

# Clinical Evaluation of Clonidine Added to Lidocaine Solution for Epidural Anesthesia

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The effects of clonidine added to lidocaine solution used for epidural anesthesia were assessed in 92 women scheduled for surgery and premedicated with diazepam 10 mg po. Patients received 18 ml 2% lidocaine with clonidine  $5 \mu\text{g} \cdot \text{ml}^{-1}$  (group C-5,  $n = 26$ ), with clonidine  $10 \mu\text{g} \cdot \text{ml}^{-1}$  (group C-10,  $n = 20$ ), with epinephrine  $5 \mu\text{g} \cdot \text{ml}^{-1}$  (group E,  $n = 26$ ), or plain (group P,  $n = 20$ ). No significant difference in the number of segments of analgesia was found at any observation period among the four groups of patients. The decreases in mean blood pressure (BP) observed 20 min after epidural injection in those given clonidine ( $5 \pm 8\%$  for C-5,  $10 \pm 11\%$  for C-10, mean  $\pm$  SD) were similar to those given plain lidocaine ( $7 \pm 12\%$ ) but significantly less than those given epinephrine ( $18 \pm 12\%$ ,  $P < 0.01$  vs. C-5 or P). The response of BP to ephedrine given for restoring BP during anesthesia was not attenuated in patients who received epidural clonidine. Heart rate (HR) decreased significantly in patients given clonidine  $10 \mu\text{g} \cdot \text{ml}^{-1}$  ( $7 \pm 8\%$ ,  $P < 0.01$ ), but not in those given clonidine  $5 \mu\text{g} \cdot \text{ml}^{-1}$ , whereas HR increased significantly in those given lidocaine plain or with epinephrine ( $10 \pm 8\%$  and  $28 \pm 14\%$ , respectively,  $P < 0.01$ ). The incidence of sinus bradycardia was similar among the four groups of patients. Significant differences were also observed in sedation score between clonidine groups and groups P or E; sedation appeared approximately 10–20 min after epidural injection in both clonidine groups. Although respiratory rate,  $\text{PaO}_2$ , and  $\text{PaCO}_2$  did not change after epidural injection in both clonidine groups,  $\text{PaO}_2$  increased significantly ( $P < 0.01$ ) in those given lidocaine plain or with epinephrine. Maximal plasma lidocaine concentrations (10–15 min after epidural injection) in group C-5 ( $n = 7$ ,  $3.4 \pm 0.2 \mu\text{g} \cdot \text{ml}^{-1}$ ) and in group C-10 ( $n = 7$ ,  $3.6 \pm 1.0 \mu\text{g} \cdot \text{ml}^{-1}$ ) were comparable to those in group P ( $n = 7$ ,  $2.9 \pm 1.0 \mu\text{g} \cdot \text{ml}^{-1}$ ) but were significantly greater ( $P < 0.05$ ) than those in group E ( $n = 7$ ,  $2.3 \pm 0.4 \mu\text{g} \cdot \text{ml}^{-1}$ ). These results indicate that the addition of clonidine to lidocaine for epidural anesthesia provides a sedative effect and relatively stable hemodynamics, and that clonidine in a concentration of 1:200,000 or 1:100,000, in contrast to 1:200,000 epinephrine, tends to increase rather than to suppress the plasma lidocaine concentrations. The latter effect may be related to altered metabolism of lidocaine by clonidine. (Key words: Anesthetic techniques: epidural. Anesthetics, local: lidocaine. Sympathetic nervous system: alpha-2 adrenergic agonists, clonidine; epinephrine.)

THE ANALGESIA, hemodynamic effects, and neurotoxicity of clonidine hydrochloride, a partial alpha-2 agonist,

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administered into the epidural or subarachnoid space has been studied extensively in animal experiments.<sup>1-8</sup> The results indicate that epidural or intrathecal administration of clonidine produces little change in local blood flow, produces no histopathologic lesions of the spinal cord,<sup>2,4,8,9</sup> and causes no significant influence on systemic hemodynamics.<sup>1,2</sup> Furthermore, clonidine has no peripheral vasodilating action<sup>10</sup> but does cause bradycardia<sup>11,12</sup> and sedation.<sup>1,13</sup> These data suggest that the addition of clonidine in epidural anesthesia may have advantages over epinephrine, which may cause hypotension and tachycardia when added to lidocaine solution.<sup>14</sup> Although several reports have described clinical administration of epidural or intrathecal clonidine,<sup>15-24</sup> observations still are limited.

The current clinical study was undertaken in surgical patients to evaluate the comparative analgesic, hemodynamic, respiratory, and sedative effects of clonidine or epinephrine when added to lidocaine solution in patients receiving epidural anesthesia. Since a significant decrease in arterial oxygen tension has been reported to occur after epidural<sup>2</sup> or intravenous<sup>25</sup> administration of clonidine in sheep, we also investigated the effect of clonidine upon arterial oxygenation. The effect of clonidine on the response to ephedrine and on plasma lidocaine concentration also was compared among patients who received lidocaine plain or lidocaine with clonidine or epinephrine.

## Materials and Methods

Ninety-two women ranging in age from 20 to 63 yr and scheduled to have epidural anesthesia for their gynecologic surgery were selected for this study. The study protocol was approved by the Jutaku Kenkyu Committee of the University of Tsukuba Hospital (Human Investigation Committee) and by our local ethical committee. Informed consent was obtained from each patient. No patient had any cardiopulmonary or neurologic disorder.

