Epidural clonidine added to a bupivacaine infusion increases analgesic duration in labor without adverse maternal or fetal effects

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Abstract

Purpose. Many obstetric patients receiving epidural analgesia are encouraged to ambulate. This current study was designed to determine the potential for maximizing the time to first epidural supplement when adding clonidine to a 0.625 mg·ml⁻¹ bupivacaine continuous epidural infusion following epidural fentanyl bolus in early labor for patients allowed to ambulate. Maternal and fetal effects secondary to clonidine were also evaluated.
Methods. Sixty-eight laboring primigravid women received a 3-ml epidural test dose of lidocaine with epinephrine, followed by a fentanyl 100-μg bolus (in a 10 ml-volume). The patients then received a 0.625 mg·ml⁻¹ bupivacaine continuous epidural infusion, either with or without clonidine (5 μg·ml⁻¹), at a rate of 10 ml·h⁻¹. Pain scores and side effects were recorded for each patient.
Results. The overall quality of analgesia was similar in both groups. The mean duration prior to request for additional analgesia was significantly longer in the clonidine group (269 ± 160 min), compared to the control group (164 ± 64 min). No patient in either group experienced any detectable motor block; one patient (clonidine group) complained of mild thigh numbness and was not allowed to ambulate. While mean blood pressure was approximately 6 mmHg lower in the clonidine group at 1, 1.5, and 3.5 h, this was not clinically significant. No adverse effects on maternal heart rate or fetal heart rate were noted.
Conclusion. In early laboring patients, addition of clonidine prolongs the analgesia duration of a 0.625 mg·ml⁻¹ bupivacaine continuous epidural infusion following 100 μg epidural fentanyl (after a lidocaine-epinephrine test dose) without a clinically significant increase in side effects.

Key words Epidural · Ambulatory · Anesthesia obstetrical · Analgesia clonidine · Analgesia epidural

Introduction

Obstetric patients in early labor at our institution commonly receive epidural analgesia and are allowed to ambulate when feasible. We have previously shown that epidural fentanyl, after a lidocaine-epinephrine test dose, provides approximately 2 h of analgesia, while allowing patients to ambulate [1–3]. In our practice, avoiding any initial bolus with local anesthetic other than the lidocaine test dose improves the patient's ability to ambulate. Previous studies have been inconsistent showing that a bolus of clonidine along with epidural fentanyl or sufentanil affects the onset or duration of analgesia [1,4–8]. A recent editorial stated, "Pharmacodynamic studies suggest continuous infusions or intermittent administration may be more appropriate" than bolus clonidine dosing [9]. Previous studies of clonidine as part of a continuous epidural infusion in labor have utilized an initial local anesthetic bolus, which limits ambulation [10,11]. An infusion of 0.625 mg·ml⁻¹ bupivacaine with fentanyl significantly prolongs the analgesic duration of epidural fentanyl in patients who are allowed to ambulate [2]. It remains unclear, however, if adding clonidine to a bupivacaine continuous epidural infusion after fentanyl (100 μg) following a lidocaine and epinephrine test dose, in primigravid patients during the early first stage of labor, would prolong the time to or need for additional epidural bolus dosing, while still allowing for prolonged ambulation.

Concern has been raised in the form of a United States Food and Drug Administration (FDA) "Black Box" warning issued in 1999 regarding the potential for hemodynamic instability, especially hypotension and bradycardia, with the use of epidural clonidine in laboring patients. It appears this concern stems from bolus epidural dosing. A study from Australia in 2000 evaluated clonidine as part of a patient-controlled epidural analgesia (PCEA) regimen in labor [11]. The authors concluded clonidine in a median dose of 28 μg·h⁻¹

improved analgesia, reduced total bupivacaine and fentanyl use, and reduced supplementation. Any increase in sedation and lower blood pressure were not clinically significant versus bupivacaine-fentanyl. Median Apgar scores at 1 min were lower in the bupivacaine-fentanyl control group ($P < 0.05$).

Prior to establishing a PCEA regimen, it would be important to determine the influence of clonidine with bupivacaine to better clarify the side effects, hemodynamic effects, and fetal effects. The PCEA combination of bupivacaine, fentanyl, and clonidine potentially confounds the ability to distinguish those effects due to clonidine versus those due to fentanyl (i.e., sedation and fetal effects).

