Effects of Hydralazine Pretreatment on Esmolol-induced Controlled Hypotension during Spine Surgery

Department of Anesthesiology, Seoul National University College of Medicine, Seoul, Korea

Kum Suk Park, M.D., Young Jin Roh, M.D., Jong Su Kim, M.D., and Sang Hwan Do, M.D.

Background: Controlled hypotension improves surgical field and decreases transfusion requirement in surgical patients and can be induced with various kinds of drugs including esmolol and hydralazine.

Methods: This study examined the effect of a combination of esmolol and hydralazine as hypotensive agents in spine surgery. In the esmolol group (n = 15), after boluses of esmolol (0.5 mg/kg) injection, esmolol was infused to maintain the mean arterial pressure of 55-65 mmHg. In the hydralazine-esmolol group (n = 15), hydralazine (0.3 mg/kg) was administered 15 minutes before esmolol injection which was done in the same way as that of the esmolol group.

Results: The mean arterial pressure decreased to the target range more rapidly in the hydralazine-èsmolol group. The heart rate was increased by hydralazine, but reduced by esmolol. The cardiac output remained elevated after hydralazine injection in the hydralazine-èsmolol group, and decreased significantly by esmolol in the esmolol group. The administered dose of esmolol was much less in the hydralazine-èsmolol group than in the esmolol group.

Conclusions: Our data suggest that hydralazine can enhance the efficacy of esmolol-induced controlled hypotension. It can reduce the requirement of esmolol and maintain a higher cardiac output during hypotension. (Korean J Anesthesiol 2006; 50: S 31–5)

Key Words: controlled hypotension, esmolol, hydralazine.

INTRODUCTION

Controlled hypotension (CH) improves the quality of the surgical field by reducing the amount of intraoperative blood loss and decreases the perioperative transfusion requirement. A variety of drugs have been used to induce CH, including β-adrenergic blockers, vasodilators and inhaled anesthetics. Esmolol is one of the most commonly used β-adrenergic blockers in the anesthesia field because its rapid onset and short duration make it easy to titrate. Moreover, esmolol was reported to be superior to nitroprusside as a hypotensive agent because it produces a better surgical field and less intraoperative hemorrhage. However, esmolol elevates the systemic vascular resistance (SVR) and a large dose of esmolol can cause a dangerous level of myocardial depression. Hydralazine decreases the blood pressure by arterial vasodilation. Although it is simple and economical to use, reflex tachycardia, slower onset and longer duration may be regarded as its disadvantages.

We hypothesized that hydralazine may offset some of the shortcomings associated with the use of esmolol during CH (myocardial depression, elevated systemic vascular resistance etc.). This study examined the effect of a hydralazine pretreatment on the hemodynamic change and clinical outcome associated with esmolol-induced CH.

MATERIALS AND METHODS

After approval of the Ethics Committee of our institution, written informed consents were obtained from the 15-65 year old patients, a total of 30 patients who received posterior spinal fusion under a diagnosis of spinal stenosis or scoliosis. Patients with cardiopulmonary disease, cerebrovascular disease, anemia, bleeding tendency or diabetes were excluded. The pa-
tients enrolled in this study were randomly assigned to receive either esmolol (E group, n = 15) or esmolol plus hydralazine (HE group, n = 15). Two surgeons, who were blind to which group the patient was assigned, performed all of the surgical procedures.

The patients were premedicated with oral midazolam 7.5 mg 30 minutes before arriving at the operating theatre. Two anesthesiologists were in charge of the anesthetic management. Anesthesia was induced with thiopental 5 mg/kg, vecuronium 0.1 mg/kg and fentanyl 2 μg/kg, and maintained with nitrous oxide (50%) and isoflurane. After tracheal intubation, no opioid was used and ventilation was controlled in order to maintain a PaCO2 between 35-40 mmHg. The radial artery and internal jugular vein were cannulated, and the Foley catheter was placed. A transesophageal Doppler ultrasound probe (CardioQ™, Deltex, UK) was inserted to monitor the cardiac output (CO).

