

Postoperative Analgesia by Intravenous Clonidine

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Clonidine, an α_2 adrenoreceptor agonist, has nonopioid antinociceptive properties, which might be an alternative for postoperative analgesia free of opioid-induced side effects. To document the analgesic properties of intravenous clonidine during the postoperative period, 50 ASA physical status 1 patients, immediately after spinal fusion, were randomly assigned to two groups, blindly administered either clonidine (5 $\mu\text{g}/\text{kg}$ infused the 1st h and then 0.3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ during 11 h) or a placebo. A visual analog scale graded from 0 (no pain) to 100 mm was used to assess pain before clonidine or placebo administration (T0), at the end of the loading dose (T1) and then every 2 h (T3, T5, T7, T9, and T11). Morphine (0.1 mg/kg) was administered intramuscularly after each pain measurement if the score was greater than 50 mm. No morphine was given at T0. Hemodynamics, blood gases and plasma clonidine concentrations were measured each time the pain score was measured. The pain score decreased from 42 ± 5 to 26 ± 3 mm (mean \pm standard error) in the clonidine group whereas it was unchanged in the placebo group despite a greater morphine requirement (dose for each patient: 3.8 ± 1 vs. 10.8 ± 1.2 mg). Clonidine delayed the onset of pain and the first request for morphine injection. Mean arterial pressure decreased to 74 ± 2 mmHg in the clonidine group (-26 ± 2 vs. $-15 \pm 2\%$ in the placebo group at T11) despite a significant increase in the cumulative fluid volume. Plasma clonidine concentration was 1.8 ± 0.1 ng/ml at T1 and 1.4 ± 0.1 ng/ml at T3 and progressively increased to 1.8 ± 0.1 ng/ml at T11. In conclusion, intravenous clonidine is a possible approach to postoperative pain treatment in patients recovering from major surgery. However, the usefulness of this technique may be limited by a decrease in blood pressure if filling pressure is inadequate. (Key words: Analgesics: morphine. Complications: hypotension. Pain: postoperative. Pharmacology: clonidine. Sympathetic nervous system, α_2 agonists: clonidine.)

TREATMENT OF PAIN after extensive spinal fusion requires large doses of systemic morphine or other opioid analgesics.¹ However, increased opioid administration may result in a major risk of postoperative respiratory depression and other side effects. Other techniques, such as use of epidural analgesia, often are not feasible in this type of surgery.

Clonidine, an α_2 -adrenoceptor agonist, provides potent spinal² and central³ antinociceptive properties. In laboratory animals, clonidine is reported to be a more potent analgesic than morphine.⁴ Although local applications of catecholamine and α_2 -adrenoceptor agonists have been

found to inhibit nociceptive responses⁵ and the release of substance P from the primary afferent nerves⁶ in the spinal dorsal horn, involvement of a supraspinal site in α_2 -adrenoceptor-mediated antinociception also is suggested.^{7,8} Lesions in the locus coeruleus attenuate the antinociceptive effect of systemically administered clonidine.⁷ Clonidine augments the antinociception produced by electrical stimulation in the locus coeruleus, whereas stimulation-produced antinociception arising from the locus coeruleus is attenuated by α_2 -adrenergic antagonists administered systemically.⁸ In addition, Marwaha *et al.* have shown that lipophilic drugs such as clonidine, when administered intrathecally, can have profound supraspinal actions, and that therefore caution should be taken in interpreting the action sites of such drugs.⁹ In humans, epidural clonidine has been shown to induce postoperative pain relief.¹⁰⁻¹² Clonidine premedication can reduce opioid requirements during surgery while providing hemodynamic stability.¹³

However, few reports have studied the pain relief of intravenous (iv) clonidine and its sparing effects on opioid requirements during the postoperative period. The present double-blind randomized study was therefore designed to document the analgesic properties of systemic clonidine, given postoperatively after extensive spinal surgery.

Materials and Methods

This study, which was approved by the Human Ethics Committee of our university, was limited to the postoperative period. Fifty ASA physical status 1 patients undergoing extensive spinal surgery (Cotrel Dubousset instrumentation) performed by the same surgeon (N.P.) were studied after informed consent was obtained.