Despite the concerns regarding epidural clonidine in pregnant patients, this Institutional Review Board (IRB)-approved study sought to determine if the analgesic duration of a continuous bupivacaine epidural infusion would be prolonged by the addition of clonidine. The pharmacodynamic advantage of clonidine administered as an infusion would also likely limit the hemodynamics effects that have been of concern following epidural clonidine bolus dosing.

Patients, materials, and methods

Institutional Review Board (IRB) approval was obtained. Sixty-eight primigravid American Society of Anesthesiologists (ASA) physical status I or II patients, at greater than 36 weeks of gestation, who had requested labor analgesia, gave written informed consent. Patients were excluded if cervical dilation was greater than 5 cm, if they had received opioid agonists or agonist/antagonists, had pre-eclampsia, or had a contraindication to bupivacaine, fentanyl, or clonidine. A normal fetal heart rate pattern (including an absence of decelerations) was required for inclusion in the study.

Prior to epidural catheter insertion, patients' vital signs, including blood pressure, heart rate, and respiratory rate, were documented and symptoms of pruritus, nausea, or vomiting were sought. A baseline assessment of pain was made using a 100-mm visual analog scale (VAS) for pain, with 0 representing no pain and 100 being the worst possible pain. Each patient received a minimum of 500 ml of Ringer's lactate solution intravenously. All procedures were performed with patients in the sitting position. A lumbar epidural catheter was inserted approximately 5 cm into the epidural space by using a Tuohy-Schiff needle (B-Braun Medical, Bethlehem, PA, USA). The patients then received a 3-ml test dose of 15 mg·ml⁻¹ lidocaine with 1:200 000 epinephrine. If the test dose was negative for intravascular injection (heart rate within 15 beats·min⁻¹ of baseline values in 2 min of monitoring) and intrathecal injection (no

spinal block after 3 min of monitoring), the patient was given fentanyl 100 µg in a total volume of 10 ml with preservative—free normal saline. Once adequate analgesia was achieved, the patients were randomized and received one of two infusions (10 ml·h⁻¹) in a double-blinded fashion determined by a computer-generated randomization list. The clonidine group received 0.625 mg·ml⁻¹ bupivacaine 47.5 ml with the addition of 2.5 ml clonidine (100 µg·ml⁻¹) to achieve a final concentration of 5 µg·ml⁻¹. The control group received 0.625 mg·ml⁻¹ bupivacaine 47.5 ml with the addition of 2.5 ml preservative-free normal saline.

Patients were placed in the recumbent position with left uterine displacement. VAS scores and the severity of side effects were recorded 10, 20, and 30 min after the administration of the study infusion, and every 30 min thereafter, until the patient either delivered or required a re-dose of the epidural. Observations were performed by an investigator blinded to the content of the infusion. At the time of each assessment, vital signs, modified Bromage motor scale scores [12], pruritus, nausea, vomiting, and sedation were evaluated. Motor block (modified Bromage motor scale) was defined as none, partial (just able to move the knees), almost complete (able to move the feet only), or complete (unable to move the lower extremities). Pruritus was rated as none, minimal (present with minimal symptoms), moderate (bothersome but not requiring therapy), or severe (requiring therapy). Sedation was categorized as none (awake), mild (drowsy), moderate (sleepy), or severe (unarousable)—in a manner used by others [4,5,8].

Fetal heart recording was carried out continuously throughout the study. The fetal heart rate pattern was evaluated continuously, and any changes were documented at each interval. Additionally, any fetal heart rate changes were noted throughout the study period. Obstetric providers evaluated any fetal heart rate concerns. After the first 30 min, patients were allowed to ambulate with assistance, provided there was no detectable motor block and the fetal heart rate pattern was reassuring. Fetal heart rate and contraction monitoring was maintained during ambulation by telemetry (Series 5OT Obstetric Telemetry Monitoring Unit; Hewlett-Packard, Germany). Vital signs, pain scores, and side effect assessments were obtained. The time at which each patient requested additional analgesia was recorded and a study evaluation was made. The study period concluded with the administration of supplemental analgesic medication, and the study infusion was discontinued. The epidural anesthetics were managed by the anesthesia team, as appropriate, for the remainder of labor. The length of labor, and incidences of cesarean delivery and post-dural puncture headache (PDPH), as well as neonatal Apgar scores were recorded.

