Epidural Clonidine after Cesarean Section

Appropriate Dose and Effect of Prior Local Anesthetic

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Epidurally administered clonidine represents a new approach to postcesarean section pain therapy, yet the appropriate bolus dose and infusion to provide effective pain relief have not been defined. In addition, whether 2-chloroprocaine, a commonly used local anesthetic for intraoperative anesthesia, interferes with clonidine’s analgesia, as it does with that of opioids, has not been examined. In this study, using a randomized, blinded design, 63 women received either bupivacaine or 2-chloroprocaine for epidural anesthesia for cesarean section and then received, upon request for analgesia in the recovery room, epidural clonidine 400 µg or 800 µg bolus, each followed by a 24-h infusion of 40 µg/h, or an equivalent volume bolus and infusion of saline. In the bupivacaine group, both clonidine doses produced equivalent analgesia, as determined by pain scores and time to first supplemental intravenous morphine request, and sustained analgesia was produced by clonidine infusion, as measured by need for supplemental morphine. In contrast, 2-chloroprocaine diminished analgesia from 800 µg by 21% and abolished analgesia from 400 µg clonidine. After 2-chloroprocaine, sustained analgesia from continuous clonidine infusion was present only in the group who had received 800 µg clonidine. Clonidine did not alter resolution of residual local anesthetic sensory blockade, as measured by 2- or 4-segment regression following either local anesthetic, but did prolong duration of motor blockade in women receiving bupivacaine.

Clonidine produced small decreases in heart rate and blood pressure. One patient received iv fluids for hypotension; one had asymptomatic bradycardia resolving without therapy; and one had mild hypoxemia with snoring during clonidine-induced sedation, responding to supplemental oxygen. These results demonstrate a profound inhibition of clonidine-induced analgesia by 2-chloroprocaine solutions and suggest that a 400-µg bolus plus 40 µg/h is an appropriate initial regimen for epidural clonidine analgesia after bupivacaine anesthesia in this patient population. (Key words: Anesthetics, local: 2-chloroprocaine; bupivacaine. Anesthetic techniques: epidural. Pain: postoperative cesarean section. Sympathetic nervous system, α-adrenergic agonist: clonidine.)

EPI DURALLY ADMINISTERED CLONIDINE produces analgesia by an α2-adrenergic mechanism and may provide postoperative analgesia without the nausea, pruritus, and respiratory depression associated with systemic or intraspinal opioid administration. Although epidural clonidine has been the subject of several investigations, the appropriate dose remains controversial. Some report sustained analgesia from 150 µg, whereas others report no effect from the same dose. We observed in an open-label, dose-ranging study that >600 µg clonidine was necessary to provide complete analgesia reliably but found in a double-blind study that 400 µg was effective following cesarean section. Whether this latter difference is due to removal of investigator bias or prolongation of epidural local anesthetic blockade by clonidine in that study is not clear.

Clonidine produces only brief analgesia following epidural bolus administration and should logically be administered by continuous infusion for sustained analgesia. Although preliminary studies suggest at least 20 µg/h is necessary to provide pain relief, either alone or in combination with morphine, supplemental opioids still are required, and analgesia and side effects from higher infusion rates have not been examined.

2-Chloroprocaine, administered even in small doses remote from the time of epidural opioid injection, dramatically interferes with opioid-induced analgesia. Although this has been suggested to be specific to the μ-opioid receptor subtype, lack of saline controls in that study leave this question in doubt. Since epidural anesthesia resolves more quickly after 2-chloroprocaine than after other local anesthetics, and since prolongation of bupivacaine-induced sensory and motor blockade for several hours is a bothersome side effect of epidural clonidine therapy, use of clonidine after 2-chloroprocaine is of clinical interest; however, it has not been examined.

To address the issues of appropriate bolus dose, use of a larger infusion rate than previously reported, and alteration by 2-chloroprocaine of epidural clonidine-induced analgesia following cesarean section, we performed the following study. Patients were randomly assigned to receive bupivacaine or 2-chloroprocaine for intraoperative epidural anesthesia; they then received, at the time of a request for analgesia when local anesthetic block was resolving, saline control or one of two clonidine bolus doses, followed by saline or a higher clonidine infusion rate, 40 µg/h, than previously examined. Analgesic efficacy and side effects were examined to provide the rationale for future use of this therapy in this patient population.
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-three women, ASA physical status 1 or 2, scheduled for elective cesarean section during epidural anesthesia were studied. Women with preeclampsia and women taking opioids, tricyclic antidepressants, or clonidine were excluded. Patients were randomly assigned to receive 3% 2-chloroprocaine or 0.5% bupivacaine epidurally for intraoperative anesthesia. 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, in the bupivacaine group, or 3% 2-chloroprocaine, 2 + 3 ml, in the 2-chloroprocaine group. Anesthesia was then established and maintained with 5-ml increments of either bupivacaine or 2-chloroprocaine, according to study group assignment. Patients receiving more than 50 ml local anesthetic or supplemental intravenous (iv) analgesia intraoperatively were excluded.

