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Intravenous or Epidural Clonidine for Intra- and Postoperative Analgesia

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Background: **Intravenous and epidural clonidine both produce postoperative analgesia. Several experimental reports demonstrate a spinal site of action for the analgesic effects of this α_2-adrenoceptor agonist. Therefore, the authors evaluated the clinical analgesic benefits of using clonidine, both intra- and postoperatively, by the epidural or the intravenous route.**

Methods: **Using a randomized prospective double-blind study design, 40 patients, between 18 and 50 yr of age, undergoing intestinal surgery under general propofol/nitrous oxide anesthesia, were enrolled. Before anesthesia, an epidural catheter was inserted at the L1-L2 interspace. At induction, a clonidine infusion was started at the doses of 4 μg/kg in 10 ml during 20 min, followed by 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (5 ml/h) during 12 h, either by the epidural (group 1) or by the intravenous (group 2) route. Intraoperatively, increased blood pressure and heart rate not responding to additional propofol bolus (0.5 mg/kg) was treated with a bolus of alfentanil (7 μg/kg). Postoperatively, morphine boluses (1.5 mg) were given through a PCA device according to the patient's need. Intraoperative analgesia was assessed by the alfentanil requirements. Postoperative analgesia was assessed by recording the morphine requirements, the visual analogue scale (VAS) at rest and after mobilization, and the patients' analgesia scale at 0, 3, 6, 12, 18, 24, and 36 postoperative hours. Sedation analogue scale and side effects were also recorded. Heart rate and blood pressure were particularly detailed during the first 2 h of the clonidine infusion. Plasma clonidine concentrations were measured after 20 min and 6, 12, and 24 h.**

Results: **Epidural clonidine significantly reduced the intraoperative alfentanil requirements (0.93 ± 1.2 in group 1 *vs.* 2.4 ± 1.8 mg in group 2). The postoperative morphine requirements were also reduced during the first 6 h (8.3 ± 5.8 in group 1 *vs.* 17.8 ± 13.4 mg in group 2). The VAS were comparable in both groups, despite the better patients' analgesia score reported in the epidural group during the first 12 h. There was no difference in sedation score at any time interval considered. Epidural and intravenous clonidine reduced heart rate and blood pressure to the same extent. The plasma clonidine concentrations were less in the epidural group only after the loading doses.**

Conclusions: **Epidural clonidine reduces the intra- and early postoperative analgesic requirements when compared with the same dose given by the intravenous route. The side effects were similar with the two routes of administration. (Key words: Analgesia, epidural, parenteral: clonidine. Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: alfentanil. Pharmacology: clonidine. Sympathetic nervous system, α_2-adrenergic agonist: clonidine.)**

EPIDURAL and intravenous clonidine produce postoperative analgesia.[1–3,§] Several experimental reports have demonstrated a spinal site of action for the analgesic effects of this α_2-adrenoceptor agonist.[4] In the spinal dorsal horn, α_2-adrenoceptor agonists depress the activity of the wide dynamic range neurons and depress the release of substance P.[5,6] A segmental spinal effect has been demonstrated, both in animals and humans.[7,8] For these reasons, it could be hypothesized that epidural clonidine is more effective than is intravenous clonidine in relieving intra- and postoperative pain. The current clinical investigation has been performed to test this hypothesis.

Materials and Methods

This double-blind study was approved by the Institutional Ethics Committee, and all subjects gave informed consent. Forty adult patients between 18 and 50 yr of age scheduled for extensive intestinal resection for inflammatory bowel disease or second-stage reanastomosis participated in this study. Exclusion criteria were: chronic use of any antiinflammatory, cardiovascular, or psychotropic medications, including benzodiazepines; any renal or hepatic dysfunction; acute inflammatory bowel process at the time of surgery; in-

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§ Kalia PK, Madan R, Batra RK, Latha V, Vardham V, Gode GR: Clinical study on epidural clonidine for postoperative analgesia. Indian J Med Res 83:550–552, 1986.

ability to understand the study protocol; and a history of allergic reaction to any of the study drugs. A previous abdominal procedure was a required inclusion criteria.

The day before surgery, the study protocol was explained to the patients. They were asked to push the analgesic demand button of the PCA device (Abbott LifeCare 4200, Chicago, IL) any time they experienced pain and until pain was relieved. The pain VAS was clearly explained. Arterial blood pressure and heart rate at rest were recorded.