A strategy for treating complaints of continued pain after initial fentanyl dosing was standardized. If, in the patient's opinion, adequate analgesia had not been achieved 20 min after the initial fentanyl dose (i.e., VAS score >3), the patient was excluded and not randomized. Any such patient received epidural bupivacaine 1.25 mg·ml⁻¹. If, after bupivacaine, the patient remained uncomfortable, the epidural catheter was replaced.

Before this study was instituted, a power analysis was performed assuming a duration of 100 µg fentanyl of 145 ± 50 min [2], and a 45-min difference in analgesic duration between the groups. The power was 80%; and the alpha chosen was 0.05. This yielded a required sample size of 21 patients per group.

Pain scores were analyzed by using the Mann-Whitney U-test. Presence or absence of side effects was analyzed by contingency testing. A Kaplan-Meier plot of the patients remaining comfortable over time was generated, and analyzed with the Cox-Mantel log rank test. Data values are expressed as means ± SD. Significance was determined at the $P < 0.05$ level.

Results

Sixty-eight patients agreed to participate in the study. Five patients did not achieve analgesic relief with the fentanyl bolus and were thus not randomized to a group; 4 of these epidurals needed to be replaced and the remaining patient was fully dilated within 15 min and required a bupivacaine bolus to achieve relief. The first 3 patients were dropped due to a protocol violation (the infusions contained fentanyl). All remaining 60 patients achieved adequate initial analgesia with the epidural fentanyl and were randomized for participation.

The groups were similar with respect to demographic variables, cervical dilation upon enrollment, rupture of membranes, and oxytocin use (Table 1). Baseline VAS pain scores and the incidence of nausea and pruritus were similar in both groups. The median VAS scores were decreased by 83.4% and 77.6% at the 10-min evaluation in the control and clonidine groups, respectively, which was not significant. At 30 min, VAS scores were reduced by 90.0% (control), and 89.8% (clonidine), which was not significant.

There were no significant differences in pain scores between the groups at 10, 20, 30, or 60 min. The VAS scores were higher in the control group at 1.5 ($P < 0.03$), 2 ($P < 0.002$), 2.5 ($P < 0.002$), 3 ($P < 0.04$), and 3.5 ($P < 0.004$) h (Fig. 1).

The duration until request for additional analgesia was significantly longer in the clonidine group (269 ± 161 min) compared to the control group (164 ± 65 min; $P < 0.002$; Fig. 2). Six patients delivered without the need for a redose (2 in the control group and 4 in the clonidine group). The mean cervical dilation was not different between the two groups at the time of redose (4.5 ± 2 cm in the control group and 5.3 ± 2 cm in the clonidine group).

Before administration of the study analgesic, 22 patients had experienced nausea (10 in the control, and 12 in the clonidine group) and no patients had vomited. During the entire study period, 8 patients had nausea (4 in the control, and 4 in the clonidine group) and 6 patients vomited (2 in the control, and 4 in the clonidine group). Twenty-eight patients experienced mild sedation at least once during the study period (14 in the control, and 14 in the clonidine group). Five patients experienced moderate sedation (2 in the control and 3 in the clonidine group). No patient had severe sedation. There were no differences in sedation scores between the two groups at any time point. Sedation scores were highest in the first 30 min of the study period. There were 41 patients who reported mild or moderate pruritus at some time during the study (20 in the control, and 21 in the clonidine group). No patient experienced severe pruritus and no patient required specific treatment for nausea, vomiting, pruritus, or sedation.

During the study period, motor block, as reflected by the Bromage score, was absent (score of 0) in all patients. One patient (clonidine group) complained of mild right thigh numbness at 1 h; she was not allowed to ambulate. Twenty-nine patients (48%) ambulated at least once during their labor (12 in the control, and 17 in the clonidine group). Five of these patients chose to ambulate through the hallway (1 in the control and 4 in the clonidine group); the remainder ambulated to the bathroom or got out of bed to a chair.