PEROPERATIVE MANAGEMENT

After oral premedication with diazepam (10 or 15 mg according to body weight < 70 kg or > 70 kg, respectively), anesthesia was induced with thiopental (5 mg/kg) and alfentanil (40 $\mu\text{g}/\text{kg}$), followed by vecuronium bromide (0.1 mg/kg) to facilitate tracheal intubation. The lungs were mechanically ventilated with an isoflurane-nitrous oxide-oxygen mixture (fractional inspired oxygen concentration = 0.5). Isoflurane was adjusted to maintain a mean end-tidal concentration equal to 0.6 vol% (Normac[®], Datex). Intraoperative analgesia was obtained with alfentanil (50 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), which was discontinued just after the first rod was in place (mean duration of admin-

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istration = 210 min; range = 195–220). For this type of surgery, we commonly use the following monitoring: a V5 ECG lead to measure heart rate, a cannula inserted in the radial artery to measure systolic and diastolic blood pressure, and a thermodilution pulmonary artery catheter to measure right atrial pressure, systolic and diastolic pulmonary arterial pressures, pulmonary capillary wedge pressure, and cardiac output in triplicate. The bladder was catheterized to measure urinary output.

POSTOPERATIVE MANAGEMENT

Immediately after surgery, patients were randomly assigned to one of two groups blindly administered either iv clonidine ($n = 25$) or a placebo ($n = 25$) for a 12-h period. Upon admission to the recovery room, a loading dose of $5 \mu\text{g}/\text{kg}$ of clonidine or placebo was infused during the 1st h in order to reach a satisfactory range of plasma concentration early, as previously suggested in a study of postoperative patients.¹⁴ Since iv clonidine in doses of $1\text{--}2 \mu\text{g}/\text{kg}$ every 3–4 h results in moderate hypotension,¹⁵ a maintenance dose of $0.3 \mu\text{g} \cdot \text{min}^{-1} \cdot \text{h}^{-1}$ subsequently was administered continuously.

Pain was scored on a visual analog scale graded from 0 (no pain) to 100 mm (severe pain) at the following times: before the beginning of clonidine or placebo (T0) administration, at the end of the loading dose (T1), and then every 2 h (T3, T5, T7, T9, and T11). In addition to the clonidine or placebo infusions, $0.1 \text{ mg}/\text{kg}$ of morphine hydrochloride was administered intramuscularly after each pain measurement as soon as the score was greater than 50 mm. However, no morphine injections were given before the end of the clonidine or placebo loading doses. At each time, sedation was also scored using a scale graded as follows: 0 = wide awake; 1 = drowsy, but easily aroused by verbal command to an alert state; 2 = dozing intermittently, but arousable by verbal command; and 3 = mostly sleeping, but arousable to a drowsy state by light tactile stimulation.

Postoperative management included oxygen administration *via* a face mask (fractional inspired oxygen concentration = 0.40), a crystalloid infusion ($70 \text{ ml}/\text{h}$), and replacement of the blood collected by suction-trap bottles with an equal volume of red blood cells. Pulmonary capillary wedge pressure of at least 4 mmHg was maintained in all patients by administering polygeline (Plasmion[®]), an oncologically active gelatin with a molecular weight between 30,000 and 40,000 D. A 30% increase in heart rate above the preanesthetic value was treated with additional fluid administration if the increase was associated with hypovolemia. Atropine was given iv in 0.5-mg increments if bradycardia (≤ 50 beats per min) occurred. Hypertension (mean arterial pressure $\geq 130\%$ of the preanesthetic value or ≥ 120 mmHg) was treated with intranasal administration of nifedipine (10 mg). Hypotension (mean arterial pressure ≤ 60 mmHg) was treated with fluid administra-

tion, which was stopped if mean arterial pressure reached 60 mmHg or if pulmonary capillary wedge pressure reached 13 mmHg and mean arterial pressure remained ≤ 60 mmHg. For this last situation, sympathomimetic amines were prescribed and patients were excluded from the study. Diuresis was noted at the end of the study.