The night before surgery, all patients received 2 mg lormetazepam. Another 2 mg were given sublingually 1 h before the procedure, followed, 30 min later, by 7 μg/kg atropine intramuscularly.

Once in the operating theater, an epidural catheter was inserted in all patients *via* the L1-L2 interspace using the loss-of-resistance technique (no local anesthetic test dose was used). At this time, patients were randomly assigned to receive either epidural clonidine and intravenous saline (group 1) or intravenous clonidine and epidural saline (group 2). In both groups, clonidine was given in 20 min at the dose of 4 μg/kg in 10 ml, followed immediately by a continuous infusion of 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (5 ml/h) during 12 h. The saline solution was infused using the same volume and pattern. The induction of anesthesia began at the end of the loading dose.

Intraoperative monitoring included an intraarterial catheter for systemic blood pressure monitoring, a central venous catheter for CVP monitoring, ECG leads V5 and II (Datex Cardiocap; Datex Capnograph, Helsinki, Finland) for analysis of expiratory CO_2 and inspiratory O_2 and N_2O, an esophageal temperature monitor, and a pulse oximeter for measurement of peripheral hemoglobin oxygen saturation (Sp_{O_2}).

Anesthetic management consisted of 7 μg/kg alfentanil, propofol titrated until there was loss of the eyelid reflex (±2 mg/kg), and atracurium (0.5 mg/kg) for induction. Anesthesia was maintained with a propofol infusion of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ and 50% nitrous oxide in oxygen. Neuromuscular blockade was maintained with a continuous infusion of atracurium (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

Additional doses of propofol were given in response to a 20% increase of the mean arterial pressure or heart rate recorded at the end of the loading dose of clonidine and before skin incision (clonidine baseline). The absence of return to this clonidine baseline after 3 min prompted the injection of a bolus of 7 μg/kg alfentanil.

The atracurium infusion was discontinued at the beginning of the closure of the peritoneum. The propofol infusion and nitrous oxide were discontinued at the last skin suture.

The following assessments were made:

1. Intraoperative anesthetic (propofol) and analgesic (alfentanil) requirements according to the hemodynamic parameters were recorded.
2. Intraoperative hemodynamics were monitored continuously throughout the study period, and, during the first 2 h following the initiation of the clonidine infusion values, were recorded at 2 min intervals.
3. Time to awakening from anesthesia was determined as the time from discontinuation of the nitrous oxide and propofol until the time the patients first opened their eyes in response to verbal command.
4. Arterial *p*H, p_{O_2}, and p_{CO_2} were measured (Corning blood gas analyzer, Medfield, MA) at arrival in the recovery room and 3 h after tracheal extubation.
5. Degree of postoperative sedation was determined according to a four-point sedation scale at 0, 1.5, 3, 6, 12, 18, 24, and 36 postoperative hours. The scale was as follows: 0 = alert; 1 = drowsy but easily aroused to an alert state by verbal command; 2 = sleeping and arousable by verbal command; and 3 = sleeping not arousable by verbal stimuli, but arousable to a drowsy state by tactile stimulation.
6. Postoperative analgesic requirements were assessed using a patient-controlled analgesic delivery system that the patient activated to deliver a preset bolus of 2 mg/ml morphine. The PCA settings were morphine bolus dose, 1.5 mg, at a lockout interval of 7 min, with a 4-h limit of 30 mg. Both the met and unmet demands were noted.
7. Pain was evaluated by an observer unaware of the routes of clonidine injection, using a 10-cm VAS (0 = no pain, 10 = maximum pain) at rest after 3, 6, 12, 18, 24, and 36 h and during mobilization from the supine position in bed to the sitting position in the armchair at 12, 18, 24, and 36 postoperative hours. A verbal rating score (0 = no pain; 1 = moderate abdominal pain but good control with the PCA pain therapy; 2 = moderate to severe abdominal pain and poor control with the PCA; and 3 = unbearable pain) was also used immediately after tracheal extubation and at 3, 6, 12, 18, 24, and 36 postoperative hours. After 48 h, patients were asked to evaluate their postoperative pain management using a three-point scale (1 = bad, 2 = simply good, and 3 = better than expected).

8. Plasma clonidine concentrations were determined in 20 patients (10 in each group, randomly sampled from the entire group) using a radioimmunoassay method on blood sampled after the loading dose, 6 h after the start, at the end of the continuous infusion, and 12 h later. The sensitivity of this assay was 0.1 ng/ml with a coefficient of variation of less than 15%.
9. Perioperative complications were recorded (*e.g.*, heart block, intraoperative hypotension, awareness, orthostatic hypotension, rebound hypertension, and nausea and vomiting.)