Interval recordings of automated blood pressure were evaluated at every evaluation time interval. Systolic and

Table 1. The demographic and outcome data in the two groups

Group (n)	Age (years)	Height (cm)	Weight (kg)	Gestational age (weeks)	Cervical dilation at initial dose	Cervical dilation at re-dose	Cesarean section (n)	Forceps/ Vacuum (n)	Oxytocin use
Control (30)	27 ± 6	164 ± 6	88 ± 17	39 ± 2	2.7 ± 1.2	4.5 ± 2.0	10/30	1/30	17/30
Clonidine (30)	26 ± 5	161 ± 9	88 ± 16	40 ± 1	2.9 ± 1.1	5.3 ± 2.2	13/30	3/30	23/30

Data values are expressed as means ± SD. There were no statistically significant demographic differences between the groups
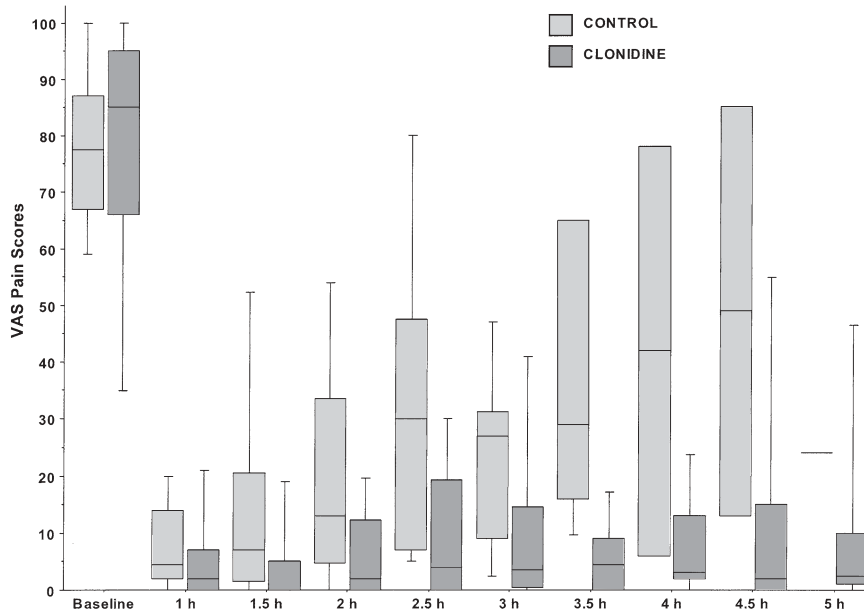
Fig. 1. The visual analog scale (*VAS*) pain scores for the two groups at time intervals of up to 5h. The *boxes* represent the 25th–75th percentiles and the medians are represented by the *solid lines*. The *extended bars* represent the 10th–90th percentiles. Pain scores were not obtained following the administration of additional analgesia, and thus there are fewer than 30 patients in each group at the later time periods. There were statistically significantly higher pain scores in the control group at 1.5, 2, 2.5, 3, and 3.5h
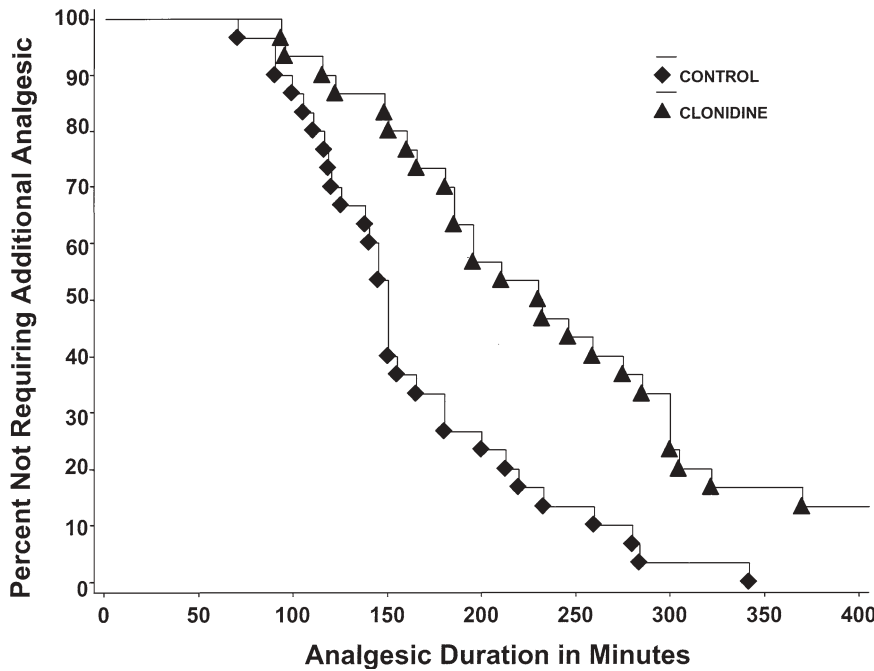
Fig. 2. Kaplan-Meier plot of the percentage of patients in each group who continued to remain comfortable. There was a significant difference ($P < 0.003$) between the groups

