

Epidural Clonidine Analgesia after Cesarean Section

Robert Mendez, D.O.*, James C. Eisenach, M.D.,† Karen Kashtan, R.N.‡

Epidurally administered clonidine has been reported to produce postoperative analgesia. To assess the efficacy, safety, and appropriate dose of epidural clonidine for post-cesarean section analgesia, we designed a double-blind, placebo-controlled study. Sixty women were randomly assigned to receive epidural administration of saline bolus followed by 24-h saline infusion, 400- μ g clonidine bolus followed by 10 μ g/h clonidine infusion, or 800- μ g clonidine bolus followed by 20 μ g/h clonidine infusion. Supplemental analgesia was provided with patient-controlled iv morphine. Compared to saline, both clonidine regimens produced analgesia, as measured by verbal pain scores and supplemental iv morphine use during the first 6 h after bolus injection. Time to first morphine use was similar for both clonidine groups and significantly greater than saline. However, compared to saline, only the 20 μ g/h clonidine infusion resulted in decreased morphine usage over the entire 24-h period. Compared to saline, both clonidine doses decreased blood pressure. This decrease was greater in the 400- μ g than in the 800- μ g clonidine group, but no patient required treatment for hypotension. Clonidine decreased heart rate (one patient required atropine for asymptomatic bradycardia) and produced transient sedation. The 800- μ g clonidine dose prolonged resolution of local anesthetic-induced motor blockade compared to saline. These results suggest that epidurally administered clonidine provides analgesia, as measured by decreased need for supplemental morphine, after cesarean section, but continuous infusion is required for analgesia of more than 6 h duration. (Key words: Anesthetic Techniques: epidural. Pain: postoperative cesarean section. Sympathetic nervous system, alpha-adrenergic agonist: clonidine.)

OPIOIDS are commonly administered epidurally for pain relief after cesarean section. Although epidurally administered opioids produce profound analgesia, their use is limited by a high incidence of side effects. The risk of life-threatening respiratory depression after epidurally administered morphine is very low in women after cesarean section,[§] but pruritus is especially common and both-

ersome.¹ Pruritus due to epidurally administered opioids may be associated with maternal herpes labialis infection,² which theoretically could present a danger to the newborn.

The discovery of other spinal mechanisms producing analgesia³ has led to interest in the clinical application of intraspinally administered nonopioid, receptor-specific agents such as the α_2 -adrenergic agonist clonidine. Phase-1 trials of epidurally administered clonidine demonstrate dose-dependent analgesia, unaccompanied by pruritus or respiratory depression, in patients with postoperative⁴ or cancer⁵ pain. However, these studies were open-label and were not placebo-controlled, and suggested only brief (<6 h) analgesia after a single injection. The current study, using a double-blind, placebo controlled design, examines the dose-dependent analgesic, respiratory, sedative, and hemodynamic effects of epidural clonidine (bolus plus continuous infusion) after cesarean section.

Materials and Methods

The Clinical Research Practices Committee approved the protocol; all patients gave written informed consent; and clonidine was supplied under Investigational New Drug approval from the Food and Drug Administration. Sixty women, ASA physical status 1 or 2, scheduled for elective cesarean section under epidural anesthesia were studied. Women with preeclampsia and women taking opioids, tricyclic antidepressants, or clonidine were excluded. An epidural catheter was inserted at the third or fourth lumbar interspace, and its tip location confirmed with injection of 2% lidocaine (2 + 5 ml). Anesthesia was provided with 0.5% bupivacaine. Patients receiving greater than 50 ml local anesthetic or supplemental iv analgesia intraoperatively were excluded.

After admission to the recovery room, patients were randomly assigned to be given, in a double-blind manner, epidural infusions of low-dose clonidine (400- μ g bolus plus 10 μ g/h), high-dose clonidine (800 μ g bolus plus 20 μ g/h), or an equal volume of saline (10-ml bolus over 30 min; 2 ml/h) with infusions lasting 24 h. Supplemental analgesia was provided by iv morphine *via* patient-controlled analgesia (PCA; dose = 2 mg, lock-out = 10 min, hourly limit = 12 mg). Blood pressure and heart rate were measured noninvasively every 5 min for 90 min after the start of study-solution injection, and then at 2, 2.5, 3, 4, 6, 8, 12, 16, 20, and 24 h postoperatively.

