Hemodynamic effects of oral clonidine premedication in lumbar epidural anesthesia*

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Abstract: Clonidine, an α_2-adrenergic agonist, has a potent sympatholytic effect and augments the pressor effect of ephedrine during general anesthesia. We evaluated whether oral clonidine premedication would alter the hemodynamic changes and enhance the pressor response to intravenous ephedrine during epidural anesthesia in 35 adult patients. They were randomly administered either premedication with clonidine approximately $5\mu g\cdot kg^{-1}$ po ($n = 17$) or no clonidine medication ($n = 18$). After establishment of epidural anesthesia, the hemodynamic response to ephedrine iv was measured in the awake state at 1-min intervals for 10min. Then, the same hemodynamic measurement was repeated in the asleep state induced with midazolam iv. There were no differences in blood pressure (BP) and heart rate values between groups during the onset of epidural anesthesia, except that BP before epidural anesthesia was lower in the clonidine group than the control group ($P < 0.05$). The magnitude and duration of pressor responses to ephedrine were comparable between groups in awake and asleep states. In conclusion, oral clonidine premedication $5\mu g\cdot kg^{-1}$ alters neither the hemodynamic changes nor the pressor response to intravenous ephedrine during epidural anesthesia.

Key words: Alpha-2 adrenergic agonists, Clonidine, Epidural anesthesia

Introduction

Systemic administration of clonidine, an α_2-adrenergic agonist, is demonstrated to have a potent sympatholytic effect [1] and augment the pressor effect of ephedrine

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or phenylephrine [2,3]. We have demonstrated that the pressor responses to sympathomimetic agents are enhanced in patients receiving oral clonidine medication when they are awake or during general anesthesia [2,3]. However, there is little information with respect to oral clonidine modulation of hemodynamic alterations associated with onset of epidural anesthesia and the pressor effect of ephedrine during epidural anesthesia.

This study was undertaken to evaluate whether oral clonidine preanesthetic medication would modify the hemodynamic changes associated with the onset of lumbar epidural anesthesia, and whether it would alter the pressor response to intravenous ephedrine during epidural anesthesia.

Materials and methods

Thirty-five ASA physical status I patients, aged 23–66 years, scheduled to have lumbar epidural anesthesia for their gynecologic or orthopedic surgery, were selected for this study. The study protocol was approved by our Institutional Human Studies Committee. Informed consent was obtained from each patient. Patients were free of any neurologic or cardiopulmonary disorder. The patients were randomly assigned to one of two groups: the clonidine group ($n = 17$) received oral preanesthetic medication of clonidine approximately $5\mu g\cdot kg^{-1}$ plus famotidine 20mg, while the control group ($n = 18$) received famotidine 20mg alone 90min before arrival in the operating room.

After the patients were placed in the lateral decubitus position, an 18-gauge epidural catheter was inserted through a Tuohy needle at the L2–3, L3–4, or L4–5 intervertebral space. Following injection of a test dose (2% lidocaine 3ml with 1:200000 epinephrine), the remaining 9–17ml of the same solution was administered into the epidural space, according to the patient's age

Table 1. Patient characteristics

	Clonidine group ($n = 17$)	Control group ($n = 18$)
Age (years)	40 ± 2	38 ± 2
Weight (kg)	58 ± 2	53 ± 2
Height (cm)	158 ± 2	155 ± 2
Sex (M/F)	2/15	3/15
Dose of clonidine ($\mu g \cdot kg^{-1}$)	4.98 ± 0.05	—
Dose of epidural 2% lidocaine (ml)	18.8 ± 0.8	18.0 ± 0.6
Segment no. of analgesia	13.7 ± 0.7	12.7 ± 0.6

Values are mean ± SE.
There were no significant differences between groups.