Upon first request for analgesia in the recovery room, patients were given, in a randomized, balanced, blinded manner, epidural infusions of low-dose clonidine (400-µg bolus + 40 µg/h), high-dose clonidine (800-µg bolus + 40 µg/h); or an equivalent volume of saline (10-ml bolus over 5 min; 2 ml/h) with infusions lasting 24 h. Supplemental analgesia was provided beginning 15 min after epidural bolus injection by iv morphine via patient-controlled analgesia (PCA; dose 2 mg, lockout 5 min, hourly limit 20 mg). Blood pressure and heart rate were measured noninvasively every 5 min for 90 min after the end of study solution injection and then at 2, 2.5, 3, 4, 6, 8, 12, 16, 20, and 24 h postoperatively. Oxygen saturation (SpO2) was continuously monitored by pulse oximetry for 2 h following study solution injection.

One of the investigators assessed sensory level to pin prick and degree of motor blockade by the method of Bromage et al.,11 every 0.5 h for 4 h following study solution injection. At these same time intervals, patients rated their level of pain on a five-point verbal scale (1 = comfortable; 2 = mild discomfort, 3 = pain; 4 = bad pain; 5 = very bad pain) and investigators assessed sedation on a five-point scale (1 = wide awake; 2 = drowsy; 3 = dozing; 4 = mostly sleeping; 5 = awakening only when aroused) and measured blood pressure and heart rate with the patient in the sitting and supine positions. From 4 to 24 h following study solution injection, pain and sedation data were recorded every 2 h by nurses on the postpartum ward. Respiratory rate was monitored and recorded every 2 h for 24 h and the presence of pruritus or nausea noted. Any medications administered during the 24-h study period were recorded, as was time of each PCA morphine use.

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

DRUGS

The following drugs were used in the study: clonidine (Fujisawa Pharmaceutical Co., Deerfield, IL), bupivacaine, 2-chloroprocaine, 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 Scheffé tests, and for noncontinuous data by chi-square analysis. Time to first morphine use was compared by Kaplan-Meier survival analysis followed by the Wilcoxon test. Time to two- and four-segment sensory block regression after epidural study solution injection, motor block regression sedation, and pain scores over the first 4 h were compared by Friedman’s ANOVA for nonparametric data. Hemodynamic and cumulative morphine use data were compared by two-way ANOVA for repeated measures. P < 0.05 was considered significant.

Results

The groups did not differ in demographic or intraoperative characteristics (table 1). Three patients withdrew from the study within 6 h of study solution injection (one bupivacaine + high-dose clonidine, one 2-chloroprocaine + high-dose clonidine, and one bupivacaine + saline) at patient request because of desire to have the epidural catheter removed. Following each of these patient dropouts, their study group assignment was reinserted in the randomization schedule. As a result, 60 patients completed the study.

The effect of clonidine infusion on pain scores and supplemental morphine use depended on the local anesthetic previously administered. Compared to saline, both low- and high-dose clonidine decreased pain scores during the first 4 h following injection in the bupivacaine group, whereas only high-dose clonidine decreased pain scores.
in the 2-chloroprocaine group (fig. 1). Clonidine produced a longer period before first use of supplemental morphine in patients who had received bupivacaine (median times: saline 0.8 h, low-dose clonidine 3.5 h, high-dose clonidine 5.5 h; \( P < 0.05 \)) than those who had received 2-chloroprocaine (median times: saline 0.5 h, low-dose clonidine 0.5 h, high-dose clonidine 0.8 h; \( P = \) not significant). Compared to saline, both low- and high-dose clonidine decreased morphine usage throughout the 24-h study in the bupivacaine group, whereas only high-dose clonidine decreased morphine usage in the 2-chloroprocaine group (figs. 2 and 3). Within the bupivacaine groups there was no difference between low- and high-dose clonidine in pain scores, time to first morphine use, or morphine use throughout the 24-h period (figs. 1 and 3).