Statistical comparisons of independent variables were based on *t* test. Analysis of variables over time was evaluated by one-way univariate ANOVA with repeated measures (CSS statistica; Statsoft, Tulsa, OK). When applicable, intergroup differences were analyzed by Tukey's least significant differences test.

Nonparametric categorical variables were analyzed by Kruskal-Wallis ANOVA by ranks test. A P value < 0.05 was considered statistically significant.

Results

The demographic data of the patients who participated in the study are summarized in table 1. There was no significant difference between the two clonidine groups with respect to age, gender, weight, height, ASA physical status, and duration of surgery. The placement of the epidural catheter was easy and successful at the first attempt in all of the patients.

Anesthesia and Intraoperative Analgesia (Table 2)

The dose of propofol required to induce anesthesia was the same in both groups (124 ± 29.7 mg in the epidural group *vs.* 129 ± 44.1 mg in the intravenous group). More anesthetic reinjections, according to the hemodynamic parameters, were required in patients of group 2 (7.4 ± 4.9 *vs.* 3.2 ± 3.1 in group 1; $P < 0.01$).

Additional alfentanil boluses were administered 1.9 ± 2.5 times in group 1 *versus* 4.7 ± 3.5 in group 2 ($P < 0.01$). The total doses of alfentanil administered were 1.7 ± 1.7 mg in group 1 *versus* 2.9 ± 1.8 mg in group 2 ($P = 0.03$). Patients in group 1 recovered sooner than patients in group 2 (11 ± 2.9 min *vs.* 14 ± 3.9 min; $P < 0.01$). The values of the arterial blood gases were comparable in both groups.

At arrival in the recovery room, *p*H was 7.33 ± 0.03 *versus* 7.34 ± 0.02, p_{O_2} (FI_{O_2} 0.4) 182 ± 21 *versus* 190 ± 21 mmHg, and p_{CO_2} 40 ± 3 *versus* 40 ± 3 mmHg in groups 1 and 2, respectively.

After 3 h, *p*H was 7.36 ± 0.03 *versus* 7.35 ± 0.02, p_{O_2} (FI_{O_2} 0.21) 96 ± 8 *versus* 100 ± 21 mmHg, and p_{CO_2} 39 ± 2 *versus* 39 ± 2 mmHg in groups 1 and 2, respectively.

Postoperative Analgesia

At the time of tracheal extubation, one patient in the epidural group complained of moderate abdominal pain, *versus* four patients in the intravenous group ($P = 0.04$). The first analgesic demand occurred 103 ± 115 min after tracheal extubation in the epidural group and 83 ± 106 min in the intravenous group ($P = 0.57$).

Table 1. Demographic Data

	Epidural Clonidine (Group 1, n = 20)	Intravenous Clonidine (Group 2, n = 20)
Age (yr)	34.2 ± 7.6	36.8 ± 10.7
Weight (kg)	67.6 ± 13.1	59.6 ± 16.2
Height (cm)	175.8 ± 8.9	169.8 ± 9.3
Male/female	13/7	13/7
Previous abdominal procedure (n)	2.0 ± 1	2.2 ± 0.7

Results are mean ± SD. No statistically significant differences were noted between the two groups.

Table 2. Intraoperative Anesthetic and Analgesic Requirements

	Epidural Clonidine (Group 1, n = 20)	*P*	Intravenous Clonidine (Group 2, n = 20)
Duration of anesthesia (min)	294 ± 84		315 ± 70
Propofol			
Induction dose (mg)	124 ± 30	NS	129 ± 44
Reinjections			
N	3.2 ± 3.1	<0.01	7.4 ± 4.9
Dose (mg)	97.5 ± 94.2	<0.01	216.4 ± 141.2
Total dose (mg) (including infusion)	858 ± 281	NS	964 ± 388
Alfentanil			
Induction dose (mg)	0.5 ± 0	NS	0.53 ± 0.1
Reinjections			
N	1.9 ± 2.5	<0.01	4.7 ± 3.5
Dose (mg)	0.93 ± 1.2	<0.01	2.4 ± 1.8
Total dose (mg)	1.4 ± 1.4	<0.05	2.9 ± 1.8

Results are mean ± SD.