Hemodynamic data and samples for blood gas determination were collected at each pain assessment, i.e., at T0, T1, T3, T5, T7, T9 and T11. Oxygen tension, carbon dioxide tension, pH (ABL 300 acid base analyzer, Radiometer), hemoglobin concentration, and hemoglobin saturation (OSM3 Hemoximeter, Radiometer) were measured in arterial and mixed venous blood. In addition, arterial blood samples were drawn in ten patients for determination of plasma clonidine concentration at each time. Blood samples were centrifuged at 4°C and 3,000 rpm and plasma frozen at -30°C before analysis. Clonidine concentrations were determined by a radioimmunoassay technique (Department of Biochemistry and Medical Chemistry, Boehringer Ingelheim KG) with detection limit of 10 pg/ml.¹⁶ Intra- and interassay coefficients of variation were 4 and 8.3%, respectively. Derived values including mean arterial pressure, mean pulmonary arterial pressure, cardiac index, systemic vascular resistance index, arteriovenous difference in oxygen contents, oxygen extraction ratio, and oxygen consumption index were computed according to standard formulas.^{17,18}

The time of the first morphine injection was compared between groups, using the log-rank test. The number of morphine injections, atropine and nifedipine administrations, sedation score, and episodes of hypotension and bradycardia were compared using the chi-squared test. Diuresis was compared using a Student's *t* test. Comparisons of blood loss, polygeline volume, and hemodynamic and metabolic data were made by analysis of variance for repeated measurements when the two factors were treatment (clonidine or placebo) and time. After a significant *F* statistic, multiple comparisons within and between groups were performed using Scheffé's method. One-way analysis of variance followed by a Scheffé's test was used for plasma clonidine concentrations. Statistical significance was assumed for $P < 0.05$. Results are reported as means \pm standard errors of the mean.

Results

Before clonidine or placebo infusion was begun, there were no significant differences between the two groups' demographic, hemodynamic, and metabolic data (table 1). No patients were excluded from the study because of sympathomimetic amine requirement.

Although similar in both groups at T0, the pain score was significantly less at T1, T5, T7, T9, and T11 in the clonidine group than in the placebo group (fig. 1). Statistical significance was achieved for a lower pain score at

TABLE 1. Comparison of Demographic, Hemodynamic, and Metabolic Variables between Clonidine and Placebo Groups before Clonidine or Placebo Infusion

	Clonidine	Placebo
Age (yr)	27 ± 3	29 ± 5
Gender (men/women)	13/12	8/17
Weight (kg)	56 ± 2	54 ± 2
Right atrial pressure (mmHg)	4 ± 1	5 ± 1
Mean pulmonary arterial pressure (mmHg)	15 ± 1	16 ± 1
Pulmonary capillary wedge pressure (mmHg)	5 ± 1	5 ± 1
Mean arterial pressure (mmHg)	96 ± 3	99 ± 3
Heart rate (beats per min)	113 ± 4	108 ± 4
Cardiac index (l · min ⁻¹ · m ⁻²)	4.9 ± 0.3	5.0 ± 0.3
Oxygen consumption index (ml O ₂ · min ⁻¹ · m ⁻²)	230 ± 15	225 ± 18
Oxygen extraction ratio (%)	30 ± 2	29 ± 2
pH	7.40 ± 0.01	7.39 ± 0.01
P _{aCO₂} (mmHg)	39 ± 1	39 ± 2
Hemoglobin concentration (g/dl)	11.0 ± 0.4	11.4 ± 0.3
Core temperature (°C)	36.2 ± 0.3	36.5 ± 0.2

All values are mean ± SEM.

T11 than T0 in the clonidine group. The number of patients who received zero, one, two, or three morphine injections was respectively 2, 4, 12, and 7 in the placebo group and 14, 5, 6, and 0 in the clonidine group ($P < 0.001$). During the first 12 h after surgery, each patient in the clonidine group received a dose of 3.8 ± 1.0 mg of morphine, compared with 10.8 ± 1.2 mg in the placebo group ($P < 0.001$). The first morphine injection was delayed in the clonidine group (fig. 2). At T0, the sedation score was 1.0 ± 0.1 in the clonidine group and 0.8 ± 0.2 in the placebo group. There was no significant change in this score within or between groups throughout the study. All patients were arousable by verbal stimuli.

