

Clonidine-Induced Analgesia in Postoperative Patients: Epidural versus Intramuscular Administration

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To compare the analgesic efficacy and plasma concentration of intramuscular (IM) versus epidural (EP) clonidine, 20 patients recovering from orthopedic or perineal surgery were randomly divided into two groups of ten. Clonidine (2 $\mu\text{g}/\text{kg}$) was administered epidurally in group 1 and intramuscularly in group 2. Analgesia was assessed using a visual analog scale (VAS) over a period of 6 h following clonidine administration. Venous blood samples were obtained at specific intervals for radioimmunoassay determination of plasma clonidine concentrations. The maximum reduction in VAS pain score was $78.5 \pm 20.6\%$ in the EP group and $68.1 \pm 31.5\%$ in the IM group (NS). Onset of analgesia was similar (within 15 min of injection), but duration tended to be longer after epidural than intramuscular administration (208 ± 87 min vs. 168 ± 95 min, mean \pm SD, $P > 0.05$). The peak plasma clonidine concentration after EP injection was 0.82 ± 0.22 ng/ml and 1.02 ± 0.76 ng/ml after IM injection. Hypotension, bradycardia, and drowsiness occurred with both methods of administration. None of these effects required treatment. Thus, in postoperative patients clonidine produces similar analgesia and side effects after parenteral or EP administration. (Key words: Analgesia: epidural, parenteral: clonidine. Anesthesia: epidural. Anesthetic techniques: epidural; intramuscular. Pharmacology: clonidine. Sympathetic nervous system, α_2 -adrenergic agonist: clonidine.)

CLONIDINE is an α_2 -adrenergic agonist that produces analgesia in animals and humans *via* a nonopiate, spinal action on the α_2 receptors of the dorsal horn of the spinal cord.¹⁻⁵ Intrathecal clonidine administration increases the duration of local anesthetic induced sensory blockade in dogs and humans.⁶⁻⁸ Epidural (EP) or intrathecal clonidine appears to produce analgesia in animals⁹⁻¹⁴ and to benefit patients with chronic pain who are tolerant of opioids.^{15,16} Therefore, clonidine might be an attractive alternative for postoperative patients who require potent analgesia¹⁷ free from opioid-induced side effects.¹⁸ Previously, we found that a single EP clonidine injection produced brief but effective postoperative analgesia in patients recovering from peripheral orthopedic and perineal surgical procedures.¹⁹ Pain relief was accompanied by side effects of drowsiness and hypotension, having the same time course as analgesia.¹⁹ In the current study we com-

pared pharmacokinetics and time course of analgesia following intramuscular (IM) or EP administration of clonidine to explore whether vascular resorption and redistribution of clonidine to supraspinal receptors might contribute to analgesia and side effects.

Materials and Methods

Following informed consent and approval from our institutional Ethics Committee we studied 20 ASA Physical Status 1 or 2 patients recovering from peripheral orthopedic or perineal surgery. Patients previously treated with clonidine, α -methyldopa, or β -adrenergic blocking drugs were excluded from the study. All patients had been anesthetized by EP injection of plain solutions of 2% lidocaine or 0.5% bupivacaine through an EP catheter. None of them received additional sedation during the surgical procedure. Postoperatively, the EP catheter remained in place. We inserted a 14-G venous catheter to obtain samples of blood for determination of plasma concentrations of clonidine after study began.

Before beginning the study patients had recovered fully from the lidocaine- or bupivacaine-induced sensory and motor blockade assessed by pin prick and the scale described by Bromage.²⁰ We considered recovery complete when no fade in tactile sensation could be discerned and when patients moved their lower limbs freely (grade 0 on Bromage scale). Patients were fully conscious and breathing spontaneously when the study began.