Clonidine did not alter resolution of motor or sensory blockade in the 2-chloroprocaine group but prolonged resolution of motor blockade in the bupivacaine group (fig. 4). Although patients in the bupivacaine group who received clonidine had a more cephalad level of sensory blockade at time of study solution injection than did those who received saline, clonidine did not alter time to two-or four-segment regression (table 2).

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 or high-dose clonidine groups in patients who received bupivacaine (average mean arterial pressure in millimeters mercury over entire study period: 83 ± 0.5 for saline, 78 ± 0.5 for low-dose clonidine, 86 ± 0.5 for high-dose clonidine; \( P < 0.05 \) only for low-dose clonidine vs. saline by two-

<table>
<thead>
<tr>
<th>Local Anesthetics</th>
<th>Treatment</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Nulliparity</th>
<th>Local Anesthetic Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>Saline</td>
<td>31 ± 1</td>
<td>165 ± 1</td>
<td>83 ± 7</td>
<td>3</td>
<td>132 ± 15</td>
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<tr>
<td>Bupivacaine</td>
<td>Clonidine-400</td>
<td>31 ± 1</td>
<td>163 ± 2</td>
<td>77 ± 4</td>
<td>1</td>
<td>164 ± 17</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Clonidine-800</td>
<td>31 ± 2</td>
<td>166 ± 3</td>
<td>83 ± 6</td>
<td>0</td>
<td>158 ± 7</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>Saline</td>
<td>30 ± 2</td>
<td>160 ± 2</td>
<td>71 ± 4</td>
<td>2</td>
<td>1143 ± 76</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>Clonidine-400</td>
<td>30 ± 1</td>
<td>159 ± 2</td>
<td>78 ± 5</td>
<td>0</td>
<td>1122 ± 65</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>Clonidine-800</td>
<td>29 ± 1</td>
<td>163 ± 2</td>
<td>78 ± 3</td>
<td>1</td>
<td>1237 ± 53</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SEM of ten patients in each group. No significant differences.

**Fig. 1.** Percentage of patients reporting no pain after epidural injection of saline (▼), low-dose clonidine (▲), or high-dose clonidine (●) in women receiving intraoperative anesthesia from 2-chloroprocaine (top) or bupivacaine (bottom). *\( P < 0.05 \). High-dose clonidine (top) and both clonidine doses (bottom) differ from their respective saline controls by Friedman's ANOVA on the entire data set.

**Fig. 2.** Morphine use following epidural injection of saline (▼), low-dose clonidine (▲), or high-dose clonidine (●) in women receiving intraoperative anesthesia from 2-chloroprocaine (top) or bupivacaine (bottom). Data expressed as mean ± SEM. *\( P < 0.05 \) versus saline control.
Clonidine produced dose-dependent sedation lasting 3–4 h in the bupivacaine groups, whereas only the high-dose clonidine treatment produced sedation in the 2-chloroprocaine group (fig. 5). One patient in the bupivacaine + saline group was observed for 2 h with a respiratory rate of 8 breaths/min. Only one patient (in the 2-chloroprocaine + high-dose clonidine group) had an oxyhemoglobin saturation <90%. Despite a respiratory rate of 16 breaths/min, her \( \text{SpO}_2 \) decreased to 84% during periods of snoring, and she was treated for 2 h with supplemental oxygen by nasal cannula. Thereafter, \( \text{SpO}_2 \) was >94% without oxygen supplementation. The groups did not differ in the incidence of nausea or pruritus, except the bupivacaine + saline group, which had a higher incidence of pruritus (60%) than did the bupivacaine + clonidine groups (0%; \( P < 0.05 \)).

Discussion

Initial experience with epidurally administered clonidine was, by ethical necessity, open-label, and designed to define dose-related side effects and tolerance; such studies were not designed to rigorously test efficacy. Subsequent double-blind, placebo-controlled trials assessing analgesic efficacy have yielded conflicting results, probably as a result of differences in study design and patient population. For example, epidurally administered clonidine, 150 \( \mu \)g, produces 3–5 h of analgesia following orthopedic or perineal surgery, as determined by change in pain scores, but the same dose produces no analgesia following

Fig. 3. Twenty-four-hour morphine use after epidural injection of clonidine in women receiving intrathecal anesthesia from 2-chloroprocaine (m) or bupivacaine (o). \( *P < 0.05 \) versus saline control. \( P < 0.05 \) versus 2-chloroprocaine group.