mean blood pressures decreased from baseline in both groups. There was no difference in systolic blood pressure, at any time interval, between the groups. The mean blood pressure was significantly lower in the clonidine group at three time intervals: 1h ($P < 0.02$), 1.5h ($P < 0.01$), and 3.5h ($P < 0.01$). The respective mean ± SD (mmHg) values in the clonidine and control groups were: 80 ± 10 and 86 ± 11 at 1h; 78 ± 9 and 84 ± 8 at 1.5h; and 85 ± 7 and 88 ± 5 at 3.5h. No patient in the study had a mean blood pressure of less than 60mmHg. There was no difference in maternal heart rate between the groups at any time during the study period.

A total of four patients required treatment with ephedrine (two in each group). Two patients (clonidine group) received ephedrine 10mg due to hypotension when dosed with lidocaine 2% for cesarean delivery. One patient requiring cesarean delivery for failure to progress had been off the clonidine infusion for greater than 2h, while the other had the infusion running for 4h prior to cesarean delivery for fetal intolerance of labor. Apgar scores were 8, 9, and 9 and 9, 9, and 9 at

1, 5, and 10 min, respectively. Another patient (clonidine group) received ephedrine 10 mg 25 min after beginning the infusion. She had an uneventful vaginal delivery several hours later. Apgar scores were 9, 9, and 9 at 1, 5, and 10 min. An additional patient (clonidine group) received ephedrine 5 mg 5 h after the infusion had begun. She also delivered uneventfully shortly thereafter, with newborn Apgar scores of 9, 9, and 9 respectively.

Apgar scores were nearly identical in the two groups. Six newborns had a 1-min Apgar score of less than 6. One newborn in the control group had a 1-min Apgar score of 2. The baby presented occiput posterior with thick meconium and was intubated and suctioned at delivery; the 5- and 10-min Apgar scores were 7 and 8, respectively. Another newborn in the control group had 1-, 5-, and 10-min Apgar scores of 5, 9, and 9 secondary to shoulder dystocia. One newborn in the clonidine group had a 1-min Apgar score of 4. The baby was delivered by forceps following a prolonged second stage of labor. The 5- and 10-min Apgar scores were 9 and 10 respectively. One newborn in the clonidine group had 1-, 5-, and 10-min Apgar scores of 5, 7, and 9. Cesarean delivery was difficult, likely secondary to macrosomia (newborn birth weight was >4000 g). Two additional newborns in the clonidine group had 1-, 5-, and 10-min Apgar scores of 5, 8, and 9 and 5, 9, and 9. Both were delivered vaginally and required intubation and suctioning secondary to meconium aspiration.

Discussion

In the current study, we investigated whether the duration of analgesia could be extended by adding clonidine to a bupivacaine continuous epidural infusion over an infusion of bupivacaine alone for patients in early labor. We administered 100 μg of fentanyl after a lidocaine and epinephrine test dose in primigravid patients, while varying the continuous epidural infusion (bupivacaine with clonidine or saline). This method of avoiding an initial epidural local anesthetic bolus dose has allowed us to permit ambulation for extended periods of time, even when patients receive epidural analgesia in early labor.

