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Clinical trial of esmolol-induced controlled hypotension with or without acute normovolemic hemodilution in spinal surgery

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Background: Drug-induced controlled hypotension (CH) combined with acute normovolemic hemodilution (ANH) is being widely used for blood conservation in surgical patients. The purpose of this study was to investigate the efficacy and safety of esmolol-induced CH combined with ANH (hematocrit down to 28%).
Methods: Thirty patients who were scheduled to receive spinal surgery were randomly divided into two groups: an esmolol-induced CH alone group (esmolol group, n=15) and a CH-ANH combined group (E-ANH group, n=15). Controlled hypotension was induced with esmolol 500 μg/kg, followed by a continuous infusion of 0–300 μg/kg/min to maintain mean arterial pressure at 55–65 mmHg.
Results: The mean infusion rate of esmolol in the esmolol-ANH group was 46±6 μg/kg/min (mean±SD), which was significantly lower than the 77±9 μg/kg/min used in the esmolol group ($P<0.05$). The number of units of homologous blood (packed RBC) transfused perioperatively was 2.2±0.6 units in the esmolol-ANH group, which was significantly less than 4.3±0.4 units used in the esmolol group ($P<0.01$). While O_2 delivery decreased significantly during CH, O_2 consumption remained unchanged in both groups. No complications resulted from CH or ANH in any of the groups.
Conclusion: Our data suggest that ANH of moderate degree can be combined with esmolol-induced CH to improve blood conservation in surgical patients.

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Key words: acute normovolemic hemodilution; blood conservation, controlled hypotension; esmolol; spinal surgery.

Drug-induced controlled hypotension (CH) has been widely used to reduce intraoperative blood loss and the requirement for a homologous transfusion. It also has its advantage in providing improved quality of the surgical field (drier field). Esmolol is a selective beta-1 blocker with a brief duration of action ($T^1/_2$; 9 min). Its usefulness has been demonstrated in orthognathic and functional sinus surgery (1,2).

Acute normovolemic hemodilution (ANH), which is the most economical and simple method of an autotransfusion, has the beneficial effects of providing rich coagulation factors and platelets (3–5). In order to maximize the effects of blood conservation and to minimize requirements for a homologous transfusion, ANH is being used increasingly in combination with CH (6–8). The most serious concern about combining CH and ANH is the risk of reduced oxygen delivery. Esmolol decreases cardiac output (CO), thus it may abolish the main compensatory mechanism of ANH (increase in CO). Because an imbalance between O_2 delivery and consumption may cause tissue hypoxia, studies on O_2 balance as well as systemic hemodynamics are necessary before a combined method of esmolol-induced CH and ANH can be considered for clinical use.

Although safety and efficacy of CH induced by agents other than esmolol have been well established in spinal surgery (6,9,10), esmolol-induced CH has not been studied either in spinal surgery or in combination with ANH. We therefore undertook this study to investigate whether the combined use of esmolol-induced CH and ANH could improve the efficacy of blood conservation compared with esmolol-induced CH alone, and whether this combined technique could be applied safely to surgical patients without cardiovascular disease.

Work was carried out at Seoul National University Hospital, Seoul, Korea.

Methods

After obtaining institutional approval of the study protocol and written informed consents from all patients, a total of 30 patients (ASA physical status I or II) who received posterior decompression and instrumental fusion under a diagnosis of spinal stenosis or spondylolisthesis were enrolled in this study. Exclusion criteria included: (1) greater than 65 years of age; (2) history of hypertension or other cardiovascular disease; (3) history of adverse reaction to beta blockers; (4) preoperative hemoglobin (Hb) level below 12 g%; (5) history or laboratory data suggesting an abnormal bleeding tendency; and (6) positive carotid bruit on auscultation. The same surgeon conducted all operations. Given the known benefits of CH in spinal surgery (9), we did not include a normotensive control group in order to avoid subjecting those patients to the risk of unnecessary high intraoperative blood loss and the possibility of a homologous transfusion later on.