and body height. Measurements of blood pressure (BP) and heart rate (HR) were made 5, 10, and 15 min after epidural injection of lidocaine, while lead II of the electrocardiogram (ECG; San-Ei Instruments, Tokyo, Japan) was continuously monitored. BP was measured by a noninvasive, oscillometric BP monitoring device (BP-308 ET, Nippon Colin, Tokyo, Japan), and HR was determined as an average of every 4s from the ECG monitor. Analgesic level was confirmed by the pin-prick method at 15 min after epidural injection of lidocaine.
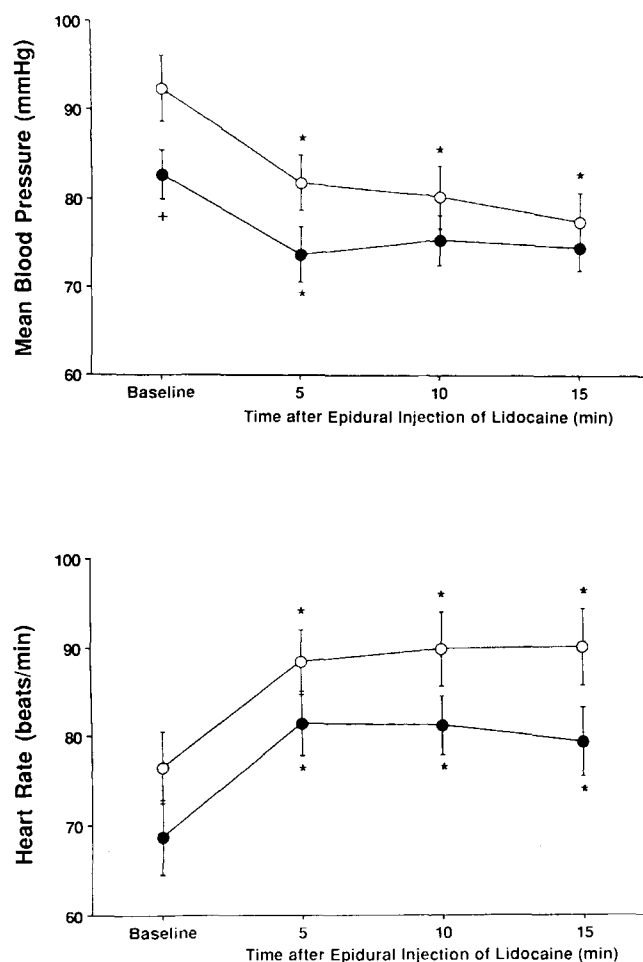
Twenty minutes after epidural injection of lidocaine, ephedrine $0.1 \, mg \cdot kg^{-1}$ was administered intravenously over 5s in all patients of each group, while they were awake and positioned supine with a pillow. Ephedrine hydrochloride solution (Dainippon, Osaka, Japan) was diluted to a concentration of $1 \, mg \cdot ml^{-1}$. BP and HR were measured at 1-min intervals for 10 min after the injection of ephedrine. Data collection, however, was completed in 17 patients of each group, because one patient of the control group was inadvertently placed in the lithotomy position during the measurement. Duration of pressor response to ephedrine was defined as duration of changes in mean BP above baseline values following ephedrine, and was obtained in each patient of both groups.

Midazolam 1 mg was injected intravenously every 30s in 17 and 16 patients of the clonidine and control groups, respectively, until the patient could not respond when spoken to. Ten minutes later, the same hemodynamic measurement was repeated after ephedrine $0.1 \, mg \cdot kg^{-1}$ had been administered intravenously over 5s, while they were asleep and positioned supine with a pillow. However, data collection was completed in 16 and 11 patients of the clonidine and control groups, respectively, because 1 and 5 patients awoke during the measurement. Duration of pressor response to ephedrine was obtained in each patient of both groups.

Values are given as mean ± SE. Statistical analyses of the results were performed by analysis of variance with repeated measurements followed by Student's t-test. Comparisons between groups were performed using two-way analysis of variance followed by unpaired Student's t-test. P values <0.05 were considered to be statistically significant.

Results

There were no differences in age, body weight, height, or sex ratio between the two groups of patients (Table 1). The clonidine dose administered was 4.98 ± $0.05 \, \mu g \cdot kg^{-1}$. These groups were similar in the dose of epidural lidocaine and segments of analgesia. There was also no difference between groups in the infusion rate of lactated Ringer's solution throughout the study.

