Labetalol Pretreatment Reduces Blood Pressure Instability During Surgical Resection of Pheochromocytoma

Peter Chi-Ho Chung, Yuet-Tong Ng, Jing-Ru Hsieh, Min-Wen Yang, Allen Hon-Lun Li*

**Background:** To evaluate the effect of pretreatment with the mixed alpha- and beta-adrenergic blocker, labetalol, on blood pressure instability during surgical resection of pheochromocytoma.

**Methods:** Blood pressure stability and surgical results were compared between patients in the saline (n = 11) and labetalol (n = 15) groups. Anesthesia was induced with fentanyl, sodium thiopental and atracurium, and maintained with isoflurane in a 50% oxygen/nitrous oxide mixture. Intravenous labetalol was administered in the labetalol group before surgical incision, with the maximal dose being 1.2 mg/kg, while normal saline was administered to patients in the control, saline, group. Supplemental intravenous sodium nitroprusside (SNP) infusion was administered whenever systolic blood pressure exceeded 180 mmHg. The number of patients with intraoperative hypertension or hypotension, dosage of SNP administered, number of intraoperative hypertension episodes, use of fluid and blood transfusion, and heart rate (defined as the mean of heart rate every 5 minutes throughout the operation) were compared between these two groups.

**Results:** The number of patients with intraoperative hypertension, number of patients receiving SNP, dose of SNP administered, and number of hypertension episodes were significantly lower in patients who received labetalol pretreatment than in control patients.

**Conclusion:** This study has demonstrated that labetalol pretreatment (1.2 mg/kg) with supplemental SNP provides more favorable blood pressure control during surgical resection of pheochromocytoma than with SNP alone. [J Formos Med Assoc 2006;105(3):189–193]

**Key Words:** anesthesia, hypertension, labetalol, pheochromocytoma, sodium nitroprusside

Pheochromocytoma is a rare catecholamine-producing tumor derived from chromaffin tissues. Intraoperative management of the fluctuating blood pressure caused by catecholamine surge during tumor resection poses a challenge to both surgeons and anesthesiologists with the potential for cardiovascular or cerebrovascular complications. Labetalol, an alpha- and beta-adrenergic blocker, has been used in pheochromocytoma surgery since 1976." However, the concern of potential hypertensive effects after tumor resection may have limited its extensive use. We previously demonstrated that intravenous labetalol (2 mg/kg) administered as a loading dose exclusively prior to tumor resection could minimize hypertensive attack, but with increased risks of hypotension after tumor resection. As preoperative oral antihypertensive medication for hypertensive patients is commonly given with the aim of providing a more stable intraoperative hemodynamic condition, we hypothesized that intravenous labetalol pretreatment could also minimize blood pressure fluctuations and decrease the dose requirement of short-acting vasodilators, such as sodium nitroprusside (SNP), during pheochromocytoma surgery. This study evaluated the effectiveness of...
pretreatment with a lower dose of labetalol (1.2 mg/kg) on perioperative hypertension and hypotension in patients undergoing surgical resection of pheochromocytoma.

Methods

From June 1992 through December 2001, after obtaining approval from our institutional clinical trial committee and informed consent from the involved patients, 26 Taiwanese patients undergoing pheochromocytoma resection and with normal 48-hour in-hospital blood pressure (defined as < 165/90 mmHg) were included in this study. Patients with orthostatic hypotension or tachyarrhythmia after preoperative medical treatment were excluded. The diagnosis of pheochromocytoma was based on clinical signs and positive MIBG (metaiodobenzylguanidine) scintigraphy. Eleven consecutive patients were assigned to the control, saline, group, and another 15 consecutive patients to the labetalol group. Individual antihypertensive agents were prescribed as routine until the morning of surgery. Pathologic proof of pheochromocytoma was eventually obtained in all cases. Twelve of 26 patients (46.7%) had received phenoxybenzamine as antihypertensive medication, and the number of patients who received phenoxybenzamine between the two groups was not significantly different.