Patients were randomly divided into two groups: an esmolol group (n=15) and an esmolol-ANH (E-ANH) group (n=15). In both groups, CH was performed using esmolol, and in the E-ANH group ANH was performed before CH. Besides routine intraoperative monitoring, a radial artery cannula was placed before induction of anesthesia with thiopental (5–6 mg/kg IV), vecuronium (0.15 mg/kg IV) and fentanyl (1.5–2 μg/kg IV). A urinary catheter was used to quantify urine output as a guide to fluid therapy. Anesthesia was maintained with N_2O (50%) and isoflurane with incremental doses of vecuronium as required, and ventilation was adjusted to an end-tidal CO_2 tension of 35–38 mmHg. After tracheal intubation, a pulmonary artery catheter was threaded through the right internal jugular vein. Cannulation was successful in 24 patients (12 patients in each group). Patients were positioned prone on a formed pad (Bardeen chest pad) to minimize abdominal compression. Intravenous fluids were titrated to maintain a urine output of 0.5–1.0 ml/kg/h.

Controlled hypotension was performed during the period of bony decompression and instrumental fusion of the spine. Following an initial bolus injection of esmolol 500 μg/kg (up to 2–3 times at intervals of 1 min if necessary), esmolol was continuously infused at a rate of 0–300 μg/kg/min to bring the mean arterial pressure (MAP) down to the target level of 55–65 mmHg. During CH, opioids were not used and the concentration of isoflurane was set at 1%.

In the E-ANH group, autologous blood was removed from the radial artery and collected in 320-ml blood salvage bags immediately after arterial cannula placement. The volume of blood to be removed (V) was calculated using the following formula:

$V = EBV \times ?(H_i - H_f)/H_{av}$[1], where EBV is the patient's estimated blood volume (male, 70 ml/kg; female, 65 ml/kg), H_i is the patient's initial hematocrit (Hct), H_f is the patient's final Hct after ANH, and H_{av} is the average Hct (average of H_i and H_f). The H_f was set at 28%. To maintain normovolemia during ANH, the first 500 ml of blood drawn was simultaneously replaced with an equal amount of 6% hydroxyethyl starch, and the blood removed thereafter was replaced with three times that volume of Lactated Ringer's solution. When the intraoperative Hct fell below 20%, the transfusion was started and a postoperative transfusion was administered at the discretion of the surgeon who was blinded to the study. In the E-ANH group, the autologous blood was used before the homologous blood.

The number of blood units (including the autologous blood) transfused intra- and postoperatively and the amount of intraoperative blood loss were recorded and compared between the two groups. Mean arterial pressure, heart rate (HR), cardiac output (CO), arterial O_2 saturation (S_aO_2) and mixed venous O_2 saturation (S_vO_2) were measured immediately before ANH and CH (control value), 30 and 60 min after CH, as well as at 15 min following the discontinuation of the esmolol infusion. Oxygen delivery, consumption and extraction ratios were calculated using the following equations:

O_2 delivery $(ml/min) = CO \times C_aO_2 \times 10$[2]$O_2$ consumption $(ml/min) = CO \times (C_aO_2 - C_vO_2) \times 10$[3]$O_2$ extraction ratio $(\%) = (O_2$ consumption$/O_2$ delivery$) \times 100$[4]C_aO_2 $(vol\%) = 1.34 \times Hb \times S_aO_2 + 0.0031 \times P_aO_2$[5]$C_vO_2$ $(vol\%) = 1.34 \times Hb \times S_vO_2 + 0.0031 \times P_vO_2$[6], where C_aO_2 indicates arterial O_2 content and C_vO_2 indicates mixed venous O_2 content.

Data are mean±SEM. The variables over time such as MAP, HR, CO, S_vO_2, O_2 delivery, O_2 consumption and O_2 extraction ratio were evaluated statistically between the two groups by using repeated measures analysis of variance. If necessary, multiple comparisons were made using Bonferroni's *t*-test. The other variables were compared between the two groups using the Student's *t*-test. A $P<0.05$ was considered significant.

Results

There were no significant differences in demographic data between the two groups. The number of vertebral levels for instrumental fusion, duration of anes-

thesia or CH and initial Hct were not different significantly between the two groups (Table 1).

