 ± 45 mmHg.

Twenty-eight patients received prazosin, 1 mg to 2 mg tid, to control extreme rises of blood pressure. The average peak systolic blood pressure recorded in this group of patients was 225 ± 41 mmHg.

The remaining 29 patients received neither POB nor prazosin. The average peak systolic blood pressure for this group (205 ± 47 mmHg) was not significantly different from average peak pressures in the prazosin group.

Ten patients also received small doses of calcium channel blockers or other nonspecific antihypertensive drugs, and 10 patients received beta-adrenergic blocking drugs.

Preoperative fluid therapy during the 48 hours prior to surgery consisted of an average of 1,291 ± 172 mL intravenous crystalloids over and above normal oral intake. Thirty patients received an average of 638 ± 35 mL packed red cells and 21 patients (all operated on before June 1985) received an average of 960 ± 26 mL whole blood. Twelve patients received no blood before surgery.

Preoperative hematocrit values were between 35% and 45% for 31 patients, greater than 45% for 19 patients (including 2 over 50%), and less than 35% for 13 patients.

Narcotics, benzodiazepines, and atropine were used as preoperative medications in addition to the drugs noted above.

Intraoperative management

The choice of monitoring techniques, anesthetic agents and techniques, muscle relaxants, and vasoactive agents was left to the anesthesiologist managing each patient.

Monitoring techniques. All patients were monitored with ECG, direct arterial pressure, and central venous pressure, using electronic equipment. In addition, pulmonary arterial lines were inserted in 13 patients prior to induction of anesthesia.

Anesthetic agents and techniques. Anesthesia was in-

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TABLE 1
PREOPERATIVE AND INTRAOPERATIVE PEAK SYSTOLIC PRESSURES AND HEART RATES

	B P (mmHg)*		H R (beats/min)*	
Group (N)	Preop	Intraop	Preop	Intraop
Prazosin (28)	224.9 ± 41	220.5 ± 33	109 ± 18	117 ± 18‡
POB (6)	197.8 ± 45	197.2 ± 21	100.8 ± 20	149.3 ± 7‡
No alpha blockers (29)	205 ± 47	221.9 ± 63†	102.5 ± 21	118 ± 20‡

* Mean ± SD
† Significantly different from preop values ($p < 0.025$)
‡ Significant difference between three groups ($p < 0.01$)

TABLE 2
OUTCOME FOR ICU PATIENTS

Case	Outcome
2	Hypertension, sodium nitroprusside for 12 hours; discharged 48 hours
10	Mediastinal mass secondary to central venous pressure placement; observed for 24 hours
23	Postop bleeding, reoperated; observed for 72 hours
24	Hypertension, tachycardia; observed for 30 hours
27	Observed for 48 hours
28	Tachycardia, MI ruled out; observed for 48 hours
29	Recovered from anesthesia in ICU; 21 hours
41	Pleural effusion, chest tube placed; 24 hours
48	Pulmonary edema corrected with diuretic, 20 hours*
51	Hypotension; norepinephrine for 72 hours
62	Fever, hypoxia; observed for 48 hours

* This patient received 28.8 mL/kg/h of crystalloids intraoperatively

duced with intravenous agents such as thiopental and various narcotic drugs, alone or in combination. Anesthesia was maintained with enflurane in 38 patients, with isoflurane in 22, and with halothane in 3 patients. All but 4 patients also received nitrous oxide. Muscle relaxants used were pancuronium (37 patients), vecuronium (11), atracurium (6), tubocurarine (4) and mixtures of metocurine, vecuronium, and pancuronium (5). One patient had a peridural block as an adjunct to general anesthesia.

Vasoactive drugs. The use of vasoactive drugs represented the most important facet in the management of these patients. Sodium nitroprusside was used in 46 patients in an average total dose of 16,800 μg (range, 1,000 to 60,000). Nitroglycerin was given intravenously in 36 patients in an average total dose of 13,000 μg (range, 160 to 72,000). Thirty patients received both nitroprusside and nitroglycerin. Six patients received phentolamine in an average dose of 8.8 mg (range, 1.25 to 25). Labetalol was used in 9 patients in a dose range of 2.5 mg to 35 mg. Trimethaphan was used in 3 patients in conjunction with both nitroprusside and nitroglycerin.

Ten patients received no nitroprusside, nitroglycerin, or phentolamine during surgery. Of these, two patients had received POB before surgery (the two highest total doses), six had received prazosin, and the remaining two patients had received neither POB nor prazosin. Anesthetic agents used in this group were enflurane in six patients, isoflurane in 3, and halothane in one.

Beta-adrenergic blocking agents were used to lower heart rates and blood pressures. Propranolol was used in 32 patients in doses ranging from 0.2 mg to 6.8 mg. Esmolol was used in 5 patients.

Vasopressors were used in 19 patients following the removal of the pheochromocytoma tumor. The drugs used included norepinephrine (3 patients; range, 485 mg to 665 mg), ephedrine (7 patients; range, 25 mg to 20 mg), dopamine (5 patients; range, 10 mg to 200 mg), and neosynephrine (10 patients; range, 30 mg to 950 mg). Five patients received more than one vasopressor.

Using paired t test, only the patients who received neither POB nor prazosin showed significant differences between peak systolic blood pressures recorded before and during surgery (*Table 1*). Comparison of pre- and intraoperative peak heart rates showed significant differences only in the group of patients who had received POB. Analysis of variance revealed significant differences between the three groups only in the intraoperative heart rates.

Fluid therapy. Intraoperative fluid intake varied widely. The total intake of crystalloids and colloids combined averaged 16.2 mL/kg/h (range, 4.9 to 43.5). Thirty-three patients received no blood transfusions during surgery and 30 patients received an average of 1,092 ± 719 mL packed red cells.

