The effect of pH-adjusted 2-chloroprocaine on the duration and quality of pain relief with a subsequent continuous epidural bupivacaine infusion

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A randomized, double-blind true experimental design with a post-test only was chosen to determine if the addition of sodium bicarbonate to 2-chloroprocaine would result in a longer duration of epidural analgesia, as well as increase the quality of pain relief in stage I parturients receiving a continuous bupivacaine epidural infusion. The experimental group (number \( N = 16 \)) received sodium bicarbonate and 2-chloroprocaine followed by a continuous bupivacaine epidural infusion. The control group \( (N = 15) \) received normal saline and 2-chloroprocaine followed by a continuous bupivacaine epidural infusion. Only ASA I or II patients in stage I labor were included in this study. Measures of pain perception were made using a self-report, visual analog scale. Measures also were made of the quality and duration of block over time, the intensity of motor block over time, and the blood pressure over time. The cephalad dermatome level of analgesia was determined by pinprick. A record of the need for a supplemental bolus of local anesthetic to maintain a sensory level of T-10 was also recorded.

The mean self-perceived level of pain was significantly different for the two groups \( (P = .024) \). Moreover, the pattern of self-perceived level of pain over time differs for the two groups in a significant way \( (P = .023) \). Additional bolus injections occurred nine times in the control group and six times in the experimental group. The differences were not found to be significant \( (P > .106) \). The differences in time and amount of local anesthetic delivered were also found to be trivial \( (P > .80) \). Multiple comparative variables included the number of gestations, live births and abortions, occurrence of meconium-stained amniotic fluid, occurrence of fetal heart rate depression, use of forceps or vacuum, and cesarean section deliveries. The obtained \( X^2 \) for analysis of motor block was 3.447 degrees of freedom \( = 7 \), \( P = .841 \), which was not significant.

The hypothesis that the pH adjustment of 2% 2-chloroprocaine would not improve the duration of analgesia in stage I parturients was not rejected. However, the hypothesis stating no improvement in the quality of pain relief was rejected by this study. This difference can be attributed to the clinical advantages of having a regional anesthetic take effect quickly, especially if delivery is imminent.

Key words: Bupivacaine infusion, duration, pH-adjusted, quality of pain relief, 2-chloroprocaine.
Regional anesthesia for labor and vaginal delivery has gained widespread use because of its effectiveness and, when properly conducted, its safety. Epidural blocks provide pain relief while allowing the parturient to be awake and to participate in labor and delivery. In contrast to parenteral or general inhalation anesthesia techniques, regional anesthesia decreases the likelihood of fetal drug depression and maternal aspiration pneumonitis.\(^1\) Regional anesthesia is the only technique that can offer quiet and gentle progress through all the painful stages of labor and delivery without undue risk and the need for systemic analgesics.\(^2\)

A large number of local anesthetics are available for the relief of pain in labor. A local anesthetic must meet five basic requirements. It must provide effective analgesia and be safe for the mother and fetus. It must not affect the expulsive forces of labor. In addition, it should produce minimal muscle relaxation, thereby permitting normal flexion and internal rotation of the fetal head and normal maternal expulsive efforts during the second stage of labor.\(^2\)\(^3\) Finally, and very important, it must not depress the fetus by placental transfer of potentially depressing drugs. This implies use of an anesthetic that minimizes placental transfer.\(^2\)

Vaginal delivery requires less intense anesthesia and analgesia than cesarean section. Generally, one can expect that more dilute solutions of local anesthetics will be adequate for labor and vaginal delivery. For continuous infusions, lower concentrations are used.