All patients received diazepam 10 mg po 90 min before arrival in the operating room. A 16-G intravenous catheter was inserted for continuous infusion of lactated Ringer's solution at a rate of  $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . After patients were placed in the lateral decubitus position, a Tuohy needle was introduced into the epidural space via the L2-L3 or L3-L4 intervertebral space, after which, a 16 gauge epidural catheter was advanced approximately 4–5 cm into the epidural space.

Patients were assigned to receive 18 ml 2% lidocaine (360 mg) plain (group P,  $n = 20$ ); with 1:200,000 clonidine

(group C-5,  $n = 26$ ;  $5 \mu\text{g} \cdot \text{ml}^{-1}$ , total dose  $90 \mu\text{g}$ ); with 1:100,000 clonidine (group C-10,  $n = 20$ ;  $10 \mu\text{g} \cdot \text{ml}^{-1}$ , total dose  $180 \mu\text{g}$ ); or with 1:200,000 epinephrine (group E;  $n = 26$ ). Three minutes after injection of a test dose (3 ml 2% lidocaine either plain, or with clonidine or epinephrine), the remaining 15 ml of the same solution was administered into the epidural space over 30 s. Analgesic level was checked by the pin-prick method at 5-min intervals for 20 min. Blood pressure (BP) and heart rate (HR) were measured at 1, 2, 3, 5, 10, 15, and 20 min after epidural injection. BP was measured by sphygmomanometer or by a blood pressure monitoring device (BP-308ET, Nippon Colin Co., Ltd.). HR was determined from continuous monitoring of the electrocardiogram. Respiratory rate (RR) was measured every 5 min. Sedation was defined on a scale of 0 to 5 (0 = very excited; 1 = alert, tense, and inquisitive; 2 = sedated, but not sleepy, with eyes opened; 3 = eyes sometimes opened, and sleepy to observers, although the patient herself does not complain of sleepiness; 4 = eyes closed almost continuously and complaints of sleepiness; and 5 = drowsy and almost no response to verbal commands). The sedation score was checked by one of the authors at 5-min intervals after epidural injection. Samples of arterial blood were obtained while patients breathed room air before and 20 min after epidural injection in 20, 24, 20, and 20 patients of groups P, C-5, C-10, and E, respectively. Specimens were analyzed for  $p\text{H}$ ,  $\text{PaCO}_2$ ,  $\text{PaO}_2$ , and base excess by 178  $p\text{H}$ /Blood Gas Analyzer (Corning).

After confirmation of an adequate epidural analgesia by the pin-prick method 20 min after epidural injection, the patients received intravenous diazepam 5–10 mg or butorphanol 1–2 mg or both for their intraoperative sedation. During the study, hypotension was defined as a decrease in systolic BP greater than 30% of the pre-anesthetic value or a systolic BP of less than 80 mmHg. Hypotension was treated with intravenous ephedrine  $0.1 \text{ mg} \cdot \text{kg}^{-1}$ . Measurement of BP and HR was made 1 min after the administration of ephedrine, and the hemodynamic responses to ephedrine were compared among the four groups. Bradycardia was defined as a HR less than 50 beats per min and was treated with intravenous atropine 0.5 mg. When ephedrine or atropine was used during the first 20-min study period, the data were excluded from the hemodynamic results (see table 2).

In order to measure plasma lidocaine concentration, we studied 28 patients (7 from each group), who, prior to puncture of the epidural space, received 1% mepivacaine for local infiltration in addition to placement of venous and arterial catheters. Arterial blood samples for measurement of plasma lidocaine concentrations were withdrawn 5, 10, 15, 20, 30, 40, 50, and 60 min after epidural injection of lidocaine. The plasma lidocaine concentration was measured by homogeneous enzyme im-

unoassay.<sup>26</sup> A 50- $\mu\text{l}$  aliquot of each plasma sample was mixed with a reagent, which contained antibodies to lidocaine together with substrates for enzyme glucose-6-phosphate dehydrogenase. An enzyme-labeled lidocaine was then added. The labeled lidocaine combines with any remaining unfilled antibody binding sites, and the enzymatic activity is proportionately reduced. Residual enzymatic activity is directly related to the concentration of lidocaine present in plasma. Unbound active enzyme converts nicotinamide adenine dinucleotide (NAD) to NADH, resulting in an absorbance change. Enzyme activity was measured spectrophotometrically as the change in optical density at 340 nm (model aca<sup>o</sup> discrete clinical analyzer, DuPont Co.). The coefficient for variability in this method was 5.8%, and the assay range, 1.0–12.0  $\mu\text{g} \cdot \text{ml}^{-1}$ . Values obtained by this technique correlate well with those obtained by high-pressure liquid chromatography (correlation coefficient 0.982).<sup>26</sup>

The following drugs were used in this study: clonidine hydrochloride (Boehringer Ingelheim Ltd.), lidocaine hydrochloride, (Fujisawa Co. Ltd.), mepivacaine hydrochloride (Fujisawa Co. Ltd.), ephedrine hydrochloride (Dainippon Co. Ltd.), and atropine sulfate (Tanabe Co. Ltd.).

Values are given as mean  $\pm$  SD unless otherwise stated. Analyses of changes in variables from baseline values were performed by one-way analysis of variance (ANOVA). Comparisons of data among groups were made by two-way ANOVA and Student's *t* test with Bonferroni corrections. Wilcoxon's signed rank test was used to compare the sedation scores among the four groups. Testing for the incidence among the groups was accomplished by chi-squared analysis. *P* values less than 0.05 were considered to be statistically significant.