Hemodynamic and metabolic data are shown in figures

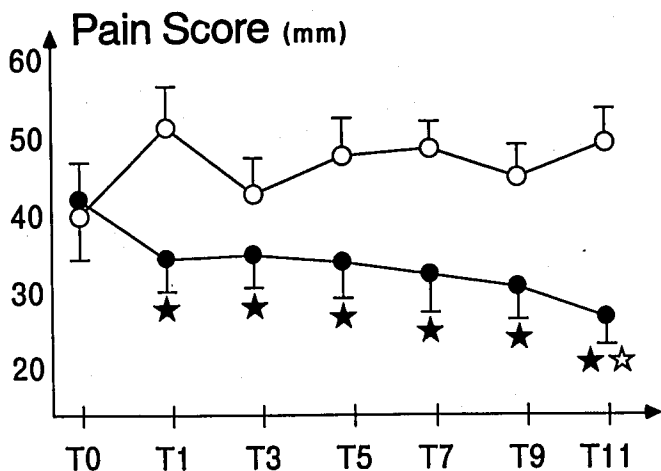


FIG. 1. Changes in pain score. T0 = before administration of clonidine (solid circles) and placebo (open circles); T1 = at the end of the loading dose; T3, T5, T7, T9, and T11 = every 2 h during continuous infusion. Values are mean ± SEM. Open stars = $P < 0.05$ versus T0; solid stars = $P < 0.05$ versus placebo.

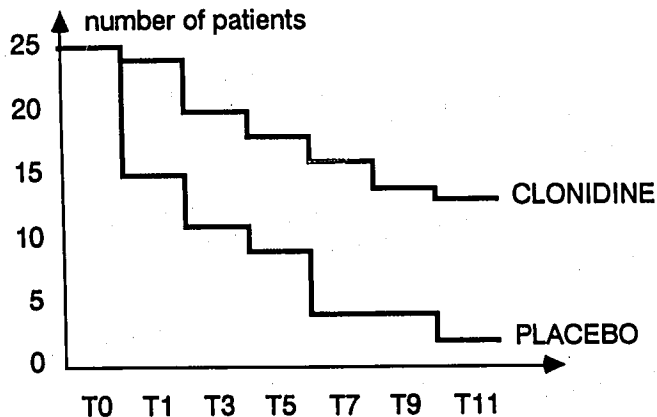


FIG. 2. Log-rank curves. Patients who received the first injection of morphine at a given time were excluded from analysis at the subsequent times. Thus, the curves represent the number of patients who had not yet received morphine injection. T0 = before administration of clonidine and placebo; T1 = at the end of the loading dose; T3, T5, T7, T9, and T11 = every 2 h during continuous infusion.