Intermittent injection of local anesthetics into the parturient's epidural space may lead to periods of inadequate pain relief requiring additional local anesthetic administration that places more demands on anesthesia personnel. If reinjection of local anesthetic is delayed until the patient experiences pain, the efficacy and goal of the technique is greatly decreased. The advantages of the continuous infusion technique include a more stable level of analgesia, less risk of systemic toxicity or total spinal block from malpositioning of the catheter, and reduced risk of hypotension as a result of less variation in sympathetic blockade.\(^3\)

Local anesthetic solutions are mixed to take advantage of the useful properties of each drug. Bupivacaine is a long-acting amide local anesthetic which is metabolized in the liver. The pH of bupivacaine ranges from 6.0-7.0. When used for epidural analgesia during labor, bupivacaine produces profound analgesia with minimal motor block and has a relatively long duration of action. The drug provides effective relief of first-stage labor pain in dilutions as low as 0.125%. Bupivacaine is currently established as the safest and most effective amide-linked local anesthetic for obstetric anesthesia. The disadvantages of bupivacaine have been a relatively slow onset of pain relief and occasionally incomplete anesthesia.

Chloroprocaine is an ester-type local anesthetic. The pH of chloroprocaine ranges from 3.0-3.5. Current evidence indicates that it is one of the safest agents for use in obstetrics.\(^4\) Its speed of breakdown is rapid in the presence of normal pseudocholinesterase. As a result, it does not reach the fetus in appreciable amounts. Chloroprocaine has a quick onset and good penetrance, but its duration of action is relatively brief. It is rapidly hydrolyzed by plasma cholinesterase, so very little drug crosses the placenta. However, because of its very short duration of action (35-50 minutes), frequent repeat injections are needed when prolonged analgesia is required.

Local anesthetics are prepared commercially as the water-soluble salt of a strong acid. The uncharged form of the anesthetic drug penetrates the nerve. An increase in pH accelerates the penetration and rapidity of onset by increasing the unionized, lipid-soluble form. Clinical application of 2-chloroprocaine may alter the activity of bupivacaine by lowering the pH.

Local anesthetics of both the amino-ester and amino-amide class are weak organic bases, because of their tertiary amine group. Since the local anesthetic is a weak organic base, it can exist in a neutral or cationic form. The neutral form is highly lipid-soluble but poorly water-soluble. By contrast, the cationic form is poorly lipid-soluble but moderately soluble in water. The proportion of drug in the neutral and cationic form is dependent upon both the pH of the solution and the pK\(_a\) of the molecule. Commercial preparations of local anesthetics predominantly contain the cationic form of the drug.

The relationship between the neutral and cationic forms of the drug is described by the Henderson-Hasselbalch equation:

\[
pK_a = \text{pH} + \log \left( \frac{\text{cationic form}}{\text{neutral form}} \right)
\]

Equal amounts of the cation and base exist in solution when the pH of the solution equals the pK\(_a\) of the local anesthetic. The pK\(_a\) of most local anesthetics is between 7.5-9.0. The solutions contain more cation than base at tissue pH. This proportionality is important because it is the neutral form that crosses the neural membrane, but the cationic form is required for neural blockade.\(^4\)
The potency of local anesthetics in blocking sodium channels is faster when the drug is applied externally at an alkaline pH. Conversely, a slightly acidic pH is favored if the drug is applied internally. The neutral form of the anesthetic dissolves in and passes through the axon membrane and, having reached its site of action, becomes protonated. Therefore, the extracellular alkaline pH favors the neutral membrane permeate form of the drug, while an acidic cytoplasmic pH favors the more potent blocking species at the site of action.

During most clinical procedures, the functional potency of local anesthetics is determined largely by the fraction of injected drug that passes through tissue barriers into the nerve bundle, and alkaline conditions that favor the penetrating, neutral species are desirable. Manipulation of the pH can be done using either a carbonated solution or by adding bicarbonate to a commercial preparation.

In summary, chloroprocaine has a duration of approximately 25-35 minutes. Bupivacaine can have an onset of as much as 40-50 minutes when started as a low volume, dilute concentration infusion, as is used in labor analgesia. Therefore, the chloroprocaine wears off before the bupivacaine starts to work, and many parturients experience pain. This study was undertaken to see if an initial epidural bolus of 2-chloroprocaine followed by an infusion of epidural bupivacaine would result in continuous analgesia sufficient for pain relief during the first stage of labor.