## Results

There were no significant differences in age, body weight, and height among the four groups (table 1), and basal values of mean BP, HR, RR, and sedation score among the four groups also were similar (tables 2 and 3). The mean dose of epidurally administered clonidine was  $1.7 \pm 0.2 \mu\text{g} \cdot \text{kg}^{-1}$  in group C-5 and  $3.3 \pm 0.5 \mu\text{g} \cdot \text{kg}^{-1}$  in group C-10, respectively. Two patients in group P, three patients in group C-5, two patients in group C-10, and two patients in group E were excluded from the hemodynamic results (table 2) because one patient each in groups C-5 and C-10 received atropine for the treatment of sinus bradycardia, and the remaining seven patients, who developed hypotension, were treated with ephedrine during the first 20-min study period. No significant difference in the extent of analgesia was noted among the four groups (table 3).

Mean BP significantly decreased, by  $7 \pm 12$ ,  $5 \pm 8$ ,  $10 \pm 11$ , and  $18 \pm 12\%$  of baseline ( $P < 0.05$ ) at 20 min

TABLE 1. Patient Characteristics of the Four Groups

Group	Agents Added to Lidocaine	n	Age (yr)	Weight (kg)	Height (cm)
P	None	20	40 ± 8	56 ± 9	156 ± 6
C-5	Clonidine 5 µg · ml <sup>-1</sup>	26	37 ± 7	52 ± 8	156 ± 4
C-10	Clonidine 10 µg · ml <sup>-1</sup>	20	39 ± 10	54 ± 9	155 ± 5
E	Epinephrine 5 µg · ml <sup>-1</sup>	26	41 ± 9	54 ± 10	155 ± 6

Values are mean ± SD.

No significant differences among the four groups.

after epidural injection in groups P, C-5, C-10, and E, respectively (table 2). Patients in group C-5 showed no significant change in HR, whereas a significant decrease in HR (7 ± 8%) was noted in group C-10 ( $P < 0.05$ , table 2). However, in a step-wise fashion, HR significantly increased, reaching a maximal value of 110 ± 8 and 128 ± 14% of baseline in the groups P and E, respectively ( $P < 0.01$ , group P vs. group E, table 2).

RR remained stable in the four groups during the 20-min study period, but significant differences in RR were found at 10–20 min after epidural injection between group P and group C-5 or C-10 (table 3). Sedation scores in clonidine groups were significantly greater than those in groups P and E at 10–20 min after epidural injection (table 3). Sixteen of 26 patients (61%) in group C-5, 18 of 20 (90%) in group C-10, and 6 of 20 (30%) in group P complained of feeling sleepy (score 4) when they were questioned by one of authors ( $P < 0.001$ , group C-10 vs. group P;  $P < 0.05$ , group C-5 vs. group P or C-10), but none of patients was sedated to the degree that she could not respond to verbal commands. In contrast, only 2 of 26 patients (7%) in group E became sleepy ( $P < 0.001$ , vs. groups C-5 and C-10;  $P < 0.05$ , vs. group P), and median values of the sedation score remained unchanged in the patients of group E (table 3).

No significant changes in PaO<sub>2</sub> were observed in the clonidine groups, although PaO<sub>2</sub> increased significantly at 20 min after epidural injection in groups E and P (table 4).

In four, six, seven, and seven patients of groups P, C-5, C-10, and E, respectively, hypotension occurred after epidural injection. Neither in the incidence of hypotension among the four groups nor in the segment numbers of analgesia was there any significant difference between patients with and without hypotension in each group. Fifteen of all 24 hypotensive episodes occurred more than 20 min after epidural injection (after administration of diazepam and butorphanol as sedatives). There was, however, no significant difference in the responses of BP and HR to ephedrine of 0.1 mg · kg<sup>-1</sup> among the four groups (table 5).

Plasma lidocaine concentration differed significantly among the groups until 40 min after epidural injection; their maximum values were 2.9 ± 1.0, 3.4 ± 0.2, 3.6 ± 1.0, and 2.3 ± 0.4 µg · ml<sup>-1</sup> in groups P, C-5, C-10, and E, respectively, 10–15 min after epidural administration (fig. 1). Plasma lidocaine concentrations in the clonidine groups showed a tendency to be greater than those in group P. However, plasma lidocaine concentrations were statistically similar among clonidine groups and group P, except at 5 min after epidural injection ( $P < 0.05$ ) in group C-5. Plasma lidocaine concentrations were higher in the clonidine groups than in group E until 30–40 min after epidural injection ( $P < 0.05$ ), but they did not differ between groups P and E (fig. 1).

Two, five, four, and one patients developed sinus bradycardia (<50 beats per min) after epidural injection in groups P, C-5, C-10, and E, respectively ( $P > 0.05$

TABLE 2. Hemodynamic Effects of 18 ml Epidural 2% Lidocaine either Plain or with an Agent Added

Hemodynamic Variables	Added Agent	Baseline	Time after Epidural Injection (min)						
			1	2	3	5	10	15	20
Mean blood pressure (mmHg)	P	89 ± 12	84 ± 11*	83 ± 12*	83 ± 13*	82 ± 13*	82 ± 10*†	82 ± 11*†	82 ± 12*†
	C-5	86 ± 11	85 ± 12	84 ± 11	84 ± 13*	82 ± 14*	82 ± 13*†	83 ± 14*†	82 ± 14*†
	C-10	88 ± 12	84 ± 10*	83 ± 11*	82 ± 9*	79 ± 11*	78 ± 10*	79 ± 11*	79 ± 11*
	E	87 ± 12	79 ± 11*	77 ± 11*	76 ± 11*	73 ± 10*	71 ± 9*	72 ± 11*	71 ± 11*
Heart rate (beats per min)	P	76 ± 12	79 ± 12*	79 ± 12*	80 ± 12*†	85 ± 15*	85 ± 16*	86 ± 16*	85 ± 14*
	C-5	71 ± 9	71 ± 10†	72 ± 10†	72 ± 10†	73 ± 10†	71 ± 8†	71 ± 10†	70 ± 10†
	C-10	76 ± 16	77 ± 17	76 ± 17	76 ± 16†	76 ± 17†	75 ± 19†	72 ± 18†	70 ± 16*†
	E	74 ± 10	84 ± 10*	87 ± 12*	91 ± 13*	94 ± 14*	95 ± 14*	92 ± 14*	92 ± 15*