There was no significant difference in the amount of intraoperative (1500±180 ml in the esmolol group, 1600±160 ml in the E-ANH group, $P>0.05$) or postoperative bleeding (883±122 ml in the esmolol group, 600±96 ml in the E-ANH group, $P>0.05$). After 1 week, Hb was 11.3±0.2 g% in the esmolol group and 11.3±0.3 g% in the E-ANH group ($P>0.05$). In the E-ANH group, 717±50 ml of autologous blood was procured. Immediately after ANH, Hct decreased from 40±1 to 28±1%. All autologous blood was returned to the patients. In the E-ANH group, no homologous blood was required in five patients (33% of the total patients). In the esmolol group, however, every patient required a homologous blood transfusion. The number of units of homologous blood (packed red blood cells) used perioperatively was 2.2±0.6 units in the E-ANH group, which was significantly less than 4.3±0.4 units used by the esmolol group ($P<0.01$). There was no significant difference in the total amount of the transfusions (including autologous and homologous blood) between the two groups (1387±128 ml in the esmolol group, 1419±168 ml in the E-ANH group, $P>0.05$).

Controlled hypotension down to the target range was rapidly and successfully produced with esmolol in both groups (Fig. 1). During CH, the mean infusion rate of esmolol was 46±6 μg/kg/min in the E-ANH group, which was significantly lower than the 77±9 μg/kg/min required by the esmolol group ($P<0.05$). In the E-ANH group, MAP decreased, but CO increased significantly after ANH (Figs 1 and 2). Between the two groups, no significant differences were found in the change patterns of all of the hemodynamic variables (MAP, HR, CO, O_2 delivery, O_2 consumption, O_2 extraction ratio and S_vO_2 etc.). Heart rate decreased after esmolol infusion and recovered up to the initial values after discontinuation of esmolol (Fig. 1). In both groups, CO decreased significantly at 30 min and 60 min after the esmolol infusion. However, 15 min after discontinuation of esmolol, CO recovered up to a level of the control value (immediately before esmolol administration) in the esmolol

Table 1

Patients' clinical characteristics.

	Esmolol group (n=15)	E-ANH group (n=15)
Sex (male/female)	8/7	9/6
Age (year)	48±4	50±3
Weight (kg)	53±3	60±2
Height (cm)	161±3	160±2
No. of spinal segment	2.3±0.4	2.0±0.5
Duration of anesthesia (min)	239±12	238±15
Duration of controlled hypotension (min)	153±14	125±8
Initial hematocrit (%)	40±1	40±1

Values are mean±SEM or numbers of patients.
E-ANH: esmolol-induced controlled hypotension combined with acute normovolemic hemodilution.

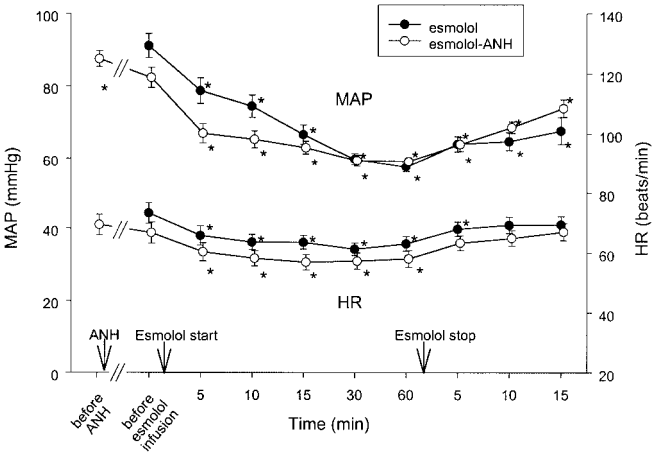

*Fig. 1. Changes in mean arterial pressure (MAP) and heart rate (HR) during esmolol-induced controlled hypotension alone (esmolol group) and combined with acute normovolemic hemodilution (esmolol-ANH group). Values are mean±SEM. *P<0.05 vs. the value measured immediately before the esmolol infusion. No differences were found between the two groups.*