Sensory level to pin prick was assessed on admission to

* Resident, Department of Anesthesiology, Portsmouth Naval Medical Center, Portsmouth, Virginia.

† Assistant Professor, Section of Obstetric Anesthesia, Wake Forest University Medical Center, Winston-Salem, North Carolina.

‡ Research Nurse, Section of Obstetric Anesthesia, Wake Forest University Medical Center, Winston-Salem, North Carolina.

Received from the Department of Anesthesia, Wake Forest University Medical Center, Winston-Salem, North Carolina. Accepted for publication June 4, 1990. Supported in part by a grant from Fujisawa Pharmaceutical Co.

Address reprint requests to Dr. Eisenach: Department of Anesthesia, Wake Forest University Medical Center, 300 South Hawthorne Road, Winston-Salem, North Carolina 27103.

§ Leicht CH, Hughes SC, Dailey PA, Shnider SM, Rosen MA: Epidural morphine sulfate for analgesia after cesarean section: a retrospective report of 1000 patients (abstract). ANESTHESIOLOGY 65:A366, 1986

and on discharge from the recovery room. The degree of motor blockade was assessed by the method of Bromage *et al.*⁶ every 0.5 h for 3 h after study-solution injection. Respiratory rate was monitored and recorded every 2 h for 24 h. Patients rated their level of pain on a 5-point verbal scale (1 = comfortable; 2 = mild discomfort; 3 = pain; 4 = bad pain; 5 = very bad pain), and investigators assessed sedation on a 5-point scale (1 = wide awake; 2 = drowsy; 3 = dozing; 4 = mostly sleeping; 5 = awakening only when aroused) every 2 h for 24 h after the injection of study solution. Any medications administered during the 24-h study period were recorded, as was time of each PCA morphine dose.

Side effects and their treatment were defined as follows: 1) for symptomatic hypotension or decrease in blood pressure by >30%: discontinuation of clonidine infusion, iv fluid administration, and if necessary, iv ephedrine 15 mg; 2) for symptomatic bradycardia or heart rate <50 beats per min: iv atropine 0.4 mg; 3) for bothersome pruritus: iv diphenhydramine 25 mg; 4) for nausea: iv droperidol 0.5 mg; and 5) for marked sedation: discontinuation of clonidine infusion.

DRUGS

The following drugs were used in the study: atropine and clonidine (Fujisawa Pharmaceutical Co., Rosemont, IL), bupivacaine and lidocaine (Astra Pharmaceuticals, Westborough, MA), and morphine sulfate (Wyeth Laboratories, Inc., Philadelphia, PA).

STATISTICAL ANALYSIS

Groups were compared for continuous demographic data by one-way analysis of variance (ANOVA) followed by Scheffe tests, and for noncontinuous data by chi-squared analysis. Time to first morphine use was compared by Kaplan-Meier survival analysis followed by the Wilcoxon test. Hemodynamic and cumulative morphine use data were compared by two-way ANOVA for repeated measures. Sedation and motor blockade data were compared by Kruskal Wallis analysis. $P < 0.05$ was considered significant.

Cerebrospinal fluid (CSF) and plasma clonidine concentrations were calculated at 30-min intervals for 8 h after beginning clonidine injection, and then at 1-h intervals for 16 h. These measurements were obtained with PCNONLIN[®] software (Statistical Consultants, Inc., Lexington, KY) and correlated with simultaneous PCA morphine use.