P = lidocaine plain. Added agents: C-5 = 1:200,000 clonidine; C-10 = 1:100,000 clonidine; E = 1:200,000 epinephrine. P, n = 18; C-5, n = 23; C-10, n = 18; E, n = 24.

Values are mean ± SD.

\*  $P < 0.05$  versus baselines.

†  $P < 0.05$  versus group E.

TABLE 3. Analgesic, Respiratory, and Sedative Effects of 18 ml Epidural 2% Lidocaine Plain or with an Agent Added

	Added Agent	Baseline	Time after Epidural Injection (min)			
			5	10	15	20
Segments of analgesia	P	—	2.6 ± 2.5	7.9 ± 3.1	11.3 ± 3.2	12.4 ± 2.3
	C-5	—	3.8 ± 3.9	8.5 ± 3.5	11.1 ± 5.0	12.3 ± 4.6
	C-10	—	4.2 ± 3.5	8.6 ± 3.2	12.3 ± 3.0	13.3 ± 2.6
	E	—	3.4 ± 2.8	8.7 ± 3.7	11.6 ± 2.8	12.8 ± 2.5
Respiratory rate (breaths·min <sup>-1</sup> )	P	16.4 ± 2.0	16.5 ± 1.9	16.5 ± 1.9	16.6 ± 1.8	16.6 ± 1.8
	C-5	15.5 ± 2.5	15.3 ± 2.3	14.8 ± 1.6*	15.0 ± 1.7*	15.1 ± 1.7*
	C-10	15.3 ± 2.2	15.2 ± 2.0	15.1 ± 2.1	14.9 ± 2.2*	14.8 ± 2.2*
	E	16.5 ± 2.1	16.4 ± 2.4	16.2 ± 2.2	16.1 ± 2.7	16.1 ± 2.7
Sedation score	P	2	2	2.5	3	3
	C-5	2	2.5	4*†	4*†	4*†
	C-10	2	2.5	4*†	4*†	4*†
	E	2	2	2	2	2

P = lidocaine plain. Added agents: C-5 = 1:200,000 clonidine; C-10 = 1:100,000 clonidine; E = 1:200,000 epinephrine. P, n = 20; C-5, n = 26; C-10, n = 20; E, n = 26.

Values of segments of analgesia and respiratory rate are mean ± SD.

Values of sedation score are median.

\*  $P < 0.05$  versus group P.

†  $P < 0.05$  versus group E.

among the four groups). Of these, three patients had basal HR lower than 60 beats per min. However, there was no difference in the segment numbers of analgesia between patients who did and did not develop sinus bradycardia. All bradycardia episodes were successfully treated with intravenous atropine 0.5 mg. In addition, first-degree atrioventricular block (PQ interval of 0.28 s) was observed approximately 30 min after epidural injection in one patient of group C-5. This block persisted during the operation. No other adverse effects possibly related to epidural clonidine were observed in the perianesthetic pe-

riod, except dryness of mouth in two patients each in groups C-5 and C-10.

## Discussion

The results of the current study indicate that the addition of 1:200,000 or 1:100,000 clonidine to lidocaine solution for epidural anesthesia produces smaller changes in BP and HR compared with the addition of epinephrine to lidocaine solution, and together with butorphanol and diazepam provides intense sedation compared with lidocaine plain or with epinephrine. The plasma lidocaine concentrations showed a tendency to be greater in patients receiving clonidine. Since clonidine could alter the hepatic metabolism of lidocaine, this effect may obscure clonidine's local effects on vascular uptake, and hence its inclusion may increase the possibility of systemic toxic reactions with larger doses or continuous infusion of local

TABLE 4. Results of  $p\text{Ha}$ ,  $\text{PaCO}_2$ ,  $\text{PaO}_2$ , and Base Excess (BE) before and 20 min after Epidural Injection of 18 ml 2% Lidocaine Plain or with an Agent Added

Group		Before	20 Min After
P (n = 20)	$p\text{Ha}$	7.40 ± 0.02	7.40 ± 0.02
	$\text{PaCO}_2$ (mmHg)	38 ± 3	38 ± 3
	$\text{PaO}_2$ (mmHg)	88 ± 10	93 ± 7*
	BE (mEq·L <sup>-1</sup> )	0.05 ± 1.6	-0.1 ± 1.5
C-5 (n = 24)	$p\text{Ha}$	7.40 ± 0.02	7.39 ± 0.02
	$\text{PaCO}_2$ (mmHg)	39 ± 3	39 ± 2
	$\text{PaO}_2$ (mmHg)	88 ± 7	91 ± 7
	BE (mEq·L <sup>-1</sup> )	0.3 ± 1.6	0.3 ± 1.7
C-10 (n = 20)	$p\text{Ha}$	7.41 ± 0.02	7.39 ± 0.02*
	$\text{PaCO}_2$ (mmHg)	38 ± 3	39 ± 4
	$\text{PaO}_2$ (mmHg)	87 ± 10	88 ± 10
	BE (mEq·L <sup>-1</sup> )	0.6 ± 1.6	0.09 ± 1.5*
E (n = 20)	$p\text{Ha}$	7.40 ± 0.01	7.39 ± 0.02
	$\text{PaCO}_2$ (mmHg)	41 ± 3	39 ± 4*
	$\text{PaO}_2$ (mmHg)	84 ± 10	94 ± 8*
	BE (mEq·L <sup>-1</sup> )	1.2 ± 2.0	0.03 ± 1.9*

P = lidocaine plain. Added agents: C-5 = 1:200,000 clonidine; C-10 = 1:100,000 clonidine; E = 1:200,000 epinephrine.