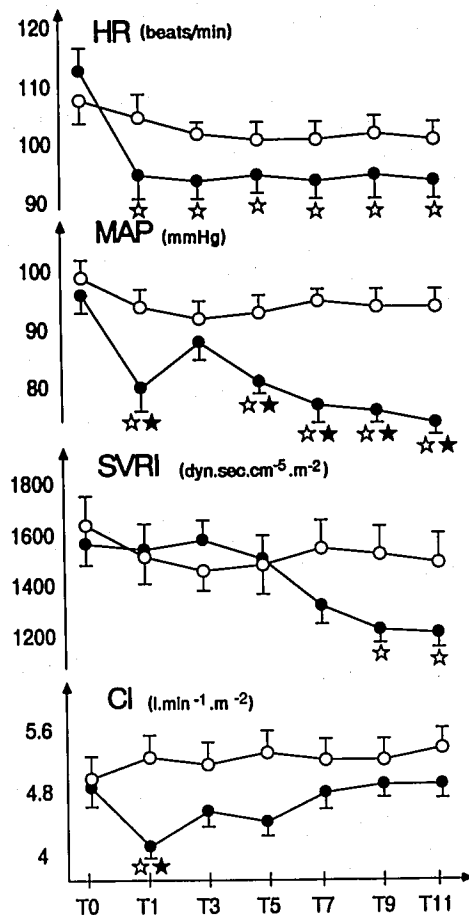


FIG. 3. Changes in heart rate (HR), mean arterial blood pressure (MAP), systemic vascular resistance index (SVRI), and cardiac index (CI) in the clonidine (solid circles) and placebo (open circles) groups. T0 = before administration of clonidine or placebo; T1 = at the end of the loading dose; T3, T5, T7, T9, and T11 = every 2 h during continuous infusion. Values are mean ± SEM. Open stars = $P < 0.05$ versus T0; solid stars = $P < 0.05$ versus placebo.

3 and 4. During clonidine infusion, there was a significant decrease in heart rate, mean arterial pressure, and oxygen consumption index at each time (except at T3 for mean arterial pressure). The cardiac index at T1, systemic vascular resistance index at T9 and T11, oxygen extraction ratio at T7 and T11, and arteriovenous difference in oxygen contents at T7, T9, and T11 decreased significantly. During placebo infusion, no statistically significant change was observed, except for a decrease in the arteriovenous oxygen contents at T7 and T11. In neither group were there significant changes in right atrial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, hemoglobin, arterial carbon dioxide tension, and pH. The clonidine group differed significantly from the placebo group for lower cardiac index at T1 and lower mean arterial pressure at T1, T5, T7, T9, and T11.

Cumulative fluid requirement was significantly greater at each time in the clonidine group than in the placebo

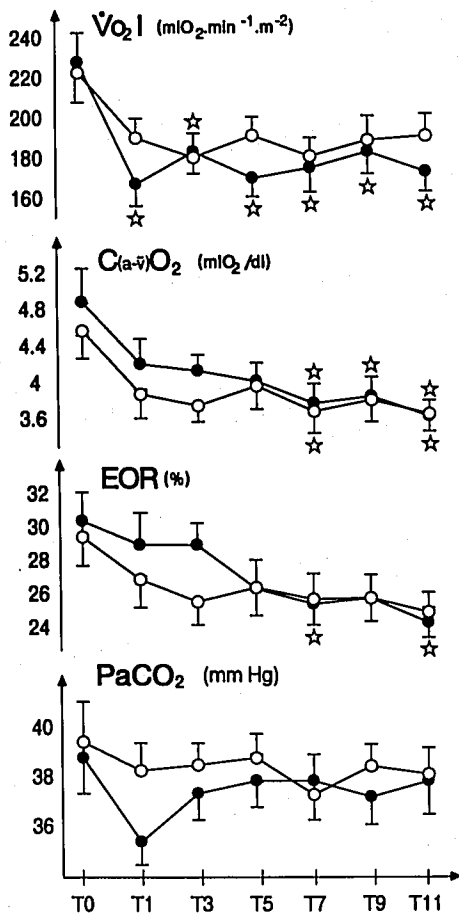


FIG. 4. Changes in oxygen consumption index ($\dot{V}_{O_2 I}$), arteriovenous difference in oxygen contents ($C_{(a-v)O_2}$), oxygen extraction ratio (EOR), and $PaCO_2$ in the clonidine (solid circles) and placebo (open circles) groups. T0 = before administration of clonidine or placebo; T1 = at the end of the loading dose; T3, T5, T7, T9, and T11 = every 2 h during continuous infusion. Values are mean \pm SEM. Open stars = $P < 0.05$ versus T0; solid stars = $P < 0.05$ versus placebo.

