Kazuhiro Murakami DDS,
Tadanori Mammoto MD PhD,
Takashi Kita MD,
Yuichirou Imai DDS,*
Takashi Mashimo MD PhD,†
Tadaaki Kirita DDS PhD,*
Masahito Sugimura DDS PhD,*
Yoshihiko Kishi MD

Oral clonidine reduces the requirement of prostaglandin E1 for induced hypotension

Purpose: To determine the effects of preanesthetic oral clonidine on the dose of prostaglandin E1 (PGE1) required to produce hypotension during anesthesia.

Method: Oral placebo, 75 μ g or 150 μ g clonidine were administered 60 min prior to induction of anesthesia. Anesthesia was maintained with O₂ : N₂O (30:70) and isoflurane 1.0 %. After hemodynamic stabilization, an infusion of prostaglandin E1 was started (0.05 μ g·kg⁻¹·min⁻¹) and the rate of infusion was adjusted to maintain mean arterial pressure (MAP) between 60-70 mmHg during operation.

Results: Duration of hypotension in placebo, 75 μ g and 150 μ g preanesthetic oral clonidine treated groups were 132 $\pm$ 46, 117 $\pm$ 37 and 129 $\pm$ 56 min, respectively. The PGE1 requirement in each group were 1563 $\pm$ 180 (28.6 $\pm$ 3.2), 594 $\pm$ 197 (10.8 $\pm$ 3.6) and 283 $\pm$ 30 (5.5 $\pm$ 3.6) μ g (μ g·kg⁻¹), respectively. In addition, blood loss in each group were 1461 $\pm$ 389, 805 $\pm$ 240 and 931 $\pm$ 40 ml, respectively.

Conclusion: Preanesthetic oral clonidine decreased the dose of PGE1 required to produce hypotension, and decreased the blood loss during operation.

Objectif : Déterminer les effets de l'administration préanesthésique de clonidine orale sur la dose de prostaglandine E1 (PGE1) nécessaire à la production d'hypotension pendant l'anesthésie.

Méthode : Un placebo oral, 75 μ g ou 150 μ g de clonidine ont été administrés 60 min avant l'induction de l'anesthésie. L'anesthésie a été maintenue avec un mélange O₂ : N₂O (30:70) et de l'isoflurane à 1,0 %. Après la stabilisation des paramètres hémodynamiques, on a commencé la perfusion de prostaglandine E1 (0,05 μ g·kg⁻¹·min⁻¹) et le débit de la perfusion a été ajusté pour conserver la tension artérielle moyenne (TAM) entre 60-70 mmHg pendant l'intervention.

Résultats : La durée de l'hypotension avec le placebo ou 75 μ g ou 150 μ g de clonidine préanesthésique orale a été de 132 $\pm$ 46, 117 $\pm$ 37 et de 129 $\pm$ 56 min, respectivement. Les besoins de PGE1 dans chaque groupe ont été de 1563 $\pm$ 180 (28,6 $\pm$ 3,2), 594 $\pm$ 197 (10,8 $\pm$ 3,6) et de 283 $\pm$ 30 (5,5 $\pm$ 3,6) μ g (μ g·kg⁻¹), respectivement. De plus, la perte sanguine dans chaque groupe a été de 1461 $\pm$ 389, 805 $\pm$ 240 et de 931 $\pm$ 40 ml, respectivement.

Conclusion : L'administration préanesthésique de clonidine diminue la dose de PGE1 nécessaire à la production d'hypotension et réduit la perte sanguine pendant l'opération.

From the Department of Anesthesiology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Department of Oral and Maxillofacial Surgery,* Nara Medical University, Nara, and the Department of Anesthesiology,† Osaka University, Osaka, Japan.

Address correspondence to: Dr. Kazuhiro Murakami, Department of Anesthesiology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3, Nakamichi, Higashinari, Osaka 537-0025, Japan.

Phone: 81-6-6972-1181; Fax: 81-6-6972-7749; E-mail: mammoto@sahs.med.osaka-u.ac.jp

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IN clinical anesthesia, deliberate hypotension is applied in certain surgical procedures¹ with the goal of reducing blood loss, thereby improving the condition of operative field or decreasing the need for blood transfusion. The potential for disease transmission by transfusion has made deliberate hypotension a more important technique than previously. Hypotension may be produced by a variety of techniques including epidural anesthesia² and the use of high concentrations of anesthetic vapors.³ Recently, hemodynamic control has been improved by the use of short acting intravenous vasodilators such as PGE1.