In studies of regional anesthesia, clonidine bolus doses above 100 μg resulted in side effects of sedation, lowering of blood pressure, and decreased heart rate [13,14]. The addition of 120 μg clonidine to 8 ml 0.125% bupivacaine improved analgesia but caused significant sedation [15]. An epidural bolus dose of 75 μg has resulted in patients exhibiting mild sedation [16]. Aveline et al. [7] determined that clonidine 60 μg by epidural bolus reduced the minimum local analgesic concentration of epidural ropivacaine required in labor; however,

increased sedation compared to control and clonidine 30 μg was noted. However, in laboring patients, 75 μg of clonidine added to epidural sufentanil did not cause a difference in patients' sedation level [1]. In the current study, we did not find any effect on sedation in the women who received clonidine (50 μg·h⁻¹) even after a cumulative dose of up to 250 μg. Possible explanations include that low intravenous levels might be associated with continuous epidural infusion compared with an epidural bolus, or that a sedation scale is not sensitive enough to determine a difference. Additionally, approximately 50% of patients in both groups indicated some level of sedation during the study period. Sedation scores were highest in the first 30 min of the study period. All patients received a fentanyl epidural bolus prior to initiating a continuous epidural infusion. Sedation could be a result of epidural fentanyl and/or sleep deprivation. Our results give no indication that clonidine by continuous epidural infusion further exacerbates sedation in this patient population.

Clonidine has been shown to prolong the analgesic duration of epidural bupivacaine in laboring patients [6,15,16]. These previous studies did not compare infusions of bupivacaine, or concentrate on "ambulatory epidurals." Our previous investigation did not show any analgesic benefit from adding a bolus of clonidine to epidural sufentanil [1]. We believed that this was due to the fact that the duration of epidural sufentanil paralleled clonidine's effect (i.e., clonidine may have a similar duration of action compared with sufentanil when administered as a bolus) [1]. The fact that clonidine, when given as part of the infusion, improved the analgesia and prolonged the analgesic duration supports our previous conclusion.

Recent literature has questioned the use of the lidocaine-epinephrine test dose in obstetric patients [17–21]. We believe it remains an important element in detecting intrathecal and intravascular catheter placement. The use of a lidocaine-and-epinephrine test dose has been implicated in a decreased ability for parturients to ambulate [20]. However, all the patients in Cohen's study [20] received an initial 12-ml epidural bolus of bupivacaine (0.0625% or 0.125%) in addition to the lidocaine-epinephrine test dose, while the patients in Calimaran's study [21] received a lidocaine-epinephrine epidural test dose after having received 2.5 mg intrathecal bupivacaine. Our use of epidural opioid after a test dose, without the use of adjuvant local anesthetic, does not result in significant motor block [1–3]. One patient in the current study, and two patients in our previous studies [2,3], complained of numbness; these symptoms were presumably due to the local anesthetic in the test dose and the bupivacaine in the infusion. Epidural 0.1% bupivacaine with sufentanil, as part of a PCEA technique, results in detectable motor block

in approximately 20% of patients [22]. We have shown that when sufficient opioid is utilized initially, and an initial bolus of local anesthesia is avoided, the ability to ambulate can be achieved in the vast majority of patients without eliminating the test dose [2]. Despite the fact that there may be certain advantages in women who ambulate during labor [23], the majority of our patients chose not to ambulate. This does not mean that avoidance of a motor block in laboring patients should not be a goal. Perhaps the goal should be encouragement of ambulation for those patients in whom it is possible. It is the desire of our obstetric colleagues for their patients in labor to be able to move well on their own and to change position when required.

Although the mean blood pressure was statistically significantly lower in the clonidine group at three time periods, this difference of approximately 6 mmHg does not appear to have any clinical significance.

The goal of an epidural infusion started in early labor is to provide prolonged analgesia with minimal maternal and fetal adverse effects; minimal interference with the course of labor; and minimal effect on the ability to ambulate. We have demonstrated the addition of clonidine to bupivacaine meets these goals in a manner superior to that of bupivacaine alone. None of the FDA concerns regarding bolus dosing of epidural clonidine in labor were supported by this study. We feel further work with epidural clonidine infusion in labor may be warranted. Given the current FDA warning, significant use of clonidine in the United States for the management of obstetric patients will probably remain limited until further work with epidural clonidine infusion during labor is published.

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