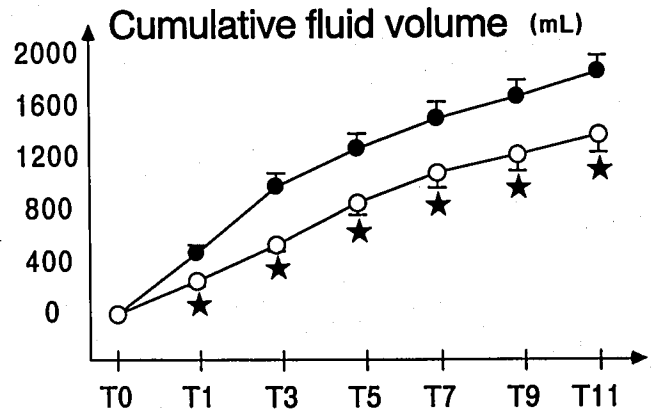


FIG. 5. Cumulative fluid replacement (red blood cells and polygeline) in the clonidine (solid circles) and placebo (open circles) groups. T0 = before administration of clonidine or placebo; T1 = at the end of the loading dose; T3, T5, T7, T9, and T11 = every 2 h during clonidine or placebo. Values are mean \pm SEM. stars = $P < 0.05$ versus placebo.

group (fig. 5) ($1,850 \pm 130$ and $1,350 \pm 150$ ml, respectively, at T11), whereas the volume of blood collected from suction-trap bottles was not different between groups. At the end of the study, diuresis was 900 ± 107 ml in the clonidine group and $1,073 \pm 96$ ml in the placebo group (difference not significant). No episodes of mean arterial pressure less than 60 mmHg were observed in the placebo group, as compared with three episodes in the clonidine group (difference not significant). These episodes, which were not accompanied by a decrease in cardiac index to less than $3 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ and by an increase in the arteriovenous oxygen content difference to more than 6 ml/dl, were treated with 300, 500, and 1000 ml of polygeline, respectively. Nifedipine was given to one patient of the placebo group and to none in the clonidine group (difference not significant). No episodes of bradycardia or hypercapnia were observed in either group.

Plasma clonidine concentrations reached 1.8 ± 0.1 ng/ml at the end of the loading dose and decreased significantly, to 1.4 ± 0.1 ng/ml at T3 and T5. Plasma clonidine concentration then reached 1.6 ± 0.1 ng/ml at T7, 1.7 ± 0.1 ng/ml at T9, and 1.8 ± 0.1 ng/ml at T11.

Discussion

ANALGESIC EFFECTS

Clonidine, when administered by the extradural route, can be effective in decreasing the need for iv opioids delivered by patient-controlled analgesia (PCA).^{10,11} Similarities in quality and duration of analgesia and side effects after extradural and intramuscular clonidine bolus injection suggest that these routes of administration share some mechanisms of action.¹² Transdermal clonidine (Cata-

pres-TTS[®], 10.5 cm²), supplemented by oral clonidine pretreatment (4.5 µg/kg at bedtime and 6 µg/kg on the morning of surgery) may induce stable plasma clonidine concentrations (1.7–1.9 ng/ml) during the perioperative period, leading to lower postoperative PCA morphine requirements than does placebo.¹⁹ Our findings provide evidence that continuous systemic administration of clonidine also is effective in reducing morphine requirements in patients recovering from extensive spinal fusion and that plasma clonidine concentrations reached levels similar to those obtained by the transdermal route.¹⁹

These data were obtained in a double-blind randomized study. Surgery and anesthesia were standardized. Pain scores were less in the clonidine group than in the placebo group, indicating that clonidine provided a slight but significant improvement in postoperative pain relief, despite the fewer morphine injections in these patients. Finally, our results indicate that systemic clonidine provided efficient analgesic properties and that continuous iv clonidine with low-dose morphine can be used for postoperative pain treatment when epidural administration or other routes are not feasible. Part of the analgesia and side effects may be due to pharmacokinetic interaction between clonidine and opioids.¹⁹ The nonsignificant changes in arterial carbon dioxide tension in our study suggest that clonidine did not increase the respiratory depression of morphine. However, a higher dose of morphine or a more sensitive assessment (occlusion pressure response) might have revealed mild respiratory depression.

Although conventional intramuscular administration of morphine gave poor results—the mean pain score was 50 mm in the placebo group—we intentionally included this type of regimen because it represents a common analgesic practice in most countries and requires no special or expensive equipment. The use of PCA for supplemental morphine might have provided a more objective measurement of analgesic efficacy (the dosage of PCA morphine) than a fixed dose of morphine given according to a pain score. However, the visual analog scale has previously been found to be a sensitive and valid measurement of pain intensity.²⁰ Although patients were unaware they would not receive morphine unless they marked the visual analog scale > 50 mm, it is possible that patients eventually understood this modality of administration, thus introducing a bias into the study. However, at T1, the pain was scored in patients without previous experience of morphine injection. Morphine requirement was different as early as T1 (fig. 2). Thus, it is likely that results of double-blind randomized studies using either the visual analog scale or the PCA requirement as an index of pain would be similar.