At the first complaint of pain upon recovery from blockade, each patient rated their pain using a visual analog scale (VAS) graded from 0 (no pain) to 10 (maximum pain).²¹ Patients were randomly assigned to receive an EP injection of 2 $\mu\text{g}/\text{kg}$ clonidine in a 15- $\mu\text{g}/\text{ml}$ isotonic saline solution administered in 2-3 min or an IM injection of 2 $\mu\text{g}/\text{kg}$ clonidine in a 5-ml isotonic saline solution. Pain score was assessed and recorded every 15 min for 2 h after EP or IM injection, then every 30 min for 4 h, by an observer unaware of the mode of injection. We observed patients closely for evidence of segmental spread of analgesia using a short, bevelled, blunt needle and for side effects, such as sedation, urinary retention, mouth dryness, hypotension, and bradycardia. At the first complaint of pain after clonidine administration, patients were given an intravenous (iv) injection of 500 mg paracetamol. Pain scores following paracetamol were deleted from analysis. We measured clonidine's analgesic effects in each

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patient²² by the percent reduction in pain after EP or IM injection using the following equation:

$$\frac{\text{initial VAS score} - \text{EP or IM VAS score}}{\text{initial VAS score}} \times 100$$

where initial VAS score is the value recorded before clonidine injection and EP or IM VAS score represents pain score for each patient after clonidine administration. In each group we determined the number of patients having a $\geq 50\%$ reduction in VAS pain score. We determined the duration of clonidine analgesia by the time elapsed between clonidine administration and the first paracetamol injection.

We measured arterial blood pressure and heart rate (HR) before and every 5 min throughout the study using an automatic blood cuff (Dinamap®, Critikon). Blood samples for determination of plasma clonidine concentrations were collected in heparin tubes *via* a venous catheter immediately before and at 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 min, and 24 h after clonidine injection. Blood samples were centrifuged at 4° C and 3,000 rpm and plasma frozen at -30° C before analysis. Clonidine concentrations were determined by radioimmunoassay technique (department of biochemistry and medical chemistry, Boehringer-Ingelheim KG) with detection limit of 10 pg/ml.²³ The intraassay coefficient of variance was less than 4%; the interassay coefficient of variance was less than 8.3%. We plotted plasma concentration *versus* time for each sampling interval and analyzed the resulting curves using a noncompartmental model (SIPHAR package, Interactive software for data modeling and statistical analysis in pharmacokinetics, SIMED). We computed the area under the curve (AUC) for each group during the first 360 min using the trapezoidal rule. Peak plasma clonidine concentration was identified as C_{\max} and the time to reach peak concentration as T_{\max} . We did not calculate elimination half-life in this series because of a limited number of samples after 360 min.

Pharmacokinetic parameters were analyzed using a one-way analysis of variance (ANOVA), completed by the estimation of the symmetric 95% confidence interval for AUC and C_{\max} ; for AUC values the logarithmic transformations were introduced because this parameter is supposed to follow a log-normal distribution. Whenever homogenous variance between groups was not verified, a nonparametric analysis (Mann-Whitney test) was performed for comparing the two modes of administration.

TABLE 1. Clinical Features of the Patients

	Sex	Age (yr)	Weight (kg)	Height (cm)
Group 1	8F/2M	45.5 ± 20.8	67.4 ± 11.9	166.7 ± 7.6
Group 2	7F/3M	52.3 ± 17.9	66.6 ± 9.0	165.1 ± 7.8

TABLE 2. Features of Clonidine Analgesia

	Pain Assessment before Clonidine Administration (VAS score)	Maximum Pain Relief (%)	Duration of Action (min)
EP group	7.8 ± 1.5	78.5 ± 20.6	208 ± 87 (range, 45–360)
IM group	7.0 ± 1.0	68.1 ± 31.5	168 ± 99 (range, 60–300)

Data are expressed as mean ± SD.

VAS scores, mean arterial blood pressure (MAP), and HR data were analyzed using a two-way ANOVA for repeated measurements and the Student's *t* test. Durations of analgesia in the two groups were compared using the Kaplan-Meier method and a log-rank test. Differences were considered significant when $P < 0.05$. Attempts to correlate plasma clonidine kinetics with VAS score, percentage, and duration of analgesia were performed by linear regression analysis.