Review of literature

In 1910, Lawen and Gros wrote the first clinical report of shortened onset time for local anesthesia by increasing the pH of the anesthetic solution. Lawen added 0.5% sodium bicarbonate to 1% procaine. An increased potency of 1% procaine was noted.

The initial use of dextran as a local anesthetic adjuvant is credited to Loder. This researcher reported the effects of controlling postoperative pain by means of regional anesthesia, primarily by intercostal nerve blocks, and the prolonged duration of blockade produced by the addition of dextran to lidocaine. Subsequent attempts to confirm Loder’s observations have yielded inconsistent findings. The dextran used in the initial study had an alkaline pH, and the duration of block with bupivacaine was prolonged. The dextran used in the subsequent studies had an acidic pH, and the duration of blockade was not prolonged.

Rosenblatt performed a study in which the duration of coccygeal nerve blocks was determined in rats using bupivacaine combined with normal saline (pH 5.5), urea (pH 7.4), mannitol (pH 8.4), folate (pH 9) or dextran (pH 8) to confirm this theory. It was determined that the mean duration of block was indeed prolonged compared to the saline control so that the more alkaline solutions produced a progressively longer blockade.

Brodsky stated that an equal volume of bupivacaine (0.75%) combined with 2-chloroprocaine (3.0%) produces a strongly acidic mixture (pH 3.7). A tachyphylaxis developed following repeated administrations of local anesthetic to tissue spaces with a limited buffering capacity. Brodsky hypothesized that continued use of the acid bupivacaine/2-chloroprocaine combination may lead to earlier exhaustion of local tissue-buffering capacity and a reduction in the effectiveness of the bupivacaine.

Many studies have followed the initial investigation of pH adjustment of local anesthetics. The results have been controversial in terms of the duration or quality of pain relief. However, the length of anesthetic blockade has been found by several investigators to be prolonged when sodium bicarbonate was added to the local anesthetic.

Many investigators have determined that the ability of 2-chloroprocaine to alter the activity of bupivacaine might depend upon the pH of the 2-chloroprocaine solution. The characteristic long duration of blockade with bupivacaine was not apparent when mixtures of the two drugs were studied. It was concluded that the nerve blockade obtained by mixing commercially available solutions of local anesthetics is unpredictable and may depend upon a number of factors which include not only the types of drugs but also the pH of the mixture.

Rosenblatt came to the following conclusions regarding the use of continuous epidural infusions for labor and delivery:

1. It is technically feasible to provide obstetrical analgesia by means of an epidural infusion with a volumetric infusion pump.
2. The pain relief provided by this method is equivalent to or better than that produced by the bolus technique, since there is no regression of analgesia.
3. The relative safety of the infusion technique for the mother and fetus appears comparable to the intermittent bolus technique.
4. The continuous infusion technique appears to be more effective in its use of anesthesia care providers. Subsequent studies support the efficacy and safety of using continuous epidural infusions for labor and delivery.
Methodology

A true experimental research design with a post-test only was chosen to determine if the addition of sodium bicarbonate to 2% 2-chloroprocaine would result in a longer duration of epidural analgesia as well as an increase in the quality of pain relief in parturients receiving a continuous bupivacaine epidural infusion. This study compared the duration of epidural analgesia and qualitative pain relief in two groups of parturients, those in group I, who received sodium bicarbonate added to 2% 2-chloroprocaine, and those in group II, who received saline with the local anesthetic.

The setting was the obstetrical suite of a mid-Atlantic university teaching hospital. A convenience sample of 31 ASA physical status I or II parturients in established and uncomplicated labor was randomly assigned to one of two groups. A nonprobability sample was chosen. The parity of the patient was not controlled in that primiparous as well as multiparous patients were studied. All patients who received narcotics prior to epidural placement or within 1 hour after the study began were excluded. The patient, as well as the anesthetist administering the regional anesthetic, was unaware of the medication being administered.