No premedication was provided. Fentanyl 100 μg and valium 5 mg were administered intravenously when the patients arrived at the operating theater. Before the induction of anesthesia, a radial artery catheter and a pulmonary arterial catheter were inserted under local anesthesia. Electrocardiography, pulse oximetry and central venous pressure (CVP) were continuously monitored. Anesthesia was induced with intravenous administration of atropine (0.3 mg), fentanyl (3–4 μg/kg), sodium thiopental (4–5 mg/kg) and atracurium (0.6–0.8 mg/kg). After intubation, anesthesia was maintained with isoflurane in a 50% oxygen/nitrous oxide mixture (2:2 L/min). The concentration of isoflurane was kept between 2% and 2.5% at the beginning of anesthesia, at 2.5% during tumor manipulation, and decreased if indicated after tumor resection. Atracurium 5 mg was given every 30 minutes and intermittently as required.

For patients in the saline group (n = 11), normal saline was given before tumor resection while SNP was infused intravenously and titrated to maintain a systolic blood pressure (SBP) < 180 mmHg during tumor manipulation. In the labetalol group (n = 15), a 10-mg bolus of intravenous labetalol was administered intermittently, before the beginning of surgical incision, to attain a maximal dose of 1.2 mg/kg, unless SBP fell below 90 mmHg, mean arterial blood pressure (MAP) below 60 mmHg, or heart rate < 45 bpm. Blood pressure lower than the above criteria or severe bradycardia was managed with fluid challenge, 0.5 mg of atropine and 5 mL of 5% calcium chloride. No further labetalol was administered after the surgical incision had begun. For this group of patients, supplemental SNP infusion was started and titrated only if SBP increased to > 180 mmHg during tracheal intubation or surgical resection of the tumor. After tumor resection, a vasopressor (norepinephrine) was used if MAP fell below 60 mmHg. Throughout the intraoperative period, glucose-sparing crystalloid solution was used for fluid maintenance. Hypoglycemia was corrected with 5% dextrose in saline. Blood transfusion was initiated when blood loss exceeded 500 mL. CVP was maintained between 10 and 12 cmH₂O. Arterial blood gas and serum electrolytes were analyzed hourly throughout the operation and in the postanesthesia care unit. Blood sugar was also measured hourly for 24 hours.

Intraoperative hypertension was defined as SBP > 180 mmHg, and intraoperative hypotension as SBP < 90 mmHg. During surgical resection of pheochromocytoma, the number of patients with intraoperative hypertension or hypotension, and those receiving SNP in the two groups were compared by the chi-square test and likelihood ratio. The dosage of SNP administered, number of intraoperative hypertension episodes, fluid and blood transfusion, and heart rate (defined as the mean
value of heart rate every 5 minutes throughout the operation) between these two groups were also compared by Student’s t test and Fisher’s exact test. A probability value of $p < 0.05$ was considered to be significant.

**Results**

The demographic and perioperative data of the two groups are shown in the Table. Hypertensive episodes occurred in 40% of patients in the labetalol group (total 13 episodes), and 100% of patients in the control, saline, group (total 41 episodes). The number of patients with hypertensive episodes and the number of hypertensive episodes in the labetalol group were both significantly lower than that in the saline group. The heart rate of the patients in the labetalol group was significantly lower than that of the saline group. The number of patients receiving SNP in the labetalol group (40%) was significantly lower than that in the saline group (100%). The mean dose of SNP used in the labetalol group ($n = 6; 2.0 \pm 1.6$ mg) was significantly lower than that used in the saline group ($n = 11; 6.0 \pm 3.7$ mg). This indicates that labetalol pretreatment is effective in managing intraoperative hypertension and reducing the frequency and dose of SNP used during surgical resection of pheochromocytoma.