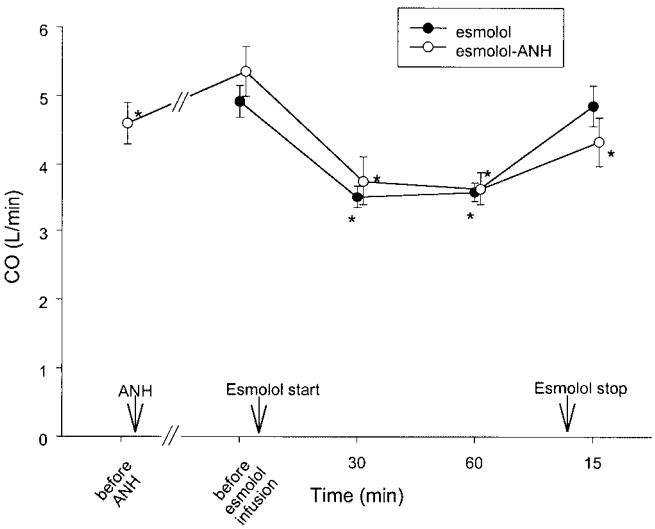

*Fig. 2. Changes in cardiac output (CO) during esmolol-induced controlled hypotension (esmolol group) alone and combined with acute normovolemic hemodilution (esmolol-ANH group). Cardiac output increased significantly after ANH, and decreased significantly after esmolol infusion in both groups. Values are mean±SEM. *P<0.05 vs. the value measured immediately before the esmolol infusion. No differences were found between the two groups.*

group (Fig. 2). Whereas O_2 delivery showed a significant decrease during esmolol administration, O_2 consumption remained unchanged throughout the study period (Fig. 3). Oxygen extraction ratios increased significantly after the esmolol infusion (Fig. 4). Mixed venous O_2 saturation decreased significantly after the esmolol infusion, but all measurements were equal to or greater than 70 mmHg. From the serial arterial blood gas profile, acidosis (arterial pH<7.35) or increased base deficit (>3 mmol/l) was not found throughout the study period. All patients were evaluated 1 week after the operation, and there were no postoperative complications (thromboembolism, neurologic sequelae or wound infection) in either group.

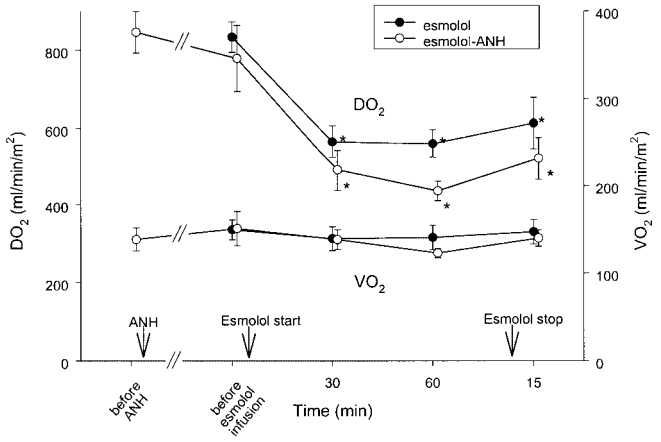

*Fig. 3. Changes in O_2 delivery and O_2 consumption during esmolol-induced controlled hypotension (esmolol group) alone and combined with acute normovolemic hemodilution (esmolol-ANH group). After the esmolol infusion, O_2 delivery decreased, while O_2 consumption remained unchanged. *P<0.05 vs. the value measured immediately before the esmolol infusion. No differences were found between the two groups.*