Fig. 1. Changes in mean blood pressure (*upper panel*) and heart rate (*lower panel*) after epidural injection of lidocaine in patients receiving oral clonidine (*solid circles*; $n = 17$) approximately $5 \, \mu g \cdot kg^{-1}$ or no clonidine (*open circles*; $n = 18$). Mean ± SE. *$P < 0.05$ vs baseline. +$P < 0.05$ vs the control group
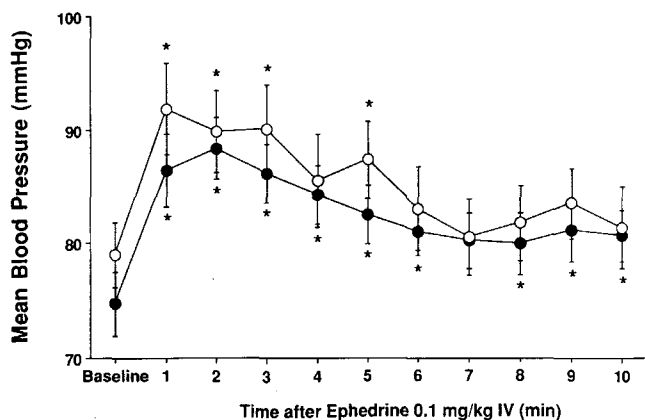
Fig. 2. Changes in mean blood pressure after intravenous ephedrine 0.1 mg·kg⁻¹ in awake patients receiving oral clonidine (*solid circles*; n = 17) approximately 5 μg·kg⁻¹ or no clonidine (*open circles*; n = 17). Mean ± SE. *P < 0.05 vs baseline

Baseline mean BP before epidural injection of lidocaine was lower in the clonidine group than the control group (P < 0.05, Fig. 1). After epidural injection, there were decreases in mean BP from baseline values at 5, 10, and 15 min in the control group (P < 0.05), but only at 5 min in the clonidine group. Although HR increased from baseline values at 5, 10, and 15 min after epidural injection in both groups (P < 0.05, Fig. 1), there were no differences between groups at any time.

Baseline mean BP before ephedrine injection (20 min after the epidural injection) was similar between groups (Fig. 2). Following ephedrine injection, mean BP elevations from baseline values (P < 0.05) were observed from 1–6 min in the clonidine group, and from 1–3 and at 5 min in the control group. However, there were neither intergroup differences in mean BP values at any time nor in the duration of pressor response to ephedrine (7.9 ± 0.6 and 5.9 ± 0.8 min in the clonidine and control groups, respectively). Maximum mean BP increase from baseline values after ephedrine in the clonidine group (15 ± 1 mmHg) was also not different from that in the control group (16 ± 3 mmHg). HR showed no changes after ephedrine injection in both groups and no difference between groups at any time. Ventricular premature contractions were noted in one patient of each group after ephedrine injection, but they disappeared spontaneously within 1 min.
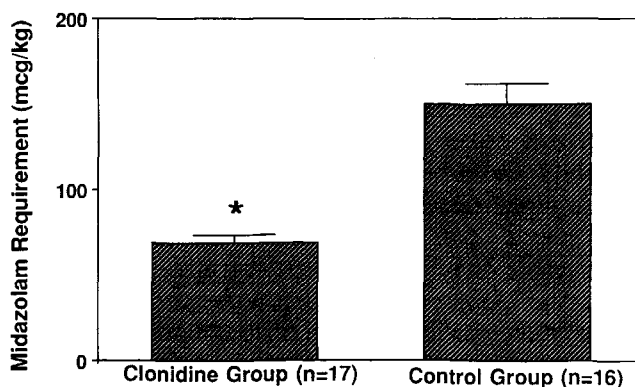
The dose of midazolam required to induce loss of consciousness was smaller in the clonidine group (69 ± 4 μg·kg⁻¹) compared with the control group (151 ± 11 μg·kg⁻¹, P < 0.05, Fig. 3). Baseline mean BP before ephedrine injection (10 min after midazolam injection) was similar between groups (Fig. 4). Following ephedrine injection, mean BP elevations from baseline val-

ues (P < 0.05) were observed from 1–9 min in the clonidine group, and from 1–3 min in the control group. However, there were neither intergroup differences in mean BP values at any time nor in the duration of pressor response to ephedrine (8.7 ± 0.5 and 8.3 ± 0.9 min in the clonidine and control groups, respectively). The maximum mean BP increase from baseline values after ephedrine in the clonidine group (16 ± 1 mmHg) also did not differ from that in the control group (16 ± 2 mmHg). HR showed no changes after ephedrine injection in both groups and no difference between groups at any time. No arrhythmia was noted after ephedrine injection in any patient.

Discussion

Our results showed that oral clonidine preanesthetic medication 5 μg·kg⁻¹ did not affect to a great extent the hemodynamic changes associated with the onset of epidural anesthesia, nor did it significantly change the pressor effect of intravenous ephedrine in both awake and asleep patients during epidural anesthesia.