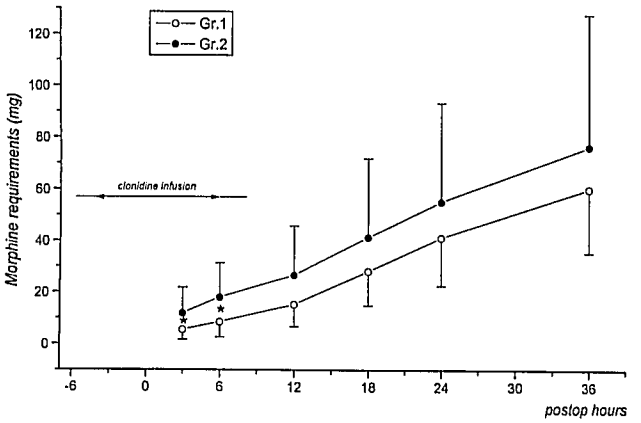

Fig. 1. Postoperative morphine requirements (mg) in patients having received epidural (group 1; n = 20) or intravenous (group 2; n = 20) clonidine at different postoperative times. Results are mean ± SD. *$P < 0.001$ (comparison between group 1 and group 2).

Epidural clonidine (group 1) reduced the morphine requirements during the first 6 postoperative hours ($P < 0.001$; fig. 1). The number of analgesic demands was also fewer at this time ($P < 0.01$; fig. 2).

After completion of surgery, but still during the infusion of clonidine, less morphine was required in the epidural group (6 ± 3.7 vs 12.4 ± 9.5 mg $p < 0.01$).

A comparable level of pain at rest and after mobilization was demonstrated by the VAS in both groups at the different postoperative time (fig. 3). Patients in the epidural group reported better pain scores ($P < 0.05$) during the first 12 postoperative hours.

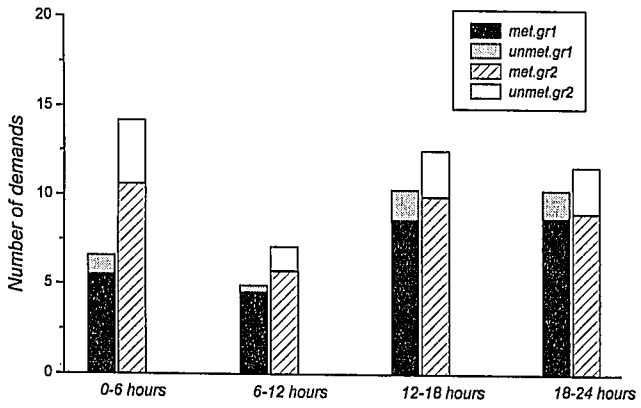

Fig. 2. Analgesic demands (both met and unmet) of the patients having received epidural clonidine (group 1; n = 20) or intravenous (n = 20) clonidine at different postoperative times. Results are mean ± SD. The difference between the two groups is significant ($P < 0.01$) only during the first period (0–6 h).

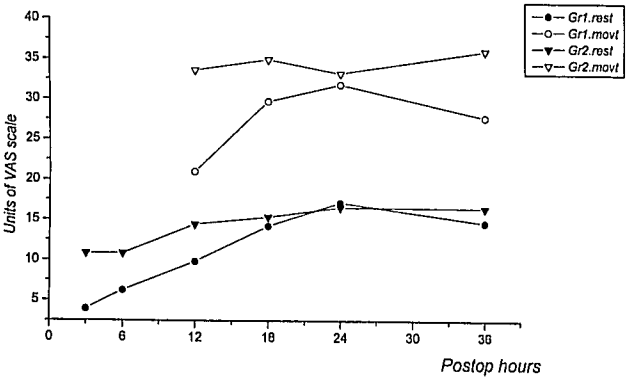

Fig. 3. Changes in VAS score in patients having received epidural (group 1; n = 20) or intravenous (group 2; n = 20) clonidine at different postoperative times.

The majority of the subjects were satisfied with their postoperative pain management. Thirty-eight patients rated their analgesia as better than expected, and two patients rated it as good (one in each group).

There was no difference in the sedation scales between the two groups at any time interval considered. No patients received a score of 4 (fig. 4).