Results

Our study groups were identical for age, weight, height, and sex ratio (table 1). High VAS scores were present before clonidine administration (table 2). Onset of analgesia was apparent within 15 min of injection in both groups (figs. 1 and 2). Nine of ten EP patients and seven of ten IM patients obtained $\geq 50\%$ reduction in VAS (NS). Maximum reduction in VAS pain score ranged from 31% to 100% in EP patients and 33–93% in IM patients (fig. 1, table 2). We detected no segmental spread of analgesia in either group. The duration of analgesia was slightly but not significantly longer in the EP group (table 2, fig. 2). The actual time elapsed between clonidine and the first paracetamol injection, similar within each group,

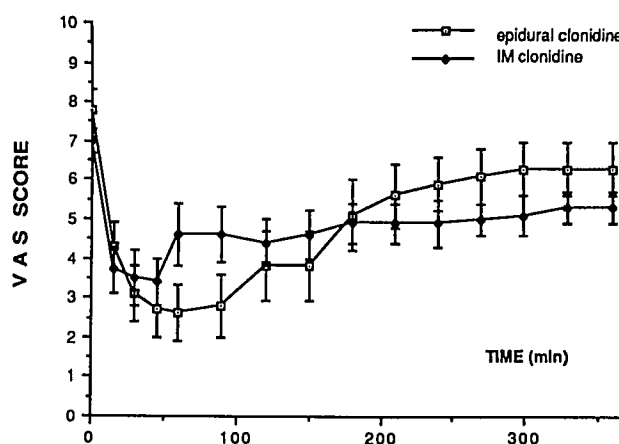


FIG. 1. Changes in VAS score following clonidine administration in the two groups of patients.

% PATIENTS WITH SATISFACTORY ANALGESIA

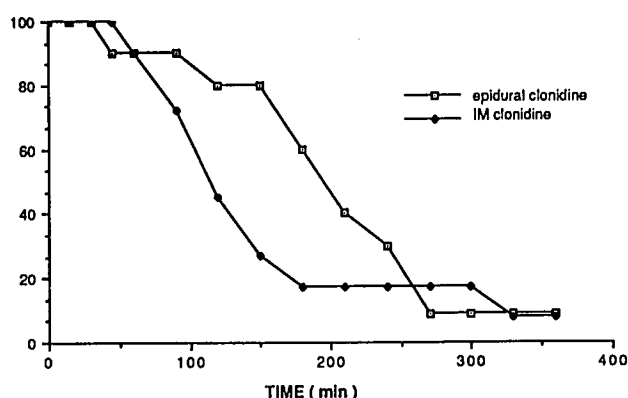


FIG. 2. Change in the percentage of patients experiencing satisfactory analgesia after epidural or IM injection of clonidine. At the first request for additional analgesia, study of the individual patient was terminated. The log-rank test indicates that the two curves representing the EP and IM groups are not significantly different.

ranged from 45 to 360 min in EP patients and from 60 to 300 min in IM patients (table 2).

We obtained plasma clonidine concentration-time curves in ten IM and nine EP patients. There was marked variability among patients in both groups in plasma concentration *versus* time (fig. 3, table 3). At the time of onset of analgesia the mean plasma clonidine concentration was 0.73 ± 0.24 ng/ml in the EP group and 0.60 ± 0.20 ng/ml in the IM group (NS). No differences in C_{max} , T_{max} , and AUC were documented between the two groups (table 3).

MAP decreased in both groups (fig. 4), with a maximum decrease of $24.2 \pm 11\%$ in the IM group and $29.5 \pm 11.5\%$ in the EP group (NS). MAP was significantly ($P < 0.01$) lower than the control value until 360 min after clonidine injection in the EP group but only from 15 to 210 min in the IM group. MAP was significantly lower ($P < 0.01$) in the EP group than in the IM group from

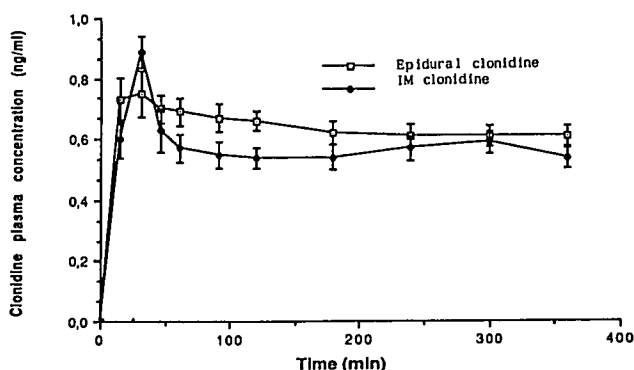


FIG. 3. Plasma clonidine concentrations after EP and IM administration. Each point represents the mean value \pm SEM.