In the present results the baseline mean BP value prior to epidural anesthesia was lower in the clonidine group compared with the control group (Fig. 1). This finding agrees with several previous reports [2–7] showing BP reduction following clonidine medication. The hypotensive effect of clonidine primarily depends on its routes of administration; BP decreases through reductions in both cardiac output and systemic vascular resistance following intravenous clonidine [4], while mainly through systemic peripheral vasodilation following oral clonidine [7]. In our results BP reduction following oral clonidine medication appears to be due primarily to a decrease in systemic vascular resistance, because mean

Fig. 3. Doses of midazolam required to induce loss of consciousness in patients receiving oral clonidine approximately 5 μg·kg⁻¹ or no clonidine. Mean ± SE. *P < 0.05 vs the control group
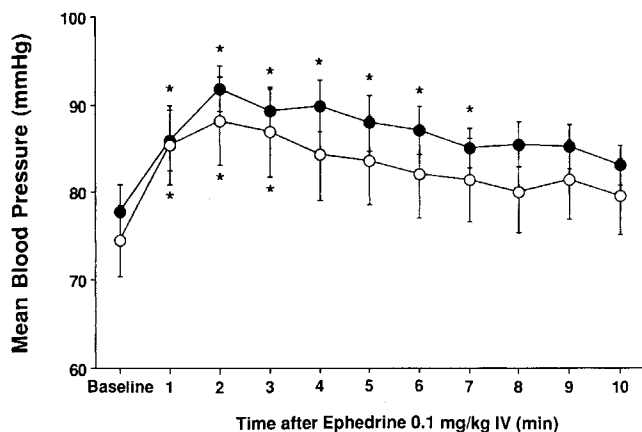
Fig. 4. Changes in mean blood pressure after intravenous ephedrine $0.1\,mg\cdot kg^{-1}$ in asleep patients receiving oral clonidine (*solid circles*; $n = 16$) approximately $5\,\mu g\cdot kg^{-1}$ or no clonidine (*open circles*; $n = 11$). Mean $\pm$ SE. $*P < 0.05$ vs baseline

BP reductions following epidural injection of lidocaine were moderate in both groups, presumably because of the lesser degree of cardiac sympathectomy in lumbar epidural anesthesia. Alternatively, the occurrence of positive chronotropic response following epidural anesthesia in our study (Fig. 1) is likely to have compensated partly for cardiac output reduction associated with upper thoracic sympathectomy in some patients. In the present results the bradycardic effect of clonidine may have been concealed by epidurally administered lidocaine with epinephrine as well as sympathetic-mediated HR acceleration secondary to vasodilation [8]. Otherwise, profound hypotension would occur after epidural anesthesia secondary to extensive sympathetic denervation and a decrease in cardiac output. Furthermore, the present results which indicate that the effect of oral clonidine medication on BP and HR responses to epidural anesthesia was relatively minimal may be attributed to the fact that aged patients were excluded from this study.

According to our previous investigations [2,3] showing enhancement of the pressor effect of ephedrine or phenylephrine following clonidine medication in awake and anesthetized patients, the vasoconstricting effect of these pressor agents is considered to be augmented as an underlying mechanism. However, such an enhanced pressor response to intravenous ephedrine was not noted in awake or asleep patients during epidural anesthesia in the present study. One can assume that systemically absorbed lidocaine and epinephrine from the epidural space as well as systemic vasodilation due to epidural anesthesia may have concealed the enhanced vasoconstricting effect of ephedrine, since both

agents produce potent vasodilation or vasoconstriction [9,10].

The anesthetic-sparing effect of clonidine is well known and is common to various kinds of anesthetic agents [6,7,11,12]. In the present study oral clonidine medication $5\,\mu g\cdot kg^{-1}$ reduced the midazolam requirement by approximately 55%, which is roughly in agreement with other previous reports [6,7,11,12]. Certainly, this finding seems to indicate the interaction among clonidine, midazolam, and lidocaine rather than that between the former two agents alone.

In summary, oral clonidine preanesthetic medication $5\,\mu g\cdot kg^{-1}$ did not alter to a great extent the hemodynamic changes associated with the onset of epidural anesthesia, nor did it significantly change the pressor effect of intravenous ephedrine in either the awake or asleep state.

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