The α_2 adrenoceptor agonist, clonidine inhibits sympathetic neural activity and stabilizes the hemodynamic parameters during anesthesia.⁴ In animal studies, intravenous co-administration of clonidine reduces the dose of vasodilator required to induce hypotension.⁵ These findings imply that preanesthetic administration of clonidine is a useful adjuvant for deliberate hypotension. This study was designed to investigate the effect of orally administered clonidine on the dose of PGE1 required to produce hypotension during radical hysterectomy.

Patients and Methods

The study was approved by the Institutional Review Board of the Osaka Medical Center for Cancer and Cardiovascular Diseases, and an informed consent was obtained.

Subjects consisted of 30 uterine cancer patients scheduled for radical hysterectomy and pelvic lymphadenectomy (ASA Physical status I or II, 34-65 yr old women). Patients were excluded if they manifested one of the following: hypertension, diabetes mellitus, organic heart disease, ECG or renal abnormalities or any gastrointestinal abnormality that would hinder enteric absorption of oral medication. The patients were randomly assigned to one of the following groups.

- 1 - Control: placebo *po* 60 min before induction of anesthesia (n=10).
- 2 - Clonidine 75: 75 μ g clonidine *po* as in placebo group (n=10).
- 3 - Clonidine 150: 150 μ g clonidine *po* as in placebo group (n=10).

Anesthetic management of these groups was otherwise identical. In the operating room, all patients were monitored with lead II ECG, and noninvasive blood pressure. After insertion of an intravenous catheter, an epidural catheter was positioned at T₁₁₋₁₂ or T₁₂-L₁ interspace.

Anesthesia was induced with 2 μ g·kg⁻¹ fentanyl and 4 μ g·kg⁻¹ pentobarbital. After patients lost consciousness, 0.1 mg·kg⁻¹ vecuronium was administered to

facilitate tracheal intubation. Respiratory gas monitor (A Hewlett Packard M1026, MA, USA) was used to monitor inspired oxygen concentration, continuous capnography, inspired and end-tidal nitrous oxide concentration, and tidal volume. Oxygen saturation was monitored by pulse oxymetry (A Hewlett Packard M1026, MA, USA). Lungs were mechanically ventilated to maintain end-tidal CO₂ between 35-40 mmHg. Arterial and central venous catheters were inserted for monitoring blood pressure and administration of vasodilators, respectively.

Anesthesia was maintained with O₂ : N₂O (30:70) and isoflurane (1% ET). Additional vecuronium was used for muscle relaxation and fentanyl was administered as needed.

After stabilizing the hemodynamics, the infusion of prostaglandin E1 was started at 0.05 μ g·kg⁻¹·min⁻¹, and the rate of infusion was adjusted to maintain the mean arterial pressure (MAP) between 60-70 mmHg by one of two staff anesthesiologist, who were blinded as to the kind of premedicant used. In case of severe hypotension (< 40 mmHg MAP) or severe bradycardia (< 40 bpm), the infusion was stopped and 4 mg ephedrine was administered. The infusion of PGE1 was stopped at the completion of hemostasis and 5 ml lidocaine 1% and 2 mg morphine were administered through epidural catheter for postoperative analgesia. Initial blood loss was replaced with crystalloid until the estimated blood loss was great enough to result in a hematocrit of 25% or less. Blood transfusion was begun if the hematocrit was < 25%. After the operation, neuromuscular blockade was antagonized by 2.5 mg neostigmine and 1mg atropine and were extubated. During the perioperative period, hemodynamic data (blood pressure and heart rate) were recorded (Hewlett Packard, M1026, MA, USA.).

Demographic data of the patients (age, height, weight, duration of anesthesia, operation and induced hypotension, infusion volume, urine output and doses of fentanyl) were examined by analysis of variance (ANOVA), and the distribution of patients regard to ASA physical status, episodes of hypotension were compared among the group using Chi-square analysis. For hemodynamic parameters (MAP and HR), the unpaired t test was used to compare the groups. Dose of PGE1 in each group was examined by ANOVA, and comparisons between groups were assessed by the Bonferroni-Dunn test.