Values are mean ± SD.

\*  $P < 0.05$  versus Before.

TABLE 5. Hemodynamic Responses to Ephedrine (0.1 mg·kg<sup>-1</sup>) in Patients Who Received Epidural Injection of 18 ml 2% Lidocaine Plain or with an Agent Added

Group		Before	After (% change)
P (n = 4)	SBP	84 ± 5	99 ± 10 (17 ± 8)
	HR	70 ± 5	75 ± 12 (6 ± 9)
C-5 (n = 6)	SBP	79 ± 2	102 ± 7 (28 ± 11)
	HR	66 ± 8	70 ± 8 (5 ± 14)
C-10 (n = 7)	SBP	79 ± 5	94 ± 9 (18 ± 7)
	HR	62 ± 8	74 ± 7 (20 ± 9)
E (n = 7)	SBP	80 ± 1	103 ± 6 (28 ± 6)
	HR	73 ± 8	79 ± 13 (7 ± 10)

Values are mean ± SD.

P = lidocaine plain. Added agents: C-5 = 1:200,000 clonidine; C-10 = 1:100,000 clonidine; E = 1:200,000 epinephrine. SBP = systolic blood pressure (mmHg), HR = heart rate (beats·min<sup>-1</sup>), % change = per cent change from values before atropine.

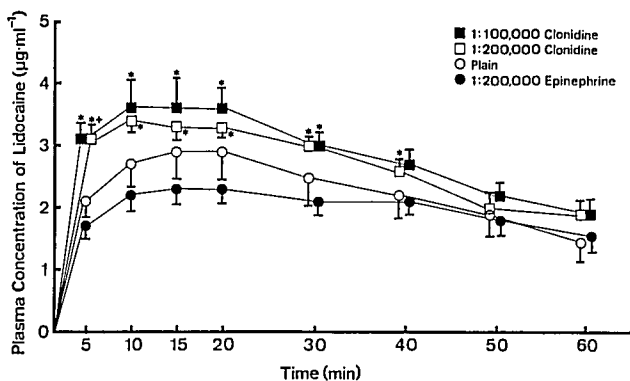


FIG. 1. Plasma concentration of lidocaine after the epidural injection of 18 ml 2% lidocaine either plain (group P, n = 7), or with 1:200,000 clonidine (group C-5, n = 7), 1:100,000 clonidine (group C-10, n = 7), or 1:200,000 epinephrine (group E, n = 7). Each bar represents the standard error. Asterisks denote significant differences ( $P < 0.05$ ) between group C-5 or C-10 and group E. A cross indicates a significant difference compared with group P ( $P < 0.05$ ).

anesthetic. However, it does not alter respiration, arterial oxygenation, and the hemodynamic responses to ephedrine.

Although the inclusion of epinephrine to local anesthetic has been a clinically accepted practice for many years, the addition of clonidine has only recently been suggested. When given epidurally or spinally, clonidine, like epinephrine,<sup>27</sup> has antinociceptive action,<sup>1,7,14,15</sup> probably through its direct suppression of spinal cord nociceptive neurons. However, we observed no clinically significant difference in either onset or extent of analgesia among the four groups (table 2). In contrast, intrathecal clonidine 50–150 µg has been reported to prolong the analgesic effect and the motor blockade of tetracaine<sup>5,6,23</sup> and of bupivacaine.<sup>22</sup> This suggests that clonidine does potentiate or prolong neuronal blockade effects of local anesthetic *per se* by reducing vascular uptake and thereby maintaining a higher concentration of lidocaine near the neuronal tissue for a longer period of time in spinal anesthesia.

According to a recent study, epidural clonidine 300 µg has been shown to decrease lidocaine absorption to the same extent as does epinephrine.<sup>21</sup> In the current study, the ratio of maximum plasma lidocaine concentration in clonidine groups and group E was approximately 1.5 (fig. 1), which is similar to that obtained in an early study comparing 2% plain lidocaine and 1:200,000 epinephrine added to 2% lidocaine.<sup>28</sup> Furthermore, the time course of appearance and decay of plasma lidocaine concentrations was not statistically different between group P and group C-5 or C-10, and between group P and group E (fig. 1). However, the plasma lidocaine concentrations appeared to be increased in the clonidine groups, although only one point, at 5-min after epidural injection, was statistically greater in group C-5 compared to that in group

P. Since plasma alfentanil concentrations are reported to be significantly higher in patients receiving transdermal clonidine,<sup>29</sup> and since the hepatobiliary clearance of sulfobromophthalein is known to be reduced by subcutaneous clonidine in rodents,<sup>30</sup> greater plasma lidocaine concentrations may suggest an altered hepatic metabolism of lidocaine by epidural clonidine, and may obscure clonidine's local effect on systemic absorption. Most previous reports have indicated that epinephrine is effective in the suppression of plasma lidocaine concentrations, possibly through the constriction of epidural vessels.<sup>28,31</sup> Although epidural clonidine has been reported to produce little change in spinal cord blood flow,<sup>2,4</sup> the effect of clonidine upon epidural vessels remains unknown. Therefore, we cannot explain the lack of a suppressive effect on plasma lidocaine concentrations with epidural clonidine.