All patients were provided with lactated Ringer’s solution 10 ml/kg intravenously until the beginning of CH, and then intravenous fluids were titrated to maintain a urine output of 0.5-1.0 ml/kg/hr. Using the randomization card method, patients were randomly divided into two groups (E group and HE group). In the E group, the method inducing hypotension was same as that of our previous study3). Esmolol (Brevibloc®, Jeil pharmaceutical, Seoul, South Korea) 0.5 mg/kg was injected repeatedly at 1-minute intervals until the systolic blood pressure went below 90 mmHg. Subsequently, esmolol was infused continuously in order to maintain the target mean arterial pressure (MAP, 55-65 mmHg). In the HE group, 15 minutes before administering the esmolol, hydralazine (Samjin Pharmaceutical, Seoul, South Korea) 0.3 mg/kg was injected intravenously over 1 minute, and then CH was induced and maintained as in the E group. In both groups, end-tidal concentration of isoflurane was fixed at 1 MAC (1.2 vol%) during the hypotensive period and esmolol was discontinued when the main operative procedure was complete.

MAP, heart rate (HR) and CO were measured immediately before injecting the hydralazine (HE group) and esmolol (both group). The above variables were also recorded 5, 10, 15, 30, 60, 90 minutes after the bolus injection of esmolol, and 5, 10, 15 minutes after discontinuing the esmolol. The total amount of esmolol administered was also recorded. The urine output, the amount of colloid and crystalloid fluid infused during anesthesia were calculated by the patient’s body weight per hour. The amount of intraoperative blood loss was estimated by measuring the volume of blood in the suction-trap bottle and by weighing the gauzes. The amount of blood loss was replaced with homologous packed RBC when the hemoglobin level was decreased below 7.0 g/dl. The amount of intraoperative blood loss and transfused units of each blood products were compared between two groups.

Hemodynamic data (MAP, HR, CO) were compared within each group and between the two groups using repeated measures of ANOVA. In within-group comparison, the control value was set at the one, which was checked immediately before the esmolol injection. The other data of the two groups were compared using the Mann-Whitney U-test. Data are mean ± SD. A P value < 0.05 was considered significant.

RESULTS

The patients’ characteristics were presented in Table 1. The preoperative hemoglobin level, the duration of CH and the anesthesia time were similar in both groups. The amount of intraoperative blood loss, the transfused units of packed RBC, urine output, and the total fluid volume were also comparable between the two groups. Fresh frozen plasma was transfused in one patients in the HE group (5 units) and in two patients in the E group (2 and 5 units respectively). Platelet concentrates was transfused only in one patient of the HE group (10 units). The bolus or infused dose of esmolol was much lower in the HE group than in the E group (P < 0.05, Table 2).

In the HE group, the MAP was decreased significantly after the hydralazine injection (Fig. 1, P < 0.05) and reached the target range within 5, 10 and 15 min after the esmolol in-

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>HE group (n = 15)</th>
<th>E group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>6/9</td>
<td>7/8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47 ± 17</td>
<td>44 ± 12</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58 ± 9</td>
<td>61 ± 8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159 ± 7</td>
<td>163 ± 10</td>
</tr>
<tr>
<td>No. of spinal segment</td>
<td>2.6 ± 3.1</td>
<td>2.1 ± 1.7</td>
</tr>
<tr>
<td>Spinal stenosis/scoliosis</td>
<td>13/2</td>
<td>14/1</td>
</tr>
<tr>
<td>Duration of CH (min)</td>
<td>185 ± 78</td>
<td>187 ± 108</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>288 ± 130</td>
<td>280 ± 133</td>
</tr>
<tr>
<td>Preoperative hemoglobin (g/dl)</td>
<td>13.9 ± 1.6</td>
<td>13.8 ± 2.0</td>
</tr>
</tbody>
</table>

The values are mean ± SD. HE group: hydralazine- esmolol group, E group: esmolol group, CH: controlled hypotension. There were no significant differences between the two groups.
jection in 9 (60%), 12 (80%) and 13 (87%) patients out of 15 patients, respectively. In the E group, the MAP decreased after the esmolol injection showing a statistical significance after 5 min. However, the MAP reached the target range at 5, 10, 15 min after the esmolol injection in 5 (33%), 6 (40%), and 12 (80%) patients out of 15 patients, respectively. Overall, the MAP was significantly higher until 10 min after the esmolol infusion in the E group than in the HE group (Fig. 1, \( P < 0.05 \)). MAP was slightly recovered after discontinuing the esmolol but not up to the initial level (before esmolol or hydralazine injection) 15 min after the discontinuation in both groups.