Anesthesiologists and surgeons. One anesthesiologist anesthetized 29 patients; a second, 12 patients; a third, 6 patients; and 10 anesthesiologists shared the remaining 16 patients. One surgeon operated on 25 patients; a second operated on 12 patients; a third had 7 patients; a fourth, 6 patients; a fifth, 4 patients; and 6 surgeons shared the remaining 9 patients.

Postoperative course

Following surgery, all patients were transferred to the Post-Anesthesia Care Unit (PACU). Of the 57 patients who did not receive POB preoperatively, 48 stayed in the PACU an average of 18.4 hours (range, 4 to 51

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hours), after which all invasive monitoring was discontinued and the patients were discharged to regular hospital units. The remaining 8 patients were transferred to the Intensive Care Unit (ICU) following short stays in the PACU. *Table 2* shows reasons for transfer to the ICU and duration of stay there. Of the 6 patients who had received POB preoperatively, 3 had an average stay in the PACU of 24.6 hours and 3 were admitted to the ICU.

There was minimal use of vasopressors in the PACU, except for the patient who had received the highest dose of POB preoperatively. He required norepinephrine support of his blood pressure for 72 hours. Fifty patients received no vasopressors and of the remaining 12 patients, 4 received dopamine, and one each received neosynephrine, norepinephrine or ephedrine. Forty-nine patients received no vasodilators of any kind and of the remaining 14 patients, 4 received labetalol (5 to 10 mg), 1 received nitroglycerin, nitroprusside, trimethaphan, phentolamine, and verapamil; 6 received nitroprusside for short durations; 2 received apresoline, and 1 used transdermal nitroglycerin and oral isosorbide (Isordil). Three patients received propranolol.

Outcome

Fifty-nine pheochromocytoma patients who underwent a total of 62 surgical procedures were discharged from the hospital after an average postoperative stay of 9.79 days (range, 7 to 23). There were no incidents of stroke. Though ECG and enzyme studies were not routinely performed on these patients in the postoperative period, there were no clinical manifestations of myocardial infarction.

One patient died in the postoperative period of causes unrelated to pheochromocytoma management. The patient was a 42-year old man who had neurofibromatosis diagnosed prior to surgery. He had had a lobectomy for a malignant schwannoma of the lung 9 months prior to admission. On admission, he suffered from progressive lethargy and disorientation as a consequence of extensive intracranial metastatic tumor. He also had an abdominal mass which was diagnosed as pheochromocytoma. Removal of the pheochromocytoma was the initial procedure. During the first 4 days after surgery, the patient made an uneventful recovery and had satisfactory neurological status. However, subsequent neurological deterioration necessitated a craniectomy to partially remove a malignant schwannoma. The patient had progressive respiratory failure and died 41 days after the adrenalectomy.

DISCUSSION

In the absence of controlled studies of large groups of pheochromocytoma patients, the use of alpha-adrenergic blocking agents, particularly POB, has a mostly theoretical pharmacologic basis. The preoperative use of POB was mainly advocated to counteract the effects of the sudden release of massive quantities of catecholamines during surgical intervention.[6,7] Yet, hypertensive crises (defined as systolic blood pressure above 250 mmHg) were reported in most pheochromocytoma patients when the tumor was manipulated, whether or not alpha blockade was used.[2]

Newell and colleagues[8] demonstrated that preoperative adrenergic blockade did not prevent severe intraoperative hypertension and that prolonged periods of preparation were not more effective in preventing intraoperative tachycardia and ventricular arrhythmias. Another theoretical benefit of alpha blockade was the correction of vasoconstriction which was assumed[9] to be responsible for the reduction in blood volume often encountered in pheochromocytoma patients.[10] However, a subsequent study of 18 pheochromocytoma patients showed that most had normal blood and plasma volumes.[11]

The present retrospective study shows that pretreatment with POB or with large doses of prazosin was not required for consistently successful outcomes in the surgical treatment of a large group of pheochromocytoma patients. There were no deaths or clinically documented cerebral or cardiac complications attributable to the lack of preoperative alpha blockade. On the contrary, the absence of POB had several advantages: For example, 80% of the patients required no vasopressors in the PACU, while the rest did so for very short periods of time. Similarly, 79% of the patients received no vasodilators in the PACU.

Another indicator of the benign postoperative course was the short length of stay in the PACU, after which invasive monitoring was discontinued and the patients discharged to regular hospital units. The few patients who required further management in the ICU also had uneventful outcomes. There were no differences in length of stay in the PACU or duration of postoperative hospitalization between patients who received POB or prazosin and those who received no alpha blockers. Another advantage was the short period of hospitalization prior to surgery, which could not have been achieved if long-term alpha adrenergic blockade with POB were routinely used. The optimal duration of POB therapy has been reported to be 10 to 14 days,[2] though

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much longer durations have also been reported.[12]

We could not document any meaningful correlation of anesthetic agents, muscle relaxants, or anesthetic techniques with cardiovascular events (intra- or postoperative) or overall outcome. And, although two anesthesiologists and two surgeons managed more than half of the patients, the other anesthesiologists and surgeons seemed to have had equally favorable results.

We conclude that advances in anesthetic and monitoring techniques and the availability of fast-acting drugs capable of correcting sudden changes in cardiovascular variables and parameters have eliminated the need for the use of POB or other drugs to produce profound and long-lasting alpha blockade in preparing pheochromocytoma patients for the surgical removal of the tumor.

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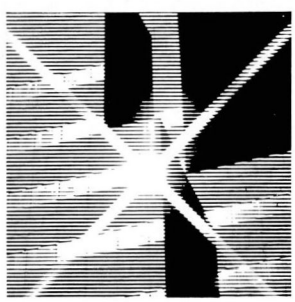

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