Hypotension during epidural anesthesia is greater after epinephrine–lidocaine solution than after lidocaine alone.<sup>22,32</sup> An approximately 10–20% decrease in mean BP has been observed during high (around the T5 dermatome)-level epidural analgesia with epinephrine–lidocaine.<sup>14,33–35</sup> These values are quite consistent with the current results of group E (18% decrease in mean BP). In groups C-5 and P, the decreases in mean BP were only 5 and 7%, respectively (significantly different compared to group E). However, the reduction of mean BP in group C-10 (10%) was similar to that in group E ( $P > 0.05$ ). Clonidine decreases BP through central effects, but produces alpha-2-adrenoceptor-mediated vasoconstriction when infused intraarterially in humans.<sup>36</sup> At plasma clonidine concentrations greater than approximately 2–3 ng · ml<sup>-1</sup>, the peripheral action predominates and a pressor response is observed<sup>37,38</sup>; below this concentration, BP decreases.<sup>38</sup> In addition, it has been reported in sheep that the peak concentration of clonidine is approximately 1 ng · ml<sup>-1</sup> after epidural injection of clonidine 300 µg,<sup>39</sup> and epidural clonidine *per se* has been demonstrated to produce no hypotension in awake sheep.<sup>1,2</sup> However, in clinical practice, mild decreases in BP have been observed after epidural injection of clonidine for pain control.<sup>15,16</sup> Since in the presence of lidocaine, alpha-adrenergic mediated vasoconstrictive effects would be potentiated,<sup>40</sup> the smaller degree of reduction in BP may be attributable, at least partly, to higher plasma lidocaine as observed in group C-5. However, it is not clear in the current results whether systemic absorption of clonidine can compensate or augment the hypotension associated with sympathetic denervation by lumbar epidural anesthesia.

Several clinical reports describe severe bradycardia or atrioventricular conduction disturbance during clonidine therapy.<sup>41–45</sup> Experimentally, epidural clonidine provokes a slowing of HR in anesthetized dogs<sup>3</sup> and in awake sheep.<sup>2</sup> In the current study, six and seven patients of groups C-5 and C-10 developed bradycardia after epidural injection. Because the incidence of bradycardia after epi-

dural injection was similar among the four groups, bradycardia may result not only from epidural clonidine but also from cardiac sympathetic blockade by epidural lidocaine. Although the responses to intravenous atropine are inconsistent and controversial,<sup>11,41,46</sup> our patients responded well to intravenous atropine. Nevertheless, epidural clonidine should be avoided in patients with sinus node dysfunction or atrioventricular conduction disturbances, or in patients who are taking drugs that have negative chronotropic effects or that slow the atrioventricular transmission.<sup>41-43,47</sup>

Although the precise site of its actions remains unclear,<sup>13</sup> and although the participation of alpha 2-adrenoceptors is controversial,<sup>1,48</sup> it has been shown that clonidine has several effects on the central nervous system. These include marked sedation, prolonged chloral hydrate sleeping time, decreased conditioned avoidance behavior, and lowered body temperature.<sup>13</sup> In humans,<sup>49</sup> sedation has been reported to occur after intrathecal clonidine 300 µg. In the current results we observed obvious sedative effects in patients in the clonidine groups compared to those in the other groups (table 3). A potential criticism of our study is that sedation was not assessed in a double-blind fashion. However, observer bias was unlikely, since we defined sedation score to be 4 only when the patient complained of feeling sleepy. The mean dose of epidural clonidine used in the current clinical study was approximately 1.7 µg · kg<sup>-1</sup> in group C-5 and 3.3 µg · kg<sup>-1</sup> in group C-10. The former dose is low, whereas the latter dose is comparable to that producing sedation in the sheep (approximately 3 µg · kg<sup>-1</sup>).<sup>1</sup> Moreover, this sedative effect of clonidine may be potentiated by concomitant use of lidocaine, since lidocaine alone produces central nervous depression<sup>50</sup> and direct suppression of spinal cord nociceptive neurons.<sup>51</sup> This sedative effect of lidocaine is obvious when comparing the incidence of sedation score 4 (30% vs. 7%) and the plasma lidocaine concentrations (fig. 1) between groups P and E. However, the higher sedation score observed in the clonidine groups can be attributed primarily to the action of clonidine, since comparable plasma lidocaine concentrations were found in group P and in the clonidine groups.

Eisenach and Grice<sup>2</sup> and Eisenach<sup>25</sup> observed hypoxemia in sheep after epidural (17–25 µg · kg<sup>-1</sup>) or intravenous (3–15 µg · kg<sup>-1</sup>) injection of clonidine. Transient platelet aggregation and pulmonary microembolism were suggested as possible causes of hypoxemia after clonidine.<sup>25</sup> In the current study, however, no significant change in PaO<sub>2</sub> and PaCO<sub>2</sub> was found 20 min after epidural injection of clonidine–lidocaine solution in either dose studied (table 4). A small increase in PaO<sub>2</sub> was noted in groups P and E (table 4). Although the mechanism of the improvement of oxygenation was not clear, the addition of clonidine may have counteracted increases in PaO<sub>2</sub> after epidural blockade. In addition, it is clinically important

in anesthesia practice to determine whether the responsiveness to ephedrine is preserved after an administration of clonidine, since ephedrine increases BP by stimulating the release of catecholamine from both alpha- and beta-adrenergic receptors, and since clonidine is reported to suppress the plasma norepinephrine appearance in humans.<sup>52</sup> However, no significant difference in the responses to ephedrine was noted among the four groups (table 5).