Substantial blood pressure drop occurred soon after loading in 46.7% of patients in the labetalol group, but blood pressure was immediately restored to normal after fluid challenge and use of medications. No patient in the labetalol group needed SNP during intubation. A vasopressor was used only when hypotension occurred, therefore, the need for vasopressor use after tumor resection was taken to reflect the frequency of hypotensive episodes after tumor resection. The need for vasopressor usage for hypotension (SBP < 90 mmHg) was not significantly different between the two groups (labetalol group, 3/15 patients; saline group, 4/11 patients), indicating that intravenous labetalol given as a loading dose does not aggravate the hypotension that might occur after tumor resection. No patient in the two groups developed hypotension within 24 hours postoperatively.

There was massive intraoperative blood loss due to tearing of the inferior vena cava in two patients (7500 mL and 3500 mL, respectively) in the

<table>
<thead>
<tr>
<th>Table. Patient demographic and perioperative data</th>
<th>Labetalol $(n = 15)$</th>
<th>Saline $(n = 11)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>7/8</td>
<td>5/7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>40.9 ± 13.9</td>
<td>44.3 ± 9.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.1 ± 10.8</td>
<td>56.2 ± 10.4</td>
</tr>
<tr>
<td>Patients with intraoperative hypertension $(n)$</td>
<td>6*</td>
<td>11</td>
</tr>
<tr>
<td>Total hypertensive episodes $(n)$</td>
<td>13*</td>
<td>41</td>
</tr>
<tr>
<td>Hypertensive episodes in patients with intraoperative hypertension $(n)$</td>
<td>2.2 ± 1.6*</td>
<td>3.7 ± 1.2</td>
</tr>
<tr>
<td>Labetalol dose administered (mg)</td>
<td>66.7 ± 19.7</td>
<td>0</td>
</tr>
<tr>
<td>Patients receiving SNP $(n)$</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>SNP dose in patients receiving SNP (mg)</td>
<td>2.0 ± 1.6*</td>
<td>6.0 ± 3.7</td>
</tr>
<tr>
<td>Range of SNP dose administered (mg)</td>
<td>0.8–5</td>
<td>2–15</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>73.3 ± 11.2*</td>
<td>103.2 ± 15.5</td>
</tr>
<tr>
<td>Patients with hypotension before tumor resection $(n)$</td>
<td>7*</td>
<td>0</td>
</tr>
<tr>
<td>Patients with hypotension during tumor resection $(n)$</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Patients with hypotension within 24 hr after operation $(n)$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Crystalloid administered (mL)</td>
<td>3816 ± 1203</td>
<td>3652 ± 1546</td>
</tr>
<tr>
<td>Blood transfused (pRBC, units)</td>
<td>3.7 ± 5.4</td>
<td>2.2 ± 1.4</td>
</tr>
</tbody>
</table>

*$p < 0.05$ vs. saline group. pRBC = packed red blood cells; SNP = sodium nitroprusside.
labetalol group. One of these patients died the following day due to intractable bleeding. The volume of fluid administered and blood transfused during operation was not significantly different between the two groups (Table). Three patients in the labetalol group and none in the saline group developed postoperative hypoglycemia after tumor resection. No neurologic deficit or mortality related to anesthesia occurred.

Discussion

This study demonstrated that 1.2 mg/kg labetalol pretreatment reduces the incidence of hypertensive episode and the requirement for SNP during surgical resection of pheochromocytoma. More importantly, we demonstrated that labetalol, at 1.2 mg/kg bolus dose, is associated with minimal risk of postoperative hypotension as shown in a previous study. Although the sample size was small, partly due to the low incidence of pheochromocytoma, and, thus, did not permit a randomized approach, the effect of labetalol pretreatment on suppressing hypertension during pheochromocytoma surgery could still be evaluated. Fewer patients in the labetalol group exhibited hypertensive episodes, and patients in this group had more stable heart rates. This indicates that labetalol pretreatment with adjuvant SNP exerts better control on blood pressure instability than SNP alone in surgical resection of pheochromocytoma.