**Table 2. Amount of Esmolol Administered and the Amount of Fluid, Blood Loss and Urine Output during Surgery**

<table>
<thead>
<tr>
<th></th>
<th>HE group (n = 15)</th>
<th>E group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose of esmolol (mg/kg)</td>
<td>0.5 ± 0.6*</td>
<td>1.2 ± 0.9</td>
</tr>
<tr>
<td>Infused dose of esmolol (µg/kg/min)</td>
<td>24 ± 13*</td>
<td>64 ± 42</td>
</tr>
<tr>
<td>Crystallloid administered (ml/kg/hr)</td>
<td>15.5 ± 7.6</td>
<td>17.1 ± 5.9</td>
</tr>
<tr>
<td>Colloid administered (ml/kg/hr)</td>
<td>2.6 ± 1.5</td>
<td>1.7 ± 1.1</td>
</tr>
<tr>
<td>Estimated blood loss (ml/kg/min)</td>
<td>0.06 ± 0.04</td>
<td>0.07 ± 0.04</td>
</tr>
<tr>
<td>Transfused units of packed RBC</td>
<td>1.7 ± 4.4</td>
<td>1.4 ± 2.8</td>
</tr>
<tr>
<td>No. of patients (transfused/non-transfused)</td>
<td>5/10</td>
<td>4/11</td>
</tr>
<tr>
<td>Urinary output (ml/kg/hr)</td>
<td>1.4 ± 1.0</td>
<td>1.6 ± 1.3</td>
</tr>
<tr>
<td>Postoperative hemoglobin (g/dl)</td>
<td>11.2 ± 1.9</td>
<td>11.4 ± 1.9</td>
</tr>
</tbody>
</table>

The values are mean ± SD. HE group: hydralazine- esmolol group, E group: esmolol group. *\( P < 0.05 \) compared with the E group.

**Fig. 1.** Comparison of the mean arterial pressure between the two groups. In most of the patients of HE group (80%), the MAP reaches the target range (55-65 mmHg) within 15 minutes after infusing the esmolol, however it takes more than 15 minutes in the E group. After discontinuing the esmolol, the MAP is restored to the baseline MAP (immediately before esmolol injection) in the HE group but not in the E group. The gray arrow means the beginning of esmolol and the black arrow means the discontinuation of esmolol. MAP: mean arterial pressure, HDR: administration of hydralazine. E group: esmolol group, HE group: hydralazine- esmolol group. *\( P < 0.05 \) vs E group. ^\( P < 0.05 \) vs baseline MAP (immediately before esmolol injection).

**Fig. 2.** Comparison of the heart rate between the two groups. In the HE group, the HR is increased by hydralazine (\( P < 0.05 \)) and maintained at a higher level than that of the E group (\( P < 0.05 \)). It is decreased by esmolol during controlled hypotension in both groups (\( P < 0.05 \)). The HR increases up to the baseline after the cessation of esmolol in both groups. The gray arrow means the beginning of the esmolol and black arrow means the discontinuation of esmolol. HR: heart rate, HDR: administration of hydralazine. E group: esmolol group, HE group: hydralazine- esmolol group. *\( P < 0.05 \) vs E group. ^\( P < 0.05 \) vs baseline HR (immediately before esmolol injection).

**Fig. 3.** Comparison of the cardiac output between the two groups. In the HE group, the cardiac output is increased by hydralazine and maintained at a higher level than that of the E group (\( P < 0.05 \)). It is decreased by esmolol during controlled hypotension in the E group (\( P < 0.05 \)). It is not changed by esmolol in the HE group. The gray arrow means the beginning of esmolol and the black arrow means the discontinuation of esmolol. CO: cardiac output, HDR: administration of hydralazine. E group: esmolol group, HE group: hydralazine- esmolol group. *\( P < 0.05 \) vs E group. ^\( P < 0.05 \) vs baseline CO (immediately before esmolol injection).
In the HE group, the HR was increased significantly after the hydralazine injection (Fig. 2, \(P < 0.05\)). It was maintained higher than that of the E group at every time point (\(P < 0.05\)). In both groups, the HR was significantly decreased after the esmolol injection (Fig. 2, \(P < 0.05\)), but it recovered to a level where no statistical significance could be observed after discontinuing the esmolol.