In conclusion, the absence of tachycardia, a smaller decrease in BP, and a pronounced sedative effect were noted in patients receiving epidural anesthesia when 1:200,000 or 1:100,000 clonidine was added to lidocaine solution compared those receiving lidocaine plain or with 1:200,000 epinephrine. Despite these potentially beneficial effects of clonidine added to lidocaine solution, a higher plasma concentration of lidocaine in patients receiving clonidine may limit widespread use of clonidine as an adjunct to epidural anesthesia.

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## References

1. Eisenach JC, Dewan DM, Rose JC, Angelo JM: Epidural clonidine produces antinociception, but not hypotension, in sheep. *ANESTHESIOLOGY* 66:496–501, 1987
2. Eisenach JC, Grice SC: Epidural clonidine does not decrease blood pressure or spinal cord blood flow in awake sheep. *ANESTHESIOLOGY* 68:335–340, 1988
3. Ghignone M, Calvillo O, Quintin L, Caple S, Kozody R: Haemodynamic effects of clonidine injected epidurally in halothane-anaesthetized dogs. *Can J Anaesth* 34:46–50, 1987
4. Gordh T Jr, Feuk U, Norlén K: Effect of epidural clonidine on spinal cord blood flow and regional and central hemodynamics in pigs. *Anesth Analg* 65:1312–1318, 1986
5. Bedder MD, Kozody R, Palahniuk RJ, Cumming MO, Pucci WR: Clonidine prolongs canine tetracaine spinal anaesthesia. *Can Anaesth Soc J* 33:591–596, 1986
6. Mensink FJ, Kozody R, Kehler CH, Wade JG: Dose–response relationship of clonidine in tetracaine spinal anesthesia. *ANESTHESIOLOGY* 67:717–721, 1987
7. Post C, Gordh T Jr, Minor BG, Archer T, Freedman J: Antinociceptive effects and spinal cord tissue concentrations after intrathecal injection of guanfacine or clonidine into rats. *Anesth Analg* 66:317–324, 1987
8. Gordh T, Jr, Post C, Olsson Y: Evaluation of the toxicity of subarachnoid clonidine, guanfacine, and a substance P-antagonist on rat spinal cord and nerve roots: Light and electron microscopic observations after chronic intrathecal administration. *Anesth Analg* 65:1303–1311, 1986
9. Crosby G, Russo M: The spinal blood flow effect of subarachnoid clonidine (abstract). *ANESTHESIOLOGY* 67:A417, 1987