Heart rate prior to study-solution injection was lower in the bupivacaine + high-dose clonidine group than in any other group. Compared to saline, low- and high-dose clonidine decreased heart rate by a similar degree (\( P < 0.01 \) by two-way ANOVA), and this response was not affected by choice of local anesthetic (average percent decrease in heart rate: in bupivacaine groups, 12% in low-dose and 4% in high-dose clonidine; in 2-chloroprocaine groups, 15% in low-dose and 12% in high-dose clonidine). One patient in the 2-chloroprocaine + high-dose clonidine group had asymptomatic bradycardia with a rate of 48 beats/min, occurring 90 min after clonidine injection. She refused atropine treatment, and her heart rate did not decrease further. Orthostatic changes in heart rate upon sitting did not differ among study groups, and maximal increase in heart rate upon sitting exceeded 15% in only 12 of 300 observations, of which 6 were in clonidine-treated patients.
Epidural clonidine after cesarean section

Table 2. Regression of Sensory Blockade to Pin Prick

<table>
<thead>
<tr>
<th>Local Anesthetic</th>
<th>Treatment</th>
<th>Initial Level (Dermatome)</th>
<th>Time to Two-segment Regression (min)</th>
<th>Time to Four-segment Regression (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>Saline</td>
<td>T_9</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Clonidine-400</td>
<td>T_9*</td>
<td>90</td>
<td>150</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Clonidine-800</td>
<td>T_5*</td>
<td>75</td>
<td>120</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>Saline</td>
<td>T_10</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>Clonidine-400</td>
<td>T_10*</td>
<td>45</td>
<td>75</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>Clonidine-800</td>
<td>T_10</td>
<td>60</td>
<td>90</td>
</tr>
</tbody>
</table>

Data expressed as median.

* P < 0.05 versus saline control for initial levels. No significant difference between groups in regression of sensory blockade.

thoracotomy, as determined by iv PCA meperidine usage.

Although this difference probably reflects in part the more severe pain following thoracotomy than after other procedures, it may as well be due to differences in definition of analgesia. One can argue that, while changes in pain scores may define a minor analgesic effect quite sensitively, operational definition of treatment to patient comfort by iv PCA is of more clinical significance.

Our initial open-label experience suggested that epidural clonidine doses greater than 500 or 600 µg were necessary for reliable analgesia. To our surprise, 400 and 800 µg doses produced equivalent analgesia in a subsequent placebo-controlled, blinded study of women following cesarean section.

However, in the latter study clonidine was injected on admission to the recovery room, and resulted in dramatic prolongation of epidural anesthesia from previously injected bupivacaine. The current study, in which clonidine was injected when pain was perceived, rather than on recovery room admission, confirms this finding, and suggests that 400 µg is an adequate bolus dose in this patient population. That clonidine prolonged motor blockade in the bupivacaine group may reflect the more cephalad sensory level at the time of injection and the tendency to have received more bupivacaine compared to the saline group.

Although, in agreement with its lipid solubility, epidurally administered clonidine produces only brief analgesia following bolus injection, there have been few examinations of continuous epidural infusions of clonidine to produce sustained analgesia. An infusion rate after cesarean section of 20 µg/h, but not 10/µg, decreases iv PCA morphine use.

When combined with epidural morphine, 18-µg/h clonidine decreases the need for supplemental opioids after abdominal surgery.

Compared to a previous study of similar design, the current study suggests that epidural clonidine infusion at 40 µg/h decreases iv PCA use following cesarean section more than does 10 or 20 µg/h, without altering the incidence of side effects. That iv PCA morphine usage dose not completely stop following epidural clonidine injection does not mean that clonidine is a poor analgesic. For example, in a study of similar design, epidural morphine 5 mg, believed to be an excellent analgesic therapy following cesarean section, decreased iv PCA usage by only 44%, compared to the 62% reduction following high-dose clonidine after bupivacaine in this study.

2-Chloroprocaine antagonizes the analgesic action of the α₂-adrenergic agonist clonidine as it does the opioid agonists fentanyl and morphine. The only previous investigation of 2-chloroprocaine and intraspinally injected α₂-adrenergic agonists demonstrated a reduction in the duration of labor analgesia following epidurally administered bupivacaine plus fentanyl and epinephrine when 2-chloroprocaine was previously injected.


Fig. 5. Sedation following epidural injection of saline (▴), low-dose clonidine (▼), or high-dose clonidine (●) in women receiving intraoperative anesthesia from 2-chloroprocaine (top) or bupivacaine (bottom). Data expressed as percentage of women with sedation score ≥ 3. *P < 0.05 versus saline control by Friedman's ANOVA on entire data set. †P < 0.05 versus high-dose clonidine–bupivacaine group.
parison with previous studies suggested that 2-chloropro-
caine was interfering with the actions of both the opioid
fentanyl and the adrenergic agonist epinephrine, although
this was not rigorously tested.