Results

The groups did not differ in demographic or intra-operative characteristics (table 1). Mean time from last bupivacaine injection to study-solution injection was 48 ± 6 min. Compared to saline, clonidine (both doses) prolonged the time to first morphine use by a similar amount (median time to first morphine dose = 2.0 h for saline, 4.5 h for clonidine 400 μ g, 5.0 h for clonidine 800 μ g; $P < 0.05$ vs. saline). Over the entire 24-h period, however, only the high-dose clonidine group used less morphine compared to those receiving saline (49 ± 5 mg for saline, 40 ± 5 mg for clonidine 400 μ g, 23 ± 4 mg for clonidine 800 μ g; $P < 0.05$). Both clonidine doses produced lower pain scores than did saline for the first 6 h (percentage of observations with no pain: 67 (saline), 89 (low-dose clonidine), and 88 (high-dose clonidine); $P < 0.01$), whereas groups did not differ in pain scores thereafter.

Mean arterial pressure prior to study-solution injection was similar in all groups. Blood pressure was lower in the low-dose clonidine group than in the saline group or high-dose clonidine groups from 2–12 h after injection (fig. 1; $P < 0.05$; blood pressure vs. time curves differed for all groups from 2–12 h by two-way ANOVA). No patient required treatment for hypotension.

Heart rate prior to study-solution injection was similar in all groups. Compared to saline, clonidine decreased heart rate for 16 h; no difference in this respect was observed between clonidine groups (fig. 2). One study patient was treated for asymptomatic bradycardia. Her heart rate decreased from 65 to 42 beats per min after clonidine 400- μ g bolus. A 12-lead electrocardiogram revealed a sinus bradycardia with normal PR interval and occasional premature atrial contractions. She received atropine 0.4 mg iv, which increased her heart rate to 62 beats per min.

TABLE 1. Patient Characteristics and Anesthetic Dosages

Group	Study Number	Age (yr)	Height (cm)	Weight (kg)	Lidocaine Dose (mg)	Bupivacaine Dose (mg)
Saline	20	29 \pm 1	165 \pm 2	81 \pm 3	150 \pm 8	181 \pm 10
400 μ g	20	29 \pm 1	162 \pm 2	77 \pm 4	141 \pm 1	168 \pm 7
800 μ g	20	29 \pm 1	164 \pm 2	81 \pm 3	144 \pm 3	180 \pm 11

No significant differences.

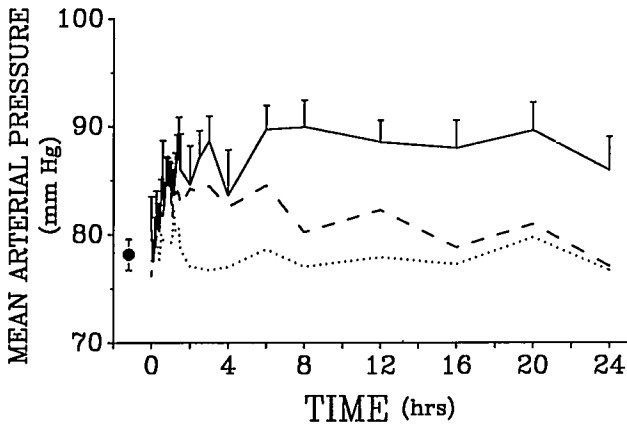


FIG. 1. Mean arterial pressure in all patients prior to injection (circle), and over 24 h in patients receiving saline (solid line), low-dose clonidine (dotted line), and high-dose clonidine (dashed line). For clarity, SEM is shown on the saline group data only. Blood pressure *versus* time curves differ for all groups from 2–12 h ($P < 0.05$). Curves for both clonidine groups differ from saline from 12–24 h ($P < 0.05$)

Eight hours later (while in her hospital room) she was again treated with atropine for asymptomatic bradycardia of 44 beats per min.

Clonidine produced dose-dependent sedation lasting 3–4 h (fig. 3). High-dose, but not low-dose, clonidine prolonged the duration of motor blockade (percentage of patients with grade 3 motor blockade 3 h after injection = 25 for saline, 55 for clonidine 400 μg , 80% for clonidine 800 μg ; high-dose clonidine differed from saline, $P < 0.05$). Groups did not differ in respiratory rate at any time, and no patient had a respiratory rate of < 12 breaths per min.