There have been many reports on the management of intraoperative hemodynamic changes with different antihypertensive agents during pheochromocytoma resection. Short acting agents were generally considered to be superior to long-acting ones because their antihypertensive effect subsides sooner, which may be considered beneficial, especially once the tumor has been resected. The availability of labetalol, which has alpha- and beta-adrenergic blocking effects, had provided an alternative choice of antihypertensive agent during resection of pheochromocytoma. Kaufman first reported its use in an intermittent intravenous bolus manner during such surgeries in 1979. However, due to its long half-life (3–4 hours) and the potential for hypotensive effects after tumor resection, labetalol use for the management of hypertension is not common during pheochromocytoma surgery, and it is generally administered only at the initiation of anesthesia, as in our hospital, to avoid the aggravation of blood pressure drop after tumor resection, which usually occurs 2–3 hours after operation. In our previous study, a total labetalol dose of 2 mg/kg was used, but resulted in a notable blood pressure drop soon after administration. Therefore, the total dose of labetalol was reduced to 1.2 mg/kg in this study. From our results, the need for vasopressor usage after tumor resection in the labetalol group was not significantly different from that in the saline group, and no patients in the labetalol group had hypotension within 24 hours postoperatively (except for one patient who suffered from intractable bleeding after tumor resection). This indicated that labetalol pretreatment given only at the initiation of anesthesia does not aggravate the hypotension which usually occurs after tumor resection, which is compatible with the results of our previous study. Although seven patients had obvious blood pressure drop soon after labetalol loading, the blood pressure was soon restored to normal after fluid challenge and the use of medications such as atropine or calcium. As the duration is more crucial than the frequency of hypotensive episodes, and since there were no cerebrovascular sequelae in the postoperative period, we considered those episodes as being not clinically hazardous.

Although phenoxybenzamine was given preoperatively in the majority of patients in this series, oral antihypertensive agents such as beta-blockers, angiotensin-converting enzyme inhibitors, labetalol, isordil, calcium channel blockers and rigitine were also used. A mean blood pressure of 50–60% of the 24-hour inhospital mean blood pressure was considered safe in maintaining autoregulation of blood flow to the brain and other vital organs. The 24-hour inhospital blood pressure of the patients scheduled for surgical resection of pheochro-
Pheochromocytoma was required to be < 165/90 mmHg in this study, and the lowest safe limit of blood pressure for patients in this study was set at 90 mmHg for SBP, or 55–65 mmHg for MAP. It has been reported that resection of pheochromocytoma may induce postoperative hypoglycemia due to increased insulin production. Since blockade of alpha-adrenoceptors may reverse insulin suppression and blockade of beta-adrenoceptors reduces muscle glycogenolysis and lipolysis, labetalol may theoretically induce hypoglycemia and aggravate hypoglycemia after tumor resection. This hypothesis was not supported in our previous study of hysterectomy, which found that high-dose intravenous labetalol did not induce hypoglycemia. Although for pheochromocytoma, the output of catecholamines also influences glucose regulation, the low incidence (18%, 3/16 patients) of postoperative hypoglycemia after tumor resection in the labetalol group suggested that this is partly caused by tumor removal and may not solely be attributed to labetalol. Our data are also in agreement with those of Orchard et al, which showed no anesthesia-related mortality.

In conclusion, this study has clearly demonstrated that labetalol pretreatment with supplemental SNP markedly reduces the hypertensive attack associated with surgical resection of pheochromocytoma. With a loading dose of 1.2 mg/kg, labetalol pretreatment was associated with minimal hypotensive episodes before tumor resection and did not lead to any hypotension after tumor resection. These findings suggest that labetalol pretreatment (1.2 mg/kg) is ideal for patients undergoing pheochromocytoma resection.

References