Results

No differences existed in the demographic data among groups except in blood loss (Table I). There were no differences in the duration of anesthesia, operation and

TABLE I Patient profiles

	control	clonidine	
		75 μ g	150 μ g
Number	10	10	10
Age (yr)	52 $\pm$ 7	54 $\pm$ 6	54 $\pm$ 12
Height (cm)	157 $\pm$ 5	155 $\pm$ 5	154 $\pm$ 6
Weight (kg)	55 $\pm$ 8	55 $\pm$ 6	52 $\pm$ 8
ASA physical status			
I	5	7	5
II	5	3	5
Dose of fentanyl (μ g·kg ⁻¹)	3.7	3.6	3.7
Duration of			
operation (min)	203 $\pm$ 64	179 $\pm$ 40	187 $\pm$ 76
anesthesia (min)	256 $\pm$ 65	231 $\pm$ 36	249 $\pm$ 81
hypotension	132 $\pm$ 46	117 $\pm$ 37	129 $\pm$ 56
Blood loss (ml)	1461 $\pm$ 389	805 $\pm$ 240	931 $\pm$ 40*
Infused volume (ml)	2914 $\pm$ 733	2015 $\pm$ 281	2767 $\pm$ 1040
Urine volume (ml)	612 $\pm$ 233	400 $\pm$ 179	413 $\pm$ 382

Values are expressed as mean $\pm$ SD, * P < 0.05 compared with control group.

TABLE II Hemodynamic variables

	control	clonidine	
		75 μ g	150 μ g
Before premedication			
MAP	92 $\pm$ 11	88 $\pm$ 11	91 $\pm$ 11
HR	68 $\pm$ 8	69 $\pm$ 7	70 $\pm$ 8
Before induction			
MAP	97 $\pm$ 10	92 $\pm$ 9	85 $\pm$ 10*
HR	83 $\pm$ 6	70 $\pm$ 7*	74 $\pm$ 9*
Post induction			
MAP	77 $\pm$ 7	72 $\pm$ 8	71 $\pm$ 12
HR	75 $\pm$ 8	68 $\pm$ 9	69 $\pm$ 11
Post intubation			
MAP	100 $\pm$ 10	85 $\pm$ 7*	80 $\pm$ 8*
HR	82 $\pm$ 7	78 $\pm$ 9	81 $\pm$ 12
Post incision			
MAP	68 $\pm$ 6	67 $\pm$ 9	66 $\pm$ 5
HR	65 $\pm$ 8	59 $\pm$ 9	60 $\pm$ 8
Episodes of hypotension	4	3	4

MAP: mean arterial pressure, HR heart rate

Values are expressed as mean $\pm$ SD. * P < 0.05 compared with control

deliberate hypotension, or in the dose of fentanyl (Table I). The mean blood losses for the control, 75 and 150 μ g clonidine groups were 1460 $\pm$ 389, 805 $\pm$ 239 and 931 $\pm$ 40 (μ g), respectively (P < 0.01).

In each group, the infusion of PGE1 was started after the skin incision and the durations of hypotension in control, 75 μ g and 150 μ g clonidine groups were 132 $\pm$ 46, 117 $\pm$ 37 and 129 $\pm$ 56 min, respectively (Table I). The total requirements for PGE1 for deliberate hypotension in each group were 1563 $\pm$

FIGURE 1 The total requirement of PGE1 (μ g) for deliberate hypotension in the control and clonidine treated groups (75 and 150 μ g). The values are expressed as mean $\pm$ SEM, * P < 0.01 compared with control (n=10 in each group).

180 (28 $\pm$ 3), 594 $\pm$ 197 (10 $\pm$ 3), and 283 $\pm$ 3 (5.5 $\pm$ 3) μ g (μ g·kg⁻¹), respectively (Figure 1, P < 0.01). The mean infusion rates in these groups were 0.336, 0.086 and 0.038 μ g·kg⁻¹·min⁻¹, respectively.