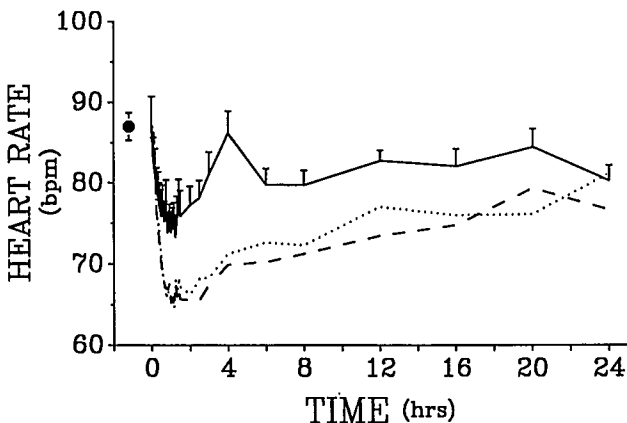


FIG. 2. Heart rate in all patients prior to injection (circle), and over 24 h in patients receiving saline (solid line), low-dose clonidine (dotted line), and high-dose clonidine (dashed line). For clarity, SEM is shown on the saline group data only. Both clonidine groups differ from saline from 15 min to 16 h.

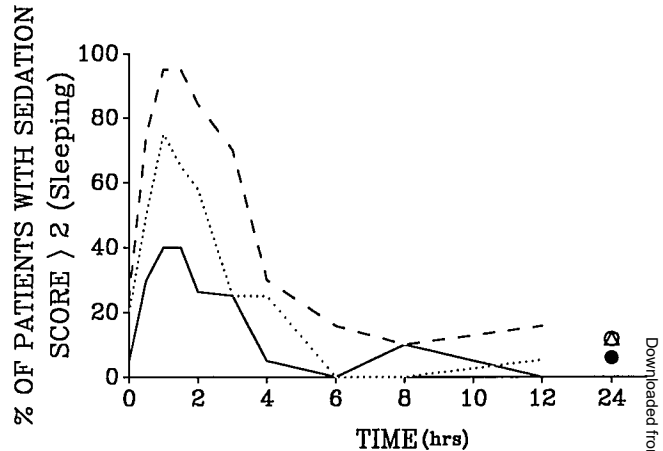


FIG. 3. Sedation, expressed as percentage of patients with sedation score > 2 over 24 h in patients receiving saline (solid line), low-dose clonidine (dotted line), and high-dose clonidine (dashed line). All groups differ only during the first 4 h.

Discussion

The effective dose of epidural clonidine for postoperative analgesia is probably 300–800 μg . Doses lower than 300 μg are either ineffective, as determined by the need for supplemental opioids,^{4,7} or produce incomplete analgesia, as determined by a change in pain scores.⁸ In contrast, Germain *et al.* described complete analgesia after injection of 10 $\mu\text{g}/\text{kg}$ clonidine,⁹ and we observed 5 h of analgesia after 700–900 μg in postoperative patients.⁴ The current study suggests that 400 and 800 μg clonidine produce analgesia of equivalent duration (4–5 h) after cesarean section, as determined by time to first morphine use and pain scores.

Previous studies demonstrate a prolongation of intraspinal local anesthetic neural blockade with co-administered clonidine,^{10,11} and the current study suggests a similar effect when clonidine is administered as late as 2 h after bupivacaine injection. Assessment of analgesia in the initial period after clonidine injection was complicated in this protocol by its prolongation of epidural anesthesia. Nonetheless, these results agree with results found in patients not receiving epidural local anesthetics⁴: clonidine, in this dose range, produces complete analgesia for 5 h after abdominal surgery.