The etiology of 2-chloroprocaine’s antagonism of in-
traspinal analgesics is not clear. Long-acting inhibition of
both opioid and $\alpha_2$-adrenergic analgesia argue against
an action of 2-chloroprocaine itself or a receptor-specific an-
tagagonist phenomenon. One could argue that 2-chloro-
procaine produces less dense epidural anesthesia than does
bupivacaine, allowing more nociceptive stimulation of the
spinal cord during surgery and hence plastic changes in
spinal cord nociceptive processing leading to increased
postoperative pain. Clinical experience argues against
this hypothesis, as does the study in labor cited above. 
Alternatively, 2-chloroprocaine or, more likely, a metab-
olite could activate a spinal excitatory system and antag-
onize intraspinaly applied analgesics. Against this
argument are the observations that, compared to bupi-
vacaine, iv morphine usage is increased after 2-chloro-
procaine anesthesia for cesarean section for only the first
few hours, yet the antagonism of intraspinal opioids and
$\alpha_2$-adrenergic agonists is much longer-lasting.

A more plausible explanation for 2-chloroprocaine’s
antagonism of intraspinal analgesia is the presence of di-
sodium ethylenediamine tetraacetic acid (EDTA), found
only in commercial preparations of Nesacaine-MPF.
Relevance of disodium EDTA is supported by two obser-
vations. First, high local concentrations of the calcium
chelator, disodium EDTA, may produce local effects by
reducing extracellular calcium. This may explain hind
limb myoclonus observed following intrathecal disodium
EDTA administration in animals and severe low back
pain following epidural administration of 2-chloropro-
caine with disodium EDTA in humans. We have ob-
served anecdotally, as has been reported, that iv calcium
administration reverses this back pain. Second, extracel-
ular calcium is important to the analgesic actions of sp-
inally administered opioid and $\alpha_2$-adrenergic agonists, with
inhibition of analgesia by calcium blockade and poten-
tiation by calcium itself. Whereas it should be noted that
2-chloroprocaine inhibits analgesia but not side effects
produced by opioids and $\alpha_2$-adrenergic agonists, this does
not necessarily argue against a calcium-chelation mecha-
nism, since the role of calcium in the generation of these
side effects has not been determined.

The current study adds to previous investigations de-
fining the safety and side effects produced by epidurally
administered clonidine in the postoperative setting. The
most worrisome side effect, hemodynamic depression, is
rarely of significant degree; occurs within the first 1–2 h
following injection; responds readily to iv fluid, ephedrine,
or atropine therapy; and is not exacerbated by continuous
infusion in healthy postoperative patients. However, car-
diovascular safety of this therapy in patients with cardiac
or pulmonary pathology remains to be determined. Un-
like opioids, clonidine produces minor respiratory ef-
fects, and unlike benzodiazepines, does not enhance
opioid-induced respiratory depression. Mild hypoxemia
in our patient at the peak time of clonidine-induced se-
dation suggests patients should be closely monitored fol-
lowing bolus clonidine administration. As would be ex-
pected, iv PCA morphine but not epidural clonidine was
associated with pruritus. The only patient with a slow re-
spiratory rate in this study received only iv PCA morphine
and not clonidine.

The ultimate usefulness of epidural clonidine analgesia
following cesarean section or other surgery will be deter-
mined by large comparative studies. Although clonidine
offers unique advantages in certain pain syndromes, such
as intractable cancer pain, neuropathic pain, and reflex
sympathetic dystrophy in the postoperative setting, aside
from the lack of respiratory depression, it appears to
have few definite advantages over traditional opioid
therapy. Whether exploitation of synergistic interactions
between $\alpha_2$-adrenergic agonists and opioids, local an-
esthetics, or cholinergic systems, or development of
more selective $\alpha_2$-adrenergic agonists of differing lipid
solubility will suggest unique advantages for this class of
compounds is unknown.

In summary, epidural clonidine analgesia following ce-
sarean section is inhibited by previously injected 2-chloro-
procaine. After bupivacaine anesthesia, epidural cloni-
dine 400 g produces analgesia equivalent to 800 g
while causing less sedation, and continuous infusion of
40 g/l/h is well tolerated and reduces the need for sup-
plemental morphine. Epidural clonidine therapy may de-
crease blood pressure and heart rate, and intense sedation
following bolus administration may lead to intermittent
upper respiratory tract obstruction. Whether the advan-
tages of this nonopioid therapy for postoperative pain
outweigh these side effects or can be minimized by com-
bination drug therapy is now under investigation.

† Personal observations.

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