Hemodynamic values at rest the day before surgery were comparable in the two groups. Preinduction heart rate was significantly higher in the epidural group ($P < 0.05$). Intravenous and epidural clonidine given during the induction of anesthesia significantly reduced the preinduction values of heart rate and mean arterial blood pressure to the same extent ($P < 0.01$, 10 min

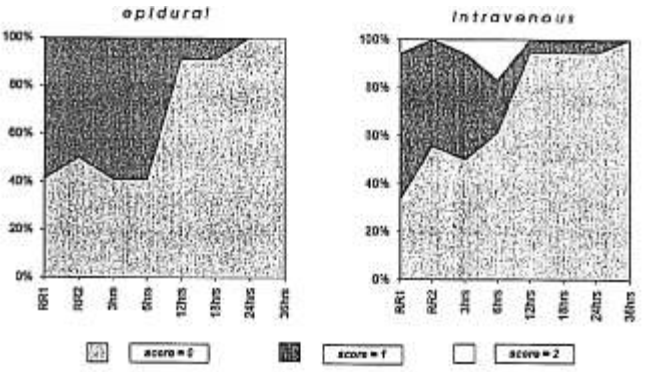

Fig. 4. Sedation scores at the arrival in the recovery room (RR1) and after 1.5 (RR2), 3, 6, 12, 18, 24, and 36 postoperative hours in patients having received epidural (group 1; n = 20) or intravenous (group 2; n = 20) clonidine. Score 0 = alert; Score 1 = drowsy but easily arousable to an alert state by verbal command; Score 2 = sleeping and arousable by verbal command; and Score 3 = sleeping and not arousable by verbal stimuli, but arousable to a drowsy state by tactile stimulation.

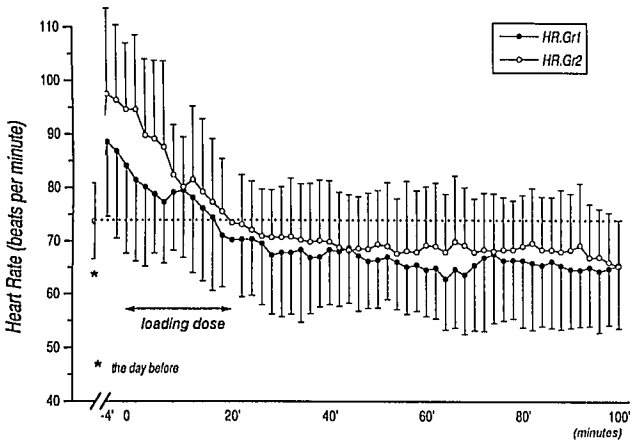

Fig. 5. Changes in heart rate after epidural (group 1) or intravenous (group 2) clonidine. Results are expressed as mean ± SD. Based on the preinduction values (−4 to 0), heart rate decreased significantly in both groups ($P < 0.01$) from 10 min after clonidine administration. The dashed line represents the values at rest the day before surgery. None of the hemodynamic values presented are significantly reduced compared with these values.

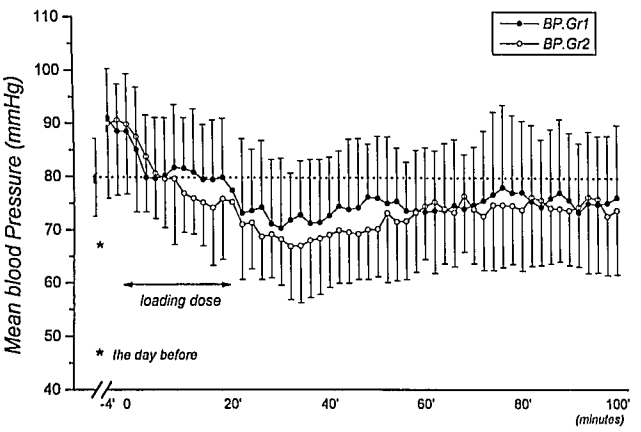

Fig. 6. Changes in mean arterial blood pressure after epidural (group 1) or intravenous (group 2) clonidine. Results are expressed as mean ± SD. Based on the preinduction values (−4 to 0), mean arterial blood pressure decreased significantly in both groups ($P < 0.01$) from 10 min after clonidine administration. The dashed line represents the values at rest the day before surgery. None of the hemodynamic values presented are significantly reduced compared with these values.

after the start of the infusion). Minimum heart rate and mean arterial blood pressure occurred approximately 10 min after the end of the loading dose in both groups. None of the hemodynamic values considered were significantly reduced compared with the values taken at rest the day before surgery (figs. 5 and 6).

In none of the patients considered was bradycardia or hypotension sufficient to require a specific intervention during the observation period. The plasma levels of clonidine were comparable in the two groups, except at the end of the loading dose, when higher circulating levels were measured after intravenous injection (fig. 7).