TABLE 3. Clonidine Pharmacokinetics

	C_{max} (ng/ml)	T_{max} (min)	AUC 360 (min \times ng/ml)	C_{end} (ng/ml)
EP group	0.82 ± 0.22	68.3 ± 83.2	217.7 ± 38.7	0.38 ± 0.14
IM group	1.02 ± 0.76	54.4 ± 76.0	198.3 ± 36.8	0.39 ± 0.10

AUC 360 = area under the curve for the first 360 min; C_{end} = plasma concentration at 24 h.

90 to 180 min after clonidine administration. No patient required treatment for hypotension (lowest limit, 89/48 mmHg). HR also decreased significantly ($P < 0.05$) but transiently (120 min) in both groups without significant difference between groups. We detected bradycardia (HR < 50 beats/min) in one IM and two EP patients. Neither patient demonstrated bradycardia requiring treatment.

Drowsiness occurred following clonidine in all patients. Patients rested quietly in their beds with eyes closed but were able to respond immediately and accurately at any order. Drowsiness lasted 118.5 ± 42.6 min (mean \pm SD; range, 45–180 min) in the IM group and 141 ± 37.5 min (range, 90–210 min) in the EP group. The duration of drowsiness correlated with the duration of analgesia ($y = 0.43x + 26.3$, $r = 0.75$, $P < 0.05$).

Discussion

Conflicting results are reported concerning the analgesic effects of clonidine in postoperative patients. A single dose of intrathecal (100 μ g) or EP (3 μ g/kg) clonidine has been previously found to be ineffective in decreasing the need for iv opioids delivered by patient-controlled analgesia after laminectomy or thoracic surgery.^{24,25} EP clonidine (150 μ g), however, decreased VAS score after

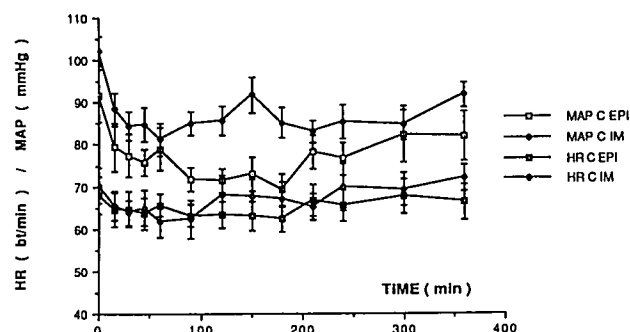


FIG. 4. Changes in mean arterial pressure (MAP) and heart rate (HR) after EP or IM clonidine. Results are expressed as mean \pm SD. In both groups MAP decreased significantly ($P < 0.01$), from 15 min after clonidine administration to the end of the study (360 min) in the EC group and from 15 to 210 min in the IMC group. HR decreased significantly after clonidine administration from 15 to 180 min in the EC group and from 15 to 90 min in the IMC group. A significant difference in MAP was documented between the two groups at 90 to 180 min ($P < 0.01$).

