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The Influence of pH-Adjusted 2-Chloroprocaine on the Quality and Duration of Subsequent Epidural Bupivacaine Analgesia during Labor: A Randomized, Double-blind Study

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A randomized, double-blind study was performed to determine whether *p*H-adjustment of 2-chloroprocaine hastens the onset of epidural analgesia, and improves the quality and duration of subsequent epidural bupivacaine analgesia during labor. One milliliter of *either* 8.4% sodium bicarbonate *or* normal saline was added to a 30-ml vial of 2% 2-chloroprocaine. At 0, 5, and 7 min, each patient received 2, 5, and 3 ml of 2-chloroprocaine, respectively. At 22 min, any patient who did not yet have satisfactory analgesia received an additional 5 ml of 2-chloroprocaine. At 35, and, again, at 36 min, each patient received 5 ml of 0.25% bupivacaine. The median onset of 2-chloroprocaine analgesia was slightly more rapid in the bicarbonate group than in the saline-control group (12 *versus* 14 min, $P < .05$). Two of 31 women in the bicarbonate group, *versus* 10 of 31 women in the saline-control group, required an additional 5 ml of 2-chloroprocaine at 22 min to achieve satisfactory analgesia ($P = .01$). There was no significant difference between groups in median duration of subsequent bupivacaine analgesia (60 min in each group) or mean (±SD) dosage of bupivacaine during the first stage of labor (64 ± 43 *versus* 72 ± 57 mg). Also, there was no significant difference between groups in pain scores over time. The authors conclude that *p*H-adjustment of 2-chloroprocaine: 1) slightly hastened the onset of epidural analgesia during labor; 2) significantly decreased the number of women who required additional 2-chloroprocaine to achieve satisfactory analgesia; and 3) did *not* significantly affect the quality or the duration of subsequent epidural bupivacaine analgesia. (Key words: Anesthesia: obstetric. Anesthetic techniques: epidural. Local anesthetics: bupivacaine; 2-chloroprocaine. Pregnancy: labor.)

IT IS COMMON CLINICAL PRACTICE to establish epidural analgesia during labor with 2-chloroprocaine, and to then maintain analgesia with bupivacaine. Advocates of this regimen claim that it is a very safe way to establish epidural analgesia, and that the rapid onset of 2-chloroprocaine analgesia is advantageous for women experiencing painful uterine contractions.[1]

However, Hodgkinson *et al.*¶ reported that epidural 2-chloroprocaine decreased the efficacy of subsequent epidural bupivacaine-induced analgesia during labor. Galindo and Witcher[2] suggested that the ability of 2-chloroprocaine to alter the activity of bupivacaine might depend upon the *p*H of the 2-chloroprocaine solution. Specifically, the low *p*H of the 2-chloroprocaine solution might decrease the fraction of bupivacaine available in the nonionized form. (The nonionized form of local anesthetic passes more quickly through the nerve sheath and membrane.[3,4]) The purpose of the present study was to address the following questions: 1) Does *p*H-adjustment of 2-chloroprocaine hasten the onset of epidural analgesia during labor? and 2) Does *p*H-adjustment of 2-chloroprocaine improve the quality and duration of subsequent epidural bupivacaine analgesia during labor?

Materials and Methods

The protocol was approved by the University of Iowa Institutional Review Board for research involving human subjects. Written informed consent was obtained from healthy women with a single, term (≥36 weeks) fetus in the vertex presentation. Each fetus had a normal heart rate pattern before epidural analgesia. Women with preeclampsia, insulin-dependent diabetes, or chorioamnionitis were excluded.

Each patient received an intravenous infusion of 750 ml of Ringer's lactate over 10–15 min before epidural analgesia. When the cervix was 3–7-cm dilated, a 20-gauge polyamide catheter was inserted into the epidural space *via* the L3–4 interspace and advanced 3–4 cm cephalad.

One milliliter of sterile study solution was freshly added to a 30-ml vial of 2% 2-chloroprocaine. Each syringe of coded study solution was freshly prepared by a hospital pharmacist according to a table of random numbers, and was administered in a double-blind manner. The study solution for the patients receiving *p*H-adjusted 2-chloroprocaine was 1 ml of 8.4% sodium bicarbonate (1 meq/ml); the study solution for patients in the saline-control group was 1 ml of normal saline. The addition of 1 ml of study solution resulted in a concentration of 2-chloroprocaine of approximately 1.94%.

The formulation of 2-chloroprocaine during the first half of the study was Nesacaine-CE (Astra Pharmaceutical Products, Westborough, MA). After 25 patients had been enrolled in the study, Nesacaine-CE was not available, and Nesacaine-MPF was used thereafter. (Nesacaine-CE