The protocol and consent forms for this study were approved by the Committee on the Conduct of Human Research. Each patient was informed of the risks and benefits of the proposed procedure. Informed consent was obtained prior to epidural placement. Three assessment scales were utilized: a visual analog scale, a sensory analgesia level determined by pinprick, and motor blockade.

The pH of the local anesthetic solution was determined using a Corning® 130 pH meter. A small pilot study was conducted to determine the pH adjustment changes of 2% 2-chloroprocaine. When 1 mL of 8.4% sodium bicarbonate was added to 30 mL of 2% 2-chloroprocaine, the pH of the solution increased from 3.65 to 7.38. Saline did not affect the pH of 2% 2-chloroprocaine.

The total volume of study solution was 30 mL. The study solution for pH-adjusted 2% 2-chloroprocaine was 1 mL of 8.4% sodium bicarbonate (1 mEq/mL). The study solution for the non-pH-adjusted 2% 2-chloroprocaine was 1 mL of saline. One milliliter of study solution was added to 29 mL of 2% 2-chloroprocaine. Each syringe of study solution was prepared by an anesthetist according to randomization.

An intravenous infusion of 500-1,000 mL of lactated Ringer’s solution was administered over 10-15 minutes before administration of epidural analgesia. Using an automated blood pressure monitor, a baseline blood pressure was recorded, further assessed at 1-minute intervals for 20 minutes, and subsequently at 15-minute intervals for 90 minutes. For the purposes of this study, maternal hypotension was defined as a decrease in systolic blood pressure of > 20% or a systolic blood pressure < 100 mmHg. Hypotension was treated promptly by increasing the rate of intravenous fluid administration and administering 5-10 mg of ephedrine intravenously.

When the cervix was dilated 3-7 cm, an epidural catheter was placed via the L2-3 or L3-4 interspace and advanced 2-4 cm cephalad. Epinephrine was not added to the local anesthetic. The loss-of-resistance technique was used to determine when the needle emerged from the ligamentum flavum into the epidural space. After accurate placement was identified, 4 mL of sterile saline were injected to determine ease of flow and to increase the size of the epidural space for subsequent local anesthetic administration. A test dose of 4 mL of 2% 2-chloroprocaine was given. After an initial test dose, the study solution was administered to achieve a T-10 analgesic level. A subsequent continuous infusion of 0.25% bupivacaine was started at 10 mL/hr using a Harvard® pump.

All patients had electronic fetal heart rate monitoring provided. Uterine displacement was maintained by having the patient turn from side to side at 30-minute intervals. The cephalad dermatome level of analgesia was determined by pinprick at 5-minute intervals for 20 minutes followed by 15-minute intervals for 90 minutes. A record of the need for a supplemental bolus of local anesthetic to maintain a sensory level of T-10 was recorded and determined by the researcher.

The anesthetist asked each patient to indicate pain scores on an unmarked 10 mm visual analogue pain scale (0 = no pain, 10 = worst possible pain). A pain score was assessed prior to starting epidural catheter placement and at subsequent 5-minute intervals for 15 minutes and repeated once at 30 minutes. Motor block was assessed according to the method of Bromage, at 15-minute intervals for 60 minutes. Apgar scores of the neonates, delayed deliveries, and the occurrence of operative deliveries (forceps, vacuum, cesarean section) were recorded.

Results

The t-test for independent means was used to examine the significance of group differences on continuous variables (Table 1). The X² test for independence was used to examine differences between categorical variables. The racial makeup of the groups was 46.7% (N = 7) white in the control group and 68.8% (N = 10) white in the experimen-
tal group. The remaining patients in both groups were black. The binomial approximation to the normal curve was used to test the significance between the two proportions. The difference was not significant ($P = .106$). Therefore, in terms of patient characteristics the differences between the two groups was not significant, which supports randomization of the groups.