The frequency of side effects was low in both groups of patients. Specifically, none of the patients experienced nausea or vomiting. The most frequent side effect was xerostomia. None of the patients developed rebound hypertension during the first postoperative week. The postoperative course was uneventful for all of the patients, except for one subject in the epidural group, who developed a severe depression requiring management with specific drugs.

Discussion

Clonidine, an imidazolin α_2-adrenoceptor agonist, reduces both intra- and postoperative analgesic requirements.[9–11] These effects are obtained using the systemic or epidural route, and there is some debate regarding the most efficient route.[8,12]

In our group of patients, all of whom had had previous postoperative pain experience, a slight but significant analgesic advantage was demonstrated using the epidural *versus* the intravenous route. In contrast, however, Bonnet *et al.* observed no difference when comparing the postoperative analgesic effects of a bolus of 2 μg/kg clonidine given by the epidural or the in-

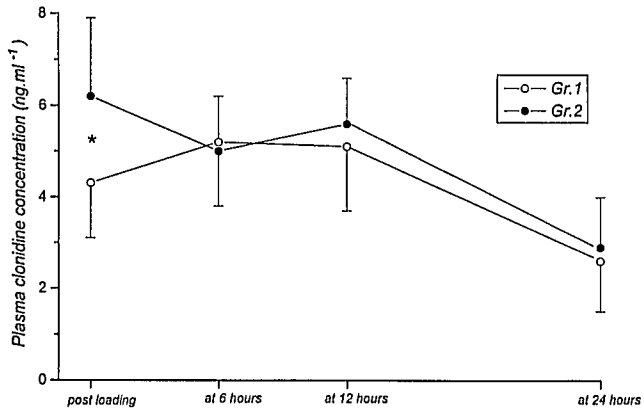

Fig. 7. Plasma clonidine concentrations after epidural (group 1; n = 10) and intravenous (group 2; n = 10) administration. Each point represents the mean value ± SD. *$P < 0.01$.

tramuscular route.[12] The major explanation for the difference may be in the amount of clonidine used.

The intravenous loading dose and continuous infusion chosen in the current study were reported to improve postoperative analgesia after abdominal surgery when compared with classic opioid management.[11] The same dose and pattern of infusion were chosen for the epidural infusion. Epidural clonidine has a relatively high CSF bioavailability and produces postoperative analgesia at doses greater than 3 μg/kg.[2] Despite a plasma elimination half life of 3–6 h, the analgesic effect of epidurally injected clonidine is short lived, and a continuous infusion is required for a sustained effect.[8,13] In volunteers in whom experimental pain is produced with cold immersion, a linear inverse correlation of CSF clonidine to VAS pain was found with maximal reduction in VAS pain at concentrations greater than 100 ng/ml.[8] Glynn obtained some pain relief in six patients suffering deafferentation pain, after epidural injection of 150 μg clonidine reaching a maximum mean CSF concentration of 228 ± 56 ng/ml; in these patients, the mean CSF elimination half life was 66 ± 2 min.[14] Keeping in mind that the epidural site acts as a "depot" for the lipophilic drugs,[14] the high dose of clonidine used in the current study, and the elevated plasma levels found after epidural infusion, indicate that such a CSF concentration was most certainly reached. It may account for the differential analgesic effect demonstrated between the two routes.

Several experimental data, and a recent human volunteer study, support a primary spinal mechanism for the antinociceptive effects of the α_2-adrenergic agonists.[4,5,8,15] A local anesthetic action was also described on isolated C-fiber afferents.[16] In the current study, the reduced opioid requirements was observed only during the epidural infusion and, despite similar plasma levels of clonidine, are in accordance with this hypothesis. However, the clinical effects observed after systemic administration of clonidine give an idea of the relative importance of its spinal, in comparison with its supraspinal, action. Although conflicting results were demonstrated after its administration to certain brainstem sites,[17,18] clonidine produces analgesia when directly injected at the locus coeruleus,[19] the site of origin of the noradrenergic axons to the dorsal horn.[20] Lesions to this nucleus attenuate the antinociceptive effect of systemically administered clonidine.[21] It is documented that systemic clonidine elicits antinociception in rodents[22] and humans,[3] but does not easily penetrate the CSF.[13,14] Because of its lipophilicity, it reaches supraspinal centers, where it mimics the postsynaptic actions of noradrenaline released at bulbospinal pathways.