Because of its relatively brief duration of action, it may be necessary to infuse epidural clonidine continuously in order to produce prolonged analgesia. Clonidine 10–40 $\mu\text{g}/\text{hr}$ produces good pain relief in patients with cancer pain,⁵ although coincident injection of morphine in that study makes it unclear whether these rates would be effective alone. The current study suggests that 20, but not

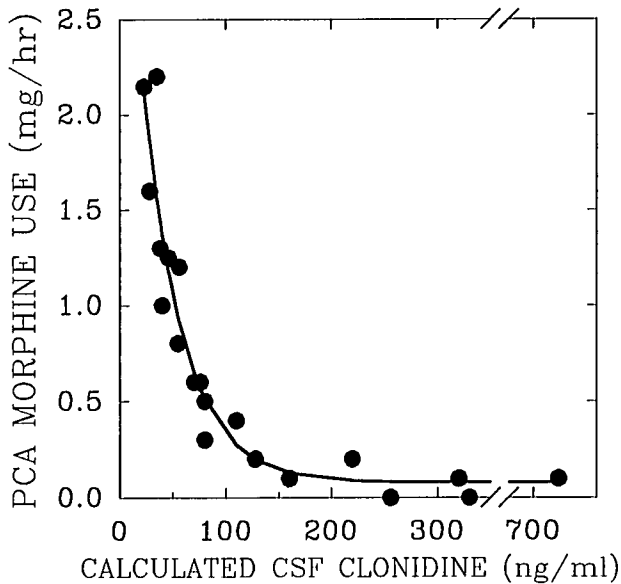


FIG. 4. PCA morphine use, in milligrams per hour, as a function of calculated CSF clonidine concentrations, in nanograms per milliliter. The curve was fitted by nonlinear regression.

10 $\mu\text{g}/\text{h}$, epidural clonidine infusion produces analgesia after surgery, as determined by the need for supplemental morphine. Based on clonidine pharmacokinetics in CSF after epidural injection in humans,^{7,12} we calculated CSF clonidine concentrations in both clonidine groups throughout the study period, and observed a strong negative correlation between calculated CSF clonidine concentration and use of supplemental morphine (fig. 4). Whereas CSF is not the site of action of clonidine to produce analgesia, these results are in close agreement with data from animal studies¹³ and suggest that CSF concentrations in excess of 100–150 ng/ml probably are required to produce complete analgesia in humans.

In the current study, clonidine altered blood pressure minimally after cesarean section, and no patient required treatment for hypotension. Adequate hydration to maintain preload, exclusion of patients with hypertension, and the choice of a lumbar site of epidural clonidine injection may have minimized clonidine's spinal sympatholytic action. Alternatively, peripheral vasoconstriction from clonidine in plasma may have limited its hypotensive actions. According to previous pharmacokinetic studies after epidural clonidine injection in humans,^{4,5} plasma clonidine concentrations would be expected to slowly decline from 1.8 to 1.2 ng/ml over 24 h in the low-dose group and from 3.5 to 2.5 ng/ml in the high-dose group. Plasma clonidine concentrations greater than 1.5–2 ng/ml are associated with minimal decrease in blood pressure,¹⁴ a

feature that possibly explains the lack of significant hypotension in this study and the greater blood pressure in the high-dose clonidine group.

Clonidine decreases resting heart rate, and in patients with cardiac conduction defects or in those taking drugs depressing cardiac conduction, may produce severe bradycardia and other arrhythmias.^{15,16} The incidence of such reactions is low: in 71 patients receiving epidural clonidine at our institution, 1 received atropine for asymptomatic bradycardia (in the current study), and 1, with a history of arrhythmias, received digoxin for atrial fibrillation.⁴ Maximal decreases in heart rate after epidural injection occurs 1–2 h after injection, at times of peak plasma clonidine concentrations.^{4,5} There have been no reports of delayed hypotension or bradycardia from cephalad spread of clonidine in CSF. Similarly, delayed effects from clonidine accumulation in plasma should not occur at infusion rates used in this protocol. This may also explain why sedation, a central effect on α_2 -adrenergic receptors, was only transient in the current protocol, despite continuous infusion.

In this first controlled study of epidurally administered clonidine after cesarean section, this therapy produced only a relatively brief period of complete analgesia and was accompanied by side effects (sedation, prolongation of epidural anesthesia, or bradycardia). Refinement of clonidine therapy and its ultimate usefulness compared to current therapies (PCA and epidural opioids) in this group of patients will be determined in future studies.