Clonidine has been shown to induce substantial drowsiness in acute postoperative patients.¹² Morphine provides obvious sedative effects as well. It is likely that we were

unable to demonstrate intergroup differences in sedation because we administered a higher dose of morphine in the placebo group than in the clonidine group.

HEMODYNAMIC AND METABOLIC EFFECTS

Clonidine premedication has been shown to blunt postoperatively the hemodynamic consequences of adrenergic stimulation.¹⁴ Our study indicates that during emergence from anesthesia, early control of tachycardia can also be obtained by 5 µg/kg of clonidine when this dose is infused immediately after surgery, during the first postoperative hour. No bradycardia was observed in these conditions. However, despite an increased fluid requirement, this dose resulted in significant hypotension due to a decrease in cardiac output. Fortunately, the decreased cardiac output was accompanied by simultaneous decreased oxygen consumption, and oxygen delivery was not compromised.

In fact, the hemodynamic consequences of clonidine therapy depend on the level of preexisting sympathetic tone²¹ and its role in the remote control of circulation. Clonidine induces a reduction in blood pressure by a variable combination of decreased vascular resistances, venous return, heart rate, and myocardial contractility.²² The initial few hours after surgery constitute a dynamic physiologic setting, with obvious sympathetic nervous discharge.²³

Our findings document the effects of clonidine on the hemodynamic profile of this period. At a plasma concentration of 1.8 ng/ml, clonidine provided early blunting of the sympathetic control of heart and venous return, whereas more than 8 h was required for similar plasma concentration of clonidine to decrease peripheral resistance. Clonidine may be detrimental to patients with hypovolemia or congestive cardiac failure, in whom the high circulating catecholamines compensate for the cardiovascular instability. However, Quintin *et al.*²⁴ have shown that during the postoperative period clonidine blunts catecholamine release and decreases oxygen uptake, concomitantly. Because our patients were free of heart disease, additional studies are needed, especially in subjects with cardiac insufficiency, to assess the beneficial effect of clonidine on oxygen demand during recovery.

PHARMACOKINETICS

Maximum hypotensive and sedative effects have been recognized for plasma clonidine concentrations between 1.5 and 2 ng/ml.²⁵ A loading dose of 5 µg/kg allowed us to reach this level early. Consequently, rapid control of pain was obtained, as shown by the near absence of need for morphine injections at the first hour in the clonidine group. Likewise, after the loading dose, continuous administration of 0.3 µg·kg⁻¹·h⁻¹ of clonidine maintained the plasma concentration close in the satisfactory

range. Despite a slight but significant decrease in plasma clonidine concentration, a continuous level of analgesia was observed. However, the effects of clonidine cannot be separated from those of morphine administered intramuscularly.

It is well established that plasma drug concentration does not reach a plateau before a time greater than 3 half-lives, when administered by continuous iv infusion.²⁶ Since the average elimination half-life of clonidine is 12 h,²⁵ it is likely that steady state was not obtained by the end of the study and that a plasma concentration greater than the range observed in this study might have occurred if the infusion had been given for > 12 h. Although our study did not document the effects of long-lasting infusion, our results suggest that to avoid plasma concentration greater than 2 ng/ml, continuous infusion of clonidine must be stopped or decreased at the end of 12 h.

In conclusion, systemic clonidine administration may be considered as a possible approach to postoperative pain treatment in patients recovering from major surgery and admitted to intensive care units. In the presence of low-dose morphine, iv clonidine can provide long-lasting stable analgesia and absence of ventilatory depression. One limitation of this technique may be a clinically significant decrease in blood pressure, especially if filling pressure is inadequate. Further studies are needed to substantiate the efficacy of this technique.

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