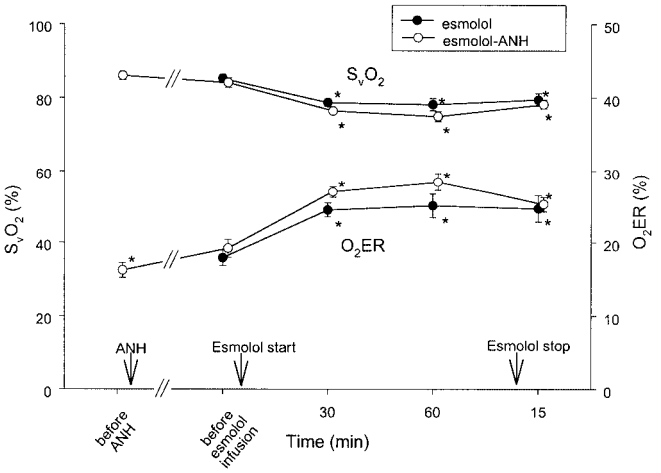

*Fig. 4. Changes in O_2 extraction ratio (O_2 ER) and mixed venous blood O_2 saturation (S_vO_2) during esmolol-induced controlled hypotension (esmolol group) alone and combined with acute normovolemic hemodilution (esmolol-ANH group). After the esmolol infusion, O_2 ER increased significantly. Mixed venous O_2 saturation (S_vO_2) decreased after esmolol infusion, but no values were less than 70%. Values are mean±SEM. *P<0.05 vs. the value measured immediately before the esmolol infusion. O_2 ER (%) = (O_2 consumption/O_2 delivery) × 100.*

Discussion

Our data indicate that esmolol-induced CH did not result in a systemic O_2 imbalance in the presence or absence of ANH. Although CO and O_2 delivery decreased significantly, oxygen consumption remained unchanged after the esmolol infusion in both groups and there were no signs of tissue hypoxia or metabolic acidosis. Acute normovolemic hemodilution is inevitably accompanied by a decrease in arterial O_2 content. When O_2 delivery decreases continuously, O_2 consumption is initially maintained without change for a certain period. However, once the O_2 delivery decreases beyond a certain limit (critical O_2 delivery), the O_2 consumption shows a proportional reduction. Shibutani *et al*. (11) reported that this critical O_2 delivery level in patients under general anesthesia is 330 ml/min/m^2, while Komatsu *et al*. (12) reported that it is 300 ml/min/m^2. In contrast, during hemodilution the level of critical O_2 delivery falls below this threshold level because of the improved microcirculation resulting from decreased blood viscosity (3); van Woerkens *et al*. (13) reported that in a case report of a patient who had severe intrapoerative bleeding, the level was 184 ml/min/m^2. In our study, the lowest level of O_2 delivery in the E-ANH group was 230 ml/min/m^2 (Hct was 21% at that time), which is well above the critical level of O_2 delivery during hemodilution mentioned earlier (184 ml/min/m^2).

Fontana *et al*. (14) investigated an extreme form of ANH in children and reported that lactic acidosis does not occur when S_vO_2 is more than 60%. In our study, there was no difference in S_vO_2 between the two groups and no values were below 70% in all patients. Kasnitz *et al*. (15) investigated the correlation between P_vO_2 and hyperlactatemia in patients with severe cardiac or lung diseases and reported that hyperlactatemia occurred when P_vO_2 was below 28 mmHg. In our study, the P_vO_2 levels during controlled hypotension were 38–48 mmHg in the E-ANH group, demonstrating no possibility of hyperlactatemia. Analyses of arterial blood gas also showed no acidemia in either group. The above results suggest that there was no systemic O_2 imbalance severe enough to cause a reduction in O_2 consumption. In our study, however, the changes in blood flow to vital organs including

heart, brain or liver were not studied. Although none of our patients suffered any clinically adverse outcomes, further detailed studies about regional hemodynamics and O_2 balance in these settings may deserve to be carried out.

Our data suggest that esmolol-induced CH combined with ANH was more effective for blood conservation than esmolol-induced CH alone. Although the Hct levels measured before and 1 week after the operation were similar in both groups, significantly less homologous blood was required in the E-ANH group than in the esmolol group (2.2 ± 0.6 vs. 4.3 ± 0.4 units, $P<0.01$). In addition, ANH caused a significant reduction in the infusion rate of esmolol during CH (46 ± 9 vs. $77\pm9\,\mu g/kg/min$, $P<0.05$), indicating a reinforcement of esmolol-induced CH by ANH. Acute normovolemic hemodilution itself reduces blood pressure, and this blood pressure-reducing effect of ANH may cause a reduced requirement for esmolol. In this study, ANH decreased MAP from 88 ± 2 mmHg to 82 ± 3 mmHg ($P<0.05$), which was also the case in a previous study (4).

In conclusion, when combined with a moderate degree of ANH in patients without cardiovascular disease, esmolol-induced CH was more effective for blood conservation, and was well tolerated without causing a systemic O_2 imbalance if a severe decrease in Hct was avoided during CH.

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