The current study was not designed to evaluate the efficacy of clonidine administered in the perioperative period. The analgesic effects of this drug may be suspected when referring to our previous studies in abdominal surgery. In a control group of 15 patients, the morphine requirements during the first 6 postoperative hours were 20.3 ± 10.4 mg. But doses of 1,168 ± 624 μg fentanyl were used intraoperatively. There were 40 analgesic demands, and the pain was reported as unbearable or severe in 5 patients.[23] In a control series of 91 patients in which no clonidine was given, the morphine requirements at 12 postoperative hours were 27.6 ± 18.1 mg, and the intraoperative dose of fentanyl was 1,050 ± 735 μg. At the same time, more than 40 analgesic demands were recorded, and the pain was reported as absent or moderate by a minority of the population.[11]

A synergistic analgesic action between the opioids and the α_2-adrenergic agonists is demonstrated at spinal and supraspinal levels.[24,25] The current results do not allow us to differentiate between a pure analgesic effect of the α_2-adrenergic agonists and a possible potentiation of the opioid analgesia.

It is unlikely that a pharmacokinetic interaction between alfentanil and clonidine can explain, by itself, the intraoperative analgesic-sparing effect of clonidine. This possibility was suggested by Segal *et al.*, based on alfentanil plasma levels after oral-transdermal clonidine.[26] The doses of alfentanil used in Segal's study were more than three times greater than the doses used in the current study, and were given by continuous infusion. In the postoperative period, a clonidine-induced interference with the biodisposition of morphine is also unlikely.

In the current study, the timing and magnitude of the reduction in blood pressure were comparable by the two routes of administration. A systemic effect may be postulated, despite the lower plasma levels of clonidine measured after the loading dose in the epidural group. It is likely that clonidine induces hypotension by stimulation of the imidazolin-preferring receptors at the nucleus reticularis lateralis.[27] Lower doses of clonidine seem to be required to trigger the imidazolin-preferring receptors' mediated effects than the α_2-adrenergic receptors' mediated effects.[28] Under the current conditions, the central hypotensive effect of clonidine may have been counterbalanced by a direct peripheral va-

soconstrictive effect. This mechanism was already suggested by Eisenach *et al.* to explain why large doses of epidural clonidine induced less hypotension than lower doses injected at the same site.[2]

In conclusion, epidural clonidine reduced the intra- and postoperative analgesic requirements compared with the same dose given by the intravenous route. However, considering the absence of important side effects, particularly in the intravenous group, the advantage of decreased opioid requirements seen in those receiving the epidural clonidine has to be weighed against possible problems related to the placement of the epidural catheter.

In addition, the results obtained cannot discern between a spinal or supraspinal analgesic effect of epidural clonidine, considering the fact that a profound supraspinal action was described to follow the intrathecal or epidural administration of this α_2-adrenergic agonist.[29,30]

References

1. Bonnet F, Boico O, Rostaing S, Saada M, Loriferne JL, Touboul C, Abhay K, Ghigone M: Postoperative analgesia with extradural clonidine. Br J Anaesth 63:465–469, 1989

2. Eisenach JC, Lysak SZ, Viscomi CM: Epidural clonidine analgesia following surgery: Phase I. ANESTHESIOLOGY 71:640–646, 1989

3. Bernard JM, Hommeril JL, Passuti N, Pinaud M: Postoperative analgesia by intravenous clonidine. ANESTHESIOLOGY 75:577–582, 1991

4. Yaksh T: Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacol Biochem Behav 2:845–858, 1985

5. Omote K, Kitahata LM, Collins JG, Nakatani K, Nakagawa I: Interaction between opiate subtype and alpha-2 adrenergic agonist in suppression of noxiously evoked activity of WDR neurons in the spinal dorsal horn. ANESTHESIOLOGY 74:737–743, 1991

6. Kuraishi Y, Hirota N, Sato Y, Kaneko S, Satoh M, Takagi H: Noradrenergic inhibition of the release of substance P from the primary afferents in the rabbit spinal dorsal horn. Brain Res 359:177–182, 1985

7. Eisenach JC, Dewan DM: Intrathecal clonidine in obstetrics: Sheep studies. ANESTHESIOLOGY 72:663–668, 1990

8. Eisenach JC, Detweiler D, Hood D: Hemodynamic and analgesic actions of epidurally administered clonidine. ANESTHESIOLOGY 78:277–287, 1993