In summary, epidural administration of clonidine (400 and 800 μg) after cesarean section produces complete analgesia of 4–5 h duration, although analgesia in the current study may have been due in part to prolongation of residual epidural anesthesia. Continuous infusion of 20 but not 10 $\mu\text{g}/\text{h}$ clonidine reduces supplemental morphine usage, and neither infusion regimen produces significant hypotension. Sedation and, rarely, bradycardia may limit bolus clonidine administration. These data provide the basis for designing bolus and infusion regimens in this patient population to produce sustained and complete analgesia.

References

1. Eisenach JC, Grice SC, Dewan DM: Patient-controlled analgesia following cesarean section: A comparison with epidural and intramuscular narcotics. *ANESTHESIOLOGY* 68:444–448, 1988
2. Crone L-AL, Conly JM, Clark KM, Crichlow AC, Wardell GC, Zbitnew A, Rea LM, Cronk SL, Anderson CM, Tan LK, Albritton WI: Recurrent herpes simplex virus labialis and the use of epidural morphine in obstetric patients. *Anesth Analg* 67: 318–323, 1988
3. Yaksh TL, Howe JR, Harty GJ: Pharmacology of spinal pain modulatory systems. *Adv Pain Res Ther* 7:57–70, 1984

4. Eisenach JC, Lysak SZ, Viscomi CM: Epidural clonidine analgesia following surgery: Phase I. *ANESTHESIOLOGY* 71:640-646, 1989
5. Eisenach JC, Rauck RL, Buzzanell C, Lysak SZ: Epidural clonidine analgesia for intractable cancer pain: Phase I. *ANESTHESIOLOGY* 71:647-652, 1989
6. Bromage PR, Burfoot MF, Crowell DE, Pettigrew RT: Quality of epidural blockade: I. Influence of physical factors. *Br J Anaesth* 54:421-428, 1982
7. Gordh T Jr: Epidural clonidine for treatment of postoperative pain after thoracotomy: A double-blind placebo-controlled study. *Acta Anaesthesiol Scand* 32:702-709, 1988
8. Bonnet F, Boico O, Rostaing S, Saada M, Loriferne J-F, Touboul C, Abhay K, Ghignone M: Postoperative analgesia with extradural clonidine. *Br J Anaesth* 63:465-469, 1989
9. Germain H, Neron A, Lomessy A: Analgesic effect of epidural clonidine, *Proceedings of the Vth World Congress on Pain*. Edited by Dunbar R, Gebhart GF, Bond MR. New York, Elsevier Scientific, 1988, pp 472-476
10. Racle JP, Benkhadra A, Poy JY, Bleizal B: Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. *Anesth Analg* 66:442-446, 1987
11. Tzeng JI, Wang JJ, Mok MS, Lippman M: Clonidine potentiates lidocaine-induced epidural anesthesia (abstract). *Anesth Analg* 68:S298, 1989
12. Teddy PJ, Glynn CJ, Jamous MA: Cerebrospinal fluid kinetics of epidural clonidine (abstract). *Pain* 5(Suppl):S105, 1990
13. Castro MI, Eisenach JC: Pharmacokinetics and dynamics of intravenous, intrathecal, and epidural clonidine in sheep. *ANESTHESIOLOGY* 71:418-425, 1989
14. Frisk-Holmberg M, Paalzow L, Wibell L: Relationship between the cardiovascular effects and steady-state kinetics of clonidine in hypertension: Demonstration of a therapeutic window in man. *Eur J Clin Pharmacol* 26:309-313, 1984
15. Kibler LE, Gazes PC: Effect of clonidine on atrioventricular conduction. *J Am Med Assoc* 238:1930-1932, 1977
16. Williams PL, Krafcik JM, Potter BB, Hooper JH, Hearne MJ: Cardiac toxicity of clonidine. *Chest* 72:784-785, 1977