Similar to the change pattern in the HR, the CO was increased significantly after the hydralazine injection in the HE group (Fig. 3, \(P < 0.05\)). However, it did not show significant changes during and after the esmolol infusion. It was also maintained at a higher level than that of the E group at every time point (\(P < 0.05\)). In the E group, the CO was reduced significantly during the esmolol infusion (Fig. 3, \(P < 0.05\)) and recovered after discontinuing the esmolol.

**DISCUSSION**

Nitroprusside has been the hypotensive agent of choice owing to its rapid, short and controllable action.\(^{12}\) However, it has many shortcomings including reflex tachycardia, platelet dysfunction and systolic pressure variations.\(^{13}\) Tachycardia should be avoided during CH because it may be a warning sign of an inadequate intravascular volume and can compromise the myocardial oxygen balance.\(^{14}\) In addition, the systolic pressure variation resulting from the increased plasma renin activity may lead to an increased amount of intraoperative haemorrhage.\(^{15}\) Recently, some investigators advocated the use of \(\beta\)-blockers over nitroprusside because \(\beta\)-blockers can avoid the problems associated with the use of nitroprusside.\(^{1,2,7}\) Although esmolol is favored over other \(\beta\)-blockers owing to its rapid onset and ultrashort action, it can cause an excessive reduction in the CO and a significant increase in the SVR, which might result in an oxygen imbalance in the vital organs.\(^{8,9}\) This unfavorable situation may be evaded with the combined use of hydralazine and esmolol to maintain the CO much higher, which is evident in the Fig. 3.

Decrease in the CO by esmolol results principally from a significant reduction in the HR.\(^{10}\) Since any negative inotropic action of a \(\beta\)-blocker is accompanied with a longer diastolic time and greater ventricular filling, a \(\beta\)-blocker leads to a minor reduction in the stroke volume compared with the HR. In addition, it is interesting to note that the ultra-short action of esmolol is limited to its effect on the chronotropic effect, but not on the inotropic effect. The length of time required for the 90% maximum decrease after esmolol administration was 4.8 ± 3.0 minutes for the HR and 42.5 ± 8.9 minutes for the MAP.\(^{16}\) This differential rapidity of the two actions of esmolol may explain the discrepancy in the recovery rate between HR and MAP following discontinuation of esmolol. Whereas the HR was recovered up to the control level 5-10 min after discontinuing the esmolol in both groups, the MAP was not recovered until 15 min (Fig. 1 and Fig. 2). (In most cases, the surgical procedure was complete and the patient was awakened from anesthesia within 30 min after the CH. Thus, the 15-min data were the last set of data obtained.) After the discontinuation of esmolol in both groups, it appears that gradual increase in the myocardial contractility coupled with the reversal of the increase in the SVR results in the slow increase in the MAP (Fig. 1). However, the slow recovery of the MAP after the discontinuation of esmolol would not cause harm to tissue perfusion because the CO increases rapidly (Fig. 3).

In this study, there were marked differences in the CO between the two groups. While the CO decreased significantly during esmolol infusion in the E group, it did not change significantly after esmolol administration in the HE group. In the HE group, the increase in the CO due to an afterload reduction by hydralazine appeared to be offset by the action of esmolol. It should be noted that the amount of intraoperative bleeding and transfusion was similar in both groups despite the marked differences in the CO. It is still unclear whether the CO influences the amount of intraoperative blood loss during CH.\(^{17,18}\) However, the results of the current study indicate that hydralazine can be effectively combined with esmolol to induce CH. Although the effect on the microcirculation was not investigated, the increased CO in the HE group may play a role in maintaining microcirculation during CH.

The esmolol dose used in this study was much less than those reported in other studies. Blau et al. reported that 160 \(\mu\)g/kg/min of esmolol was required to maintain hypotension,\(^{5}\) which is much greater than that used in this study (64 ± 42 \(\mu\)g/kg/min in the E group, 24 ± 13\(\mu\)g/kg/min in the HE group) or in a previous study (77 ± 9\(\mu\)g/kg/min).\(^{11}\) The subjects’ characteristics such as ethnicity and/or age might have contributed to this discrepancy.

In summary, hydralazine pretreatment enhanced the efficacy of esmolol-induced CH. Hydralazine could facilitate the onset of esmolol-induced hypotension and reduce the requirement of esmolol without decreasing the CO during CH. Overall, esmolol
and hydralazine appears to be a useful combination regimen for CH in spine surgery.

REFERENCES