9. Orko R, Pouttu J, Ghignone M, Rosenburg PH: Effect of clonidine on hemodynamic responses to endotracheal intubation and on gastric acidity. Acta Anaesthesiol Scand 31:730–734, 1987

10. Vercauteren M, Lauwers E, Meert T, DeHert S, Adriaensen H: Comparison of epidural sufentanil plus clonidine with sufentanil alone for postoperative pain relief. Anaesthesia 45:531–534, 1990

11. De Kock M, Pichon G, Scholtes JL: Intraoperative clonidine enhances postoperative morphine patient-controlled analgesia. Can J Anaesth 39:537–544, 1992

12. Bonnet F, Boico O, Rostaing S, Loriferne JF, Saada M: Clonidine-induced analgesia in postoperative patients: Epidural *versus* intramuscular administration. ANESTHESIOLOGY 72:423–427, 1990

13. Castro MI, Eisenach JC: Pharmacokinetics and dynamics of intravenous, intrathecal and epidural clonidine in sheep. ANESTHESIOLOGY 71:418–425, 1989

14. Glynn CJ, Jamous MA, Teddy PJ: Cerebrospinal fluid kinetics of epidural clonidine in man. Pain 49:361–367, 1992

15. Brandt SA, Livingston A: Receptor changes in the spinal cord of sheep associated with exposure to chronic pain. Pain 42:323–329, 1990

16. Gaumann DM, Brunet PC, Jirounek P: Clonidine enhances the effects of lidocaine on C-fiber action potential. Anesth Analg 74:719–725, 1992.

17. Fujimoto JM, Arts KS: Clonidine, administered intracerebroventricularly in mice, produces an anti-analgesic effect which may be mediated spinally by dynorphin A (1–17). Neuropharmacology 29:351–358, 1990

18. Ossipov MH, Gebhart GF: Absence of antinociceptive effect of alpha-2 agonists microinjected in the periaqueductal gray of the rat. Brain Res 289:349–354, 1983

19. Margalit D, Segal M: A pharmacologic study of analgesia produced by stimulation of the nucleus locus coeruleus. Psychopharmacology 62:169–183, 1979

20. Levitt P, Moore RY: Origin and organization of the brainstem catecholamine innervation in the rat. J Comp Neurol 186:505–528, 1979

21. Kostowski W, Jerlicz M: Effects of the lesions of the locus coeruleus and the ventral noradrenergic bundle on the antinociceptive action of clonidine in rats. Pol J Pharmacol Pharm 30:647–651, 1978

22. Paalzow L: Analgesia produced by clonidine in mice and rats. J Pharm Pharmacol 26:361–363, 1974

23. De Kock M, Lavand'Homme P, Scholtes JL: Patient-controlled morphine sparing-effect of intravenous clonidine and lidocaine after abdominal surgery (abstract). ANESTHESIOLOGY 77:A835, 1992

24. Ossipov MH, Suarez LJ, Spaulding TC: Antinociceptive interactions between α_2-adrenergic and opiates agonist at the spinal level in rodents. Anesth Analg 68:194–200, 1989

25. Spaulding TC, Fielding S, Venaffro JJ, Lal H: Antinociceptive activity of clonidine and its potentiation of morphine analgesia. Eur J Pharmacol 58:19–25, 1979

26. Segal IS, Jarvis DJ, Duncan SR, White PF, Maze M: Clinical efficacy of oral-transdermal clonidine combinations during the perioperative period. ANESTHESIOLOGY 74:220–225, 1991

27. Bousquet P, Feldman J, Schwartz J: Central cardiovascular effects of alpha adrenergic drugs: Differences between catecholamines and imidazolines. J Pharmacol Exp Ther 230:232–236, 1984

28. Tibirica E, Mermet C, Feldman J, Gonon F, Bousquet P: Correlation between the inhibitory effect on catecholaminergic ventrolateral medullary neurons and the hypotension evoked by clonidine: A voltametric approach. J Pharmacol Exp Ther 250:642–647, 1989

29. Marwaha J, Kehne JH, Commissaris RL, Lakoski J, Shaw W, Davis M: Spinal clonidine inhibits neural firing in locus coeruleus. Brain Res 276:379–382, 1983

30. De Kock M, Martin N, Scholtes JL: Central effects of epidural and intravenous clonidine in patients anesthetized with enflurane/nitrous oxide: An electroencephalographic analysis. ANESTHESIOLOGY 77:457–462, 1992