A number of categorical variables were examined in a contingency table. These variables included the number of gestations, live births and abortions, occurrence of meconium-stained amniotic fluid, occurrence of fetal heart rate depression, use of forceps or vacuum, and cesarean section deliveries. The obtained $X^2$ was not significant [$X^2(7, N = 30) = 3.447, P = .841$].

An analysis of covariance for systolic blood pressure was examined (Table II). The within "systole mean square" measured the variation of the mean value of systole at each point in time from the overall mean. The mean level of response did not significantly vary in any systematic way over time. The "within mean square" for group by systole interaction measured the extent to which patterns of variation over time for the individual groups differed from the overall pattern for both groups and, therefore, from one another. The pattern over time within the groups as compared to between the groups was not significantly different ($P = .05$).

Measures of pain perception were made using a self-report visual analog scale. The mean self-perceived level of pain was significantly different for the two groups. Moreover, there was an interaction effect; the pattern of self-perceived level of pain over time differed for the two groups in a significant way (Table III).

Motor block was assessed according to Borge's method. The data were examined by the $X^2$ test of independence, both at each point in time and overall. None of these values was significant (Table IV).

<table>
<thead>
<tr>
<th>Table I</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Mean difference</td>
</tr>
<tr>
<td>Height (in)</td>
<td>0.20</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>6.71</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>0.84</td>
</tr>
<tr>
<td>Gestation (wks)</td>
<td>0.68</td>
</tr>
<tr>
<td>Dilation cervix (cm)</td>
<td>0.05</td>
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<tr>
<td>Active Phase 1 (min)</td>
<td>2.53</td>
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<tr>
<td>Active Phase 2 (min)</td>
<td>0.21</td>
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<tr>
<td>Duration of bupivacaine infusion (min)</td>
<td>66.75</td>
</tr>
<tr>
<td>Total bupivacaine dose (mg)</td>
<td>41.03</td>
</tr>
<tr>
<td>Initial block dose (mg)</td>
<td>1.42</td>
</tr>
<tr>
<td>Infant weight (kg)</td>
<td>283.42</td>
</tr>
<tr>
<td>Apgar 1 min</td>
<td>1.16</td>
</tr>
<tr>
<td>Apgar 5 min</td>
<td>0.20</td>
</tr>
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</table>

*The experimental group had no variance (all 9s), so the t-test was not applicable; however, a difference of this magnitude is trivial.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Analysis of covariance for systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Sum of squares</td>
</tr>
<tr>
<td>Between</td>
<td>Group</td>
</tr>
<tr>
<td>Error</td>
<td>16,906.99</td>
</tr>
<tr>
<td>Within</td>
<td>Systole over time</td>
</tr>
<tr>
<td>Group times systole</td>
<td>877.99</td>
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<tr>
<td>Error</td>
<td>16,871.26</td>
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</table>

*df=Degrees of freedom

<table>
<thead>
<tr>
<th>Table III</th>
<th>Analysis of covariance for the visual analog scale</th>
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<tr>
<td>Source</td>
<td>Sum of squares</td>
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<td>Between</td>
<td>Group</td>
</tr>
<tr>
<td>Error</td>
<td>99.55</td>
</tr>
<tr>
<td>Within</td>
<td>Scale over time</td>
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<tr>
<td>Group times scale</td>
<td>12.85</td>
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<tr>
<td>Error</td>
<td>107.68</td>
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</tbody>
</table>

*P < .05

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Analysis of motor block scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Chi-square</td>
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<tr>
<td>15 minutes</td>
<td>1.036</td>
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<tr>
<td>30 minutes</td>
<td>0.267</td>
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<tr>
<td>45 minutes</td>
<td>0.027</td>
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<tr>
<td>60 minutes</td>
<td>0.819</td>
</tr>
<tr>
<td>Overall</td>
<td>0.045</td>
</tr>
</tbody>
</table>

*df=Degrees of freedom
An induction dose of the study solution was administered to achieve a T-10 analgesic level. The group effect was not significant; that is, the means for the individual groups did not differ from the overall mean. There was a significant effect for level over time; that is, the means for both groups at each point in time differed from the overall mean. However, there was no significant interaction effect. The patterns over time were the same in both groups (Table V).