There were no differences in mean arterial pressure (MAP) and heart rate (HR) among groups before premedication (Table II). At the preinduction period, 150 μ g clonidine reduced MAP and HR, and 75 μ g clonidine reduced HR (Table II, P < 0.05). At the postinduction and post incision period, no differences among groups existed in MAP and HR (Table II). In addition, 75 and 150 μ g clonidine attenuated the increase in MAP during tracheal intubation (Table II, P < 0.05). During deliberate hypotension, MAP was identical in each group while HR tended to be lower in the clonidine treated groups (Figure 2, P < 0.05 at 60 min in 150 μ g clonidine group, no differences at other points). No differences existed among groups in the number of episodes of hypotension (Table II).

Discussion

Our results indicated that preanesthetic oral clonidine (75 and 150 μ g) decreased the requirement for PGE1 to produce deliberate hypotension. In addition, clonidine attenuated the hemodynamic responses to tracheal intubation and reduced blood loss during operation.

The α_2 adrenoceptor agonist, clonidine is known to inhibit sympathetic neural activity and, consequently, stabilizes hemodynamic variables during anesthesia.⁴

FIGURE 2 The mean arterial pressure and heart rate (HR) during deliberate hypotension in the control and clonidine treated groups (75 and 150 µg) (■: control, ●: clonidine 75 µg, ▲: clonidine 150 µg). The values are expressed as mean $\pm$ SEM, * $P < 0.05$ compared with control ($n=10$ in each group).

Clonidine also decreased the release norepinephrine and enhanced baroreflex in animal investigation.^{6,7} These properties would be responsible for the vasodilator sparing actions of clonidine in this study.

In addition to sympatholytic actions, clonidine exerts hypnosis and analgesia via activation of α_2 adrenoceptors in the central nervous system.^{8,9} In the clinical setting, preanesthetic clonidine reduces the requirement of volatile anesthetics and/or opioid.⁴ Recently, we reported that preanesthetic oral cloni-

dine (150 µg) relieved anxiety and reduced the dose of propofol required for minor surgery.¹⁰ These properties might affect the depth of anesthesia and, consequently, reduce the dose of PGE1 required to produce hypotension. In this study, the hemodynamic responses to skin incision were identical in each group and the maintenance of anesthesia (isoflurane 1% ET and nitrous oxide 70% with 4 µg·kg⁻¹ fentanyl) was sufficient for surgery. Thus, it is speculated that, at the doses we used, clonidine exerted its beneficial action primarily by inhibiting the sympathetic neural activity.

Although the main goal of deliberate hypotension is to reduce blood loss, blood flow to organs such as brain, liver and kidney should be preserved and hypotension should be easily controlled. Therefore, short acting vasodilators are ideal for producing deliberate hypotension. Among several short acting vasodilators, PGE1 preserves organ blood flow, and protects these organs.^{11,12,13} It has been reported that PGE1 preserves the local cerebral blood flow without changing CO₂ reactivity of the cerebral vessels during deliberate hypotension¹⁴ and maintains the spinal and epidural blood flow.^{15,16} In addition, PGE1 protects against ischemic liver injury¹¹ and preserves renal function.¹² Therefore, PGE1 is often infused during liver and renal transplantation.^{17,18} Other vasodilators, such as sodium nitroprusside, do not protect the visceral organs during deliberate hypotension.¹⁹ In this study, the mean infusion rates of PGE1 in the clonidine treated groups were 0.086 (75 µg) and 0.038 (150 µg) µg·kg⁻¹·min⁻¹. Considering that optimal dose of PGE1 to maintain visceral organ blood flow is approximately 0.01 µg·kg⁻¹·min⁻¹,²⁰ blood flow to the kidney and liver would be preserved in the clonidine treated groups during hypotension. Therefore, we consider that PGE1 is an ideal vasodilator for deliberate hypotension. However, the vasodilating action of PGE1 is mild and a larger dose (>0.1 µg·kg⁻¹·min⁻¹) would be needed to induce hypotension without clonidine. The cost of PGE1 would limit the usage of this agent for deliberate hypotension. The cost of clonidine (75 µg=0.42\$) is low compared with that of PGE1 (500 µg=277\$). Our results indicated that preanesthetic medication of clonidine reduced the cost of PGE1. The use of preanesthetic clonidine would resolve the problems of the cost of vasodilators in producing deliberate hypotension.

In conclusion, administration of clonidine (75 and 150 µg) *po* before anesthesia reduced the dose of PGE1 required to maintain hypotension and decreased blood loss during surgery. These findings indicate that clonidine is a useful adjuvant in producing deliberate hypotension with PGE1.

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