10. Lowenstein J: Clonidine. *Ann Intern Med* 92:74-77, 1980
11. Naylor WG, Stone J: An effect of ST 155 (clonidine), 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride, Catapres<sup>®</sup> on relationship between blood pressure and heart rate in dogs. *Eur J Pharmacol* 10:161-167, 1970
12. Cavero I, Roach AG: Effects of clonidine on canine cardiac neuroeffector structures controlling heart rate. *Br J Pharmacol* 70:269-276, 1980
13. Laverty R, Taylor KM: Behavioural and biochemical effects of 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride (St 155) on the central nervous system. *Br J Pharmacol* 35:253-264, 1969
14. Bonica JJ, Akamatsu TJ, Berges PU, Morikawa K, Kennedy WF, Jr: Circulatory effects of peridural block: II. Effects of epinephrine. *ANESTHESIOLOGY* 34:514-522, 1971
15. Tamsen A, Gordh T: Epidural clonidine produces analgesia. *Lancet* 2:231-232, 1984
16. Kalia PK, Mandan R, Batra RK, Latha V, Vardhan V, Gode GR: Clinical study on epidural clonidine for postoperative analgesia. *Indian J Med Res* 83:550-552, 1986
17. Coventry DM, Todd G: Epidural clonidine in lower limb deafferentation pain. *Anesth Analg* 69:424-425, 1989
18. Eisenach JC, Rauck RL, Buzzanell C, Lysak SZ: Epidural clonidine analgesia for intractable cancer pain: Phase I. *ANESTHESIOLOGY* 71:647-652, 1989
19. Eisenach JC, Lysak SZ, Viscomi CM: Epidural clonidine analgesia following surgery: Phase I. *ANESTHESIOLOGY* 71:640-646, 1989
20. Tzeng JI, Wang JJ, Mok MS, Lippmann M: Clonidine potentiates lidocaine-induced epidural anesthesia (abstract). *Anesth Analg* 68:S298, 1989
21. Veillette Y, Orhant E, Benhamou D, Labaille T, Mazoit JX: Addition of clonidine decreases lidocaine absorption after epidural injection (abstract). *ANESTHESIOLOGY* 71:A267, 1989
22. Racle JP, Benkhadra A, Poy JY, Gleizal B: Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. *Anesth Analg* 66:442-446, 1987
23. Bonnet F, Brun-Buisson V, Saada M, Boico O, Rostaing S, Touboul C: Dose-related prolongation of hyperbaric tetracaine spinal anesthesia by clonidine in humans. *Anesth Analg* 68:619-622, 1989
24. Coombs DW, Jensen LB, Murphy C: Microdose intrathecal clonidine and morphine for postoperative analgesia (abstract). *ANESTHESIOLOGY* 67:A238, 1987
25. Eisenach JC: Intravenous clonidine produces hypoxemia by a peripheral alpha-2 adrenergic mechanism. *J Pharmacol Exp Ther* 244:247-252, 1988
26. Clement GE, Havassy J, Foery RF, Lewis LM, Lee CK, Adams K, Vaughn R, Scholer A, Günther M: An evaluation of the lidocaine method for the Du Pont aca<sup>®</sup> discrete clinical analyzer. *Wilmington, Du Pont Company*, 1983, pp 1-55
27. Collins JG, Kitahata LM, Matsumoto M, Homma E, Suzukawa M: Spinally administered epinephrine suppresses noxiously evoked activity of WDR neurons in the dorsal horn of the spinal cord. *ANESTHESIOLOGY* 60:269-275, 1984
28. Scott DB, Jebson PJR, Braid DP, Örtengren B, Frisch P: Factors affecting plasma levels of lignocaine and prilocaine. *Br J Anaesth* 44:1040-1049, 1972
29. Segal IS, Jarvis DA, Duncan SR, White PF, Maze M: Perioperative use of transdermal clonidine as an adjunctive agent (abstract). *Anesth Analg* 61:S250, 1989
30. Ben-Zvi Z, Hurwitz A: Clonidine effects on disposition of xenobiotics in the rats: Inhibited elimination of flow-limited but not extraction-limited agents. *Br J Pharmacol* 94:97-102, 1988
31. Ohno H, Watanabe M, Saitoh J, Saegusa Y, Hasegawa Y, Yonezawa T: Effect of epinephrine concentration on lidocaine disposition during epidural anesthesia. *ANESTHESIOLOGY* 68:625-628, 1988
32. Bonica JJ, Berges PU, Morikawa K: Circulatory effects of peridural block: I. Effects of level of analgesia and dose of lidocaine. *ANESTHESIOLOGY* 33:619-626, 1970
33. Bonica JJ, Kennedy WF Jr, Akamatsu TJ, Gerbershagen HU: Circulatory effects of peridural block: III. Effects of acute blood loss. *ANESTHESIOLOGY* 36:219-227, 1972
34. Stanton-Hicks M, Berges PU, Bonica JJ: Circulatory effects of peridural block: IV. Comparison of the effects of epinephrine and phenylephrine. *ANESTHESIOLOGY* 39:308-314, 1973
35. Ward RJ, Bonica JJ, Freund FG, Akamatsu T, Danziger F, Englesson S: Epidural and subarachnoid anesthesia: Cardiovascular and respiratory effects. *JAMA* 191:275-278, 1965
36. Kiowski W, Hulthen UL, Ritz R, Bühler FR:  $\alpha_2$  Adrenoceptor-mediated vasoconstriction of arteries. *Clin Pharmacol Ther* 34:565-569, 1983
37. Wing LMH, Reid JL, Davies DS, Neill EAM, Tippett P, Dollery CT: Pharmacokinetic and concentration-effect relationships of clonidine in essential hypertension. *Eur J Clin Pharmacol* 12:463-469, 1977
38. Domino LE, Domino SE, Stockstill MS: Relationship between plasma concentrations of clonidine and mean arterial pressure during an accidental clonidine overdose. *Br J Clin Pharmacol* 21:71-74, 1986
39. Castro MI, Eisenach JC: Pharmacokinetics and dynamics of intravenous, intrathecal, and epidural clonidine in sheep. *ANESTHESIOLOGY* 71:418-425, 1989
40. Blair MR: Cardiovascular pharmacology of local anaesthetics. *Br J Anaesth* 47:247-252, 1975
41. Byrd BF III, Collins HW, Primm RK: Risk factors for severe bradycardia during oral clonidine therapy for hypertension. *Arch Intern Med* 148:729-733, 1988
42. Kibler LE, Gazes PC: Effect of clonidine on atrioventricular conduction. *JAMA* 238:1930-1932, 1977
43. Williams PL, Krafek JM, Potter BB, Hooper JH, Hearne MJ: Cardiac toxicity of clonidine. *Chest* 72:784-785, 1977
44. Abiuso P, Abelow G: Atrioventricular dissociation in a patient receiving clonidine. *JAMA* 240:108-109, 1978
45. Etta LV, Burchell H: Severe bradycardia with clonidine. *JAMA* 240:2047, 1978
46. Duchene-Marullaz P, Lavarenne J, Lapalus P, Boucher M, Mongheal Y: Effect of clonidine on heart rate in dogs with acute or chronic heart block. *Eur J Pharmacol* 28:76-80, 1974
47. Thormann J, Neuss H, Schlepper M, Mitrovic V: Effects of clonidine on sinus node function in man. *Chest* 80:201-206, 1981
48. Drew GM, Gower AJ, Marriott AS:  $\alpha_2$ -Adrenoceptors mediate clonidine-induced sedation in the rat. *Br J Pharmacol* 67:133-141, 1979
49. Coombs DW, Saunders RL, Lachance D, Savage S, Ragnarsson TS, Jensen LE: Intrathecal morphine tolerance: Use of intrathecal clonidine, DADLE, and intraventricular morphine. *ANESTHESIOLOGY* 62:358-363, 1985
50. Wagman IH, de Jong RH, Prince DA: Effects of lidocaine on the central nervous system. *ANESTHESIOLOGY* 28:155-172, 1967
51. Dohi S, Kitahata LM, Toyooka H, Ohtani M, Namiki A, Taub A: An analgesic action of intravenously administered lidocaine on dorsal-horn neurons responding to noxious thermal stimulation. *ANESTHESIOLOGY* 51:123-126, 1979
52. Veith RC, Best JD, Halter JB: Dose-dependent suppression of norepinephrine appearance rate in plasma by clonidine in man. *J Clin Endocrinol Metab* 59:151-155, 1984