![Table V](image)

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of squares</th>
<th>df</th>
<th>Mean square</th>
<th>Frequency</th>
<th>P</th>
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<tbody>
<tr>
<td>Between</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>31.26</td>
<td>1</td>
<td>31.26</td>
<td>2.74</td>
<td>.109</td>
</tr>
<tr>
<td>Error</td>
<td>331.06</td>
<td>29</td>
<td>11.42</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Within</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level over</td>
<td>36.01</td>
<td>6</td>
<td>6.00</td>
<td>6.85</td>
<td>.001</td>
</tr>
<tr>
<td>time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group times</td>
<td>3.24</td>
<td>6</td>
<td>0.54</td>
<td>0.62</td>
<td>.716</td>
</tr>
<tr>
<td>level</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Error</td>
<td>152.38</td>
<td>174</td>
<td>0.88</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

df—Degrees of freedom

Additional bolus injections occurred nine times in the control group and six times in the experimental group. The difference in proportions was examined by a binomial approximation to the normal curve and not found to be significant (P > .106). Also, the times and amounts of rebolus injections were examined by the t-test, and differences in means were found to be trivial (P > .80).

Based on the results of this study, the hypothesis stating that the pH adjustment of 2% 2-chloroprocaine will not improve the duration of analgesia in stage I parturients was not rejected. However, the hypothesis stating that there was no improvement in the quality of pain relief was rejected by this study.

Discussion

The purpose of this study was to determine whether the addition of sodium bicarbonate to 2-chloroprocaine for lumbar epidural anesthesia in obstetrical patients would increase the duration and qualitative pain relief when combined with a continuous bupivacaine infusion. The addition of sodium bicarbonate to local anesthetics is a safe and expeditious process, and if the efficacy and goal of the technique are greatly increased, anesthetists could use it more often.

There was no increase in anesthetic duration found in the present study, which is in agreement with Chestnut. The particular features of 2-chloroprocaine may differ from other local anesthetics. The high pKa of 2-chloroprocaine favored the ionized form across a range of pH values. Also, the size and shape of the 2-chloroprocaine molecule allowed passage across the nerve sheath rapidly, regardless of its ionic state.

The discrepancies between the present findings and previous studies may have occurred because different local anesthetics were pH-adjusted in those studies, with different physicochemical properties than 2-chloroprocaine. The pH adjustment of 2-chloroprocaine may require a further increase in pH from 7.3 to 7.7, or an upward pH adjustment of bupivacaine instead of 2-chloroprocaine may achieve the desired results.

The mean self-perceived level of pain was significantly different for the two groups. There was no significant difference between groups in terms of cervical dilation prior to epidural placement. Previous research findings have shown a faster onset when local anesthetic pH was adjusted upward with sodium bicarbonate. An increased quality of pain relief was attributed to a probable decrease in onset time of the 2-chloroprocaine, although data on onset time were not collected. This difference can be attributed to the clinical advantages of having a regional anesthetic take effect quickly, especially if delivery is imminent.

This study supported the previous findings in which continuous epidural infusions provided good analgesia during the first stage of labor, with infrequent hypotension and modest motor blockade. Also, no significant effect on fetal heart rate, Apgar scores, or instrument deliveries occurred.

The major limitation of this study was the small sample size. A time limitation was placed on data collection. A greater sample size might lead to a significant difference in duration of analgesia. Also, many patients could not be included in this study because of incorrect placement of the epidural catheter, one-sided analgesic blockade, or lack of compliance with the protocol.

To date, there remain many conflicting findings associated with the pH adjustment of local anesthetics for use in regional blockade. Perhaps with larger populations, better guidelines in gathering data and increased knowledge of the physiologic changes at the site of action of local anesthetics can improve the efficacy of alkalinization of local anesthetics for regional anesthesia.