hysterectomy.²⁶ A 5- μ g/kg dose of clonidine administered orally before surgery and associated with a 4–5 μ g/kg dose delivered by a transdermal patch improved VAS score in the postoperative period but did not reduce postoperative narcotic requirements.²⁷ In a previous prospective, controlled, double-blind study we demonstrated that, compared with EP saline, EP clonidine (2 μ g/kg) produced significant pain relief after orthopedic surgery.¹⁹ This effect had a short latency and lasted about 210 min. This result was confirmed by an open study using EP clonidine in patients following thoracotomy²⁸ and by an EP open-label, dose-ranging study performed after abdominal surgery or total knee arthroplasty.²⁹ In the current study pain relief was detectable within 15 min after IM or EP injection of a single dose of clonidine and ranged from 50% to 100% in nine of ten patients given an EP injection and seven of ten patients receiving an IM injection. We believe we defined the effect of clonidine alone in our postoperative patients by ensuring complete recovery from the effects of drugs used to induce intraoperative sensory blockade before beginning study, administering only clonidine until additional analgesia was requested, and isolating the duration of clonidine's effect by measuring the time elapsed between injection of clonidine and additional analgesic. However, we relied on our patients' tolerance for pain to define the end of clonidine's analgesic effect, and this end point varied markedly, according to each patient's capacity for pain. Therefore, the method does not preclude the possibility that clonidine analgesia may have persisted beyond the subjective end point, nor does it preclude the possibility that residual concentrations contribute to the pain relief provided by the first injection of paracetamol. Comparing the results of this study with those of earlier studies, it appears that discrepancies may be explained by differences in doses and routes of administration. First, a single dose of clonidine given either intrathecally, epidurally, or parenterally produces analgesia of limited duration^{19,27–31} and does not decrease opioid requirements over a long postoperative period.^{24,25,27} Second, analgesia is dose-related after both EP²⁹ or parenteral³⁰ administration and may explain the lack of significant analgesic efficacy of small clonidine doses. In the current study we found that analgesia was more profound and longer acting after EP clonidine administration than after IM administration, although the difference was not significant. The small sample size may explain why statistical significance was not achieved. Nevertheless, the occurrence of analgesia and similar side effects after clonidine administration by both routes suggests that they may have similar mechanisms of action. Because plasma is not the active site of clonidine effect, no clear-cut relationship was documented between plasma clonidine concentrations and analgesia or side effects. By contrast, there is a great deal of evidence that

clonidine induces analgesia by stimulation of α -2 receptors of the spinal dorsal horn.^{2–5} Although systemic clonidine is documented to elicit antinociception in rats, an analgesic effect is shown when clonidine is injected into the locus coeruleus, suggesting that a supraspinal mechanism is not involved in clonidine-induced analgesia.³² In addition, the possibility of a supraspinal site of action of systemic clonidine appears unlikely because the effect of systemic clonidine was not significantly decreased in pithed mice.²

Clonidine decreases blood pressure and HR by enhancing parasympathetic nervous system activity,^{33,34} and decreasing sympathetic nervous system activity³³ at brain stem sites and by inhibiting sympathetic outflow in the spinal cord.^{35,36} The latter effect may explain the more pronounced decrease in blood pressure in the EP than the IM group. Animal studies have shown that EP administration does not result in hypotension.^{3,10,37,38} However, we have found the hemodynamic effects of EP and IM clonidine to be significant in our postoperative patients. This result is not surprising, given the plasma concentrations obtained in both groups. The difference in hemodynamic outcome between our results and previous animal studies may be species- or dose-related. Although our patients did not require treatment for hypotension or bradycardia, the risks associated with these effects suggest a cautious approach in hypovolemic patients or patients with hemodynamic instability. One infrequent but known effect of clonidine is hypertension due to increased systemic vascular resistance secondary to stimulation of α 2 postsynaptic vascular receptors.^{39,40} Hypertension was not observed in our patients but might occur with higher clonidine doses.¹⁰

Drowsiness was apparent in our patients, likely mediated by supraspinal stimulation of α 2-adrenergic receptors.⁴¹ The magnitude of drowsiness was similar in both groups, and its onset and duration correlated with the duration of analgesia. However, the presence of drowsiness neither compromised nor complicated the VAS measurement of pain because patients were able to measure their pain score on the VAS when required. Moreover, drowsiness was distinguishable from analgesia; some patients reported pain and sedation simultaneously.

In conclusion, EP and IM clonidine (2 μ g/kg) appears to produce satisfactory analgesia in postoperative patients recovering from peripheral orthopedic or perineal surgery. Similarities in quality and duration of analgesia and side effects of EP and IM clonidine suggest that these routes of administration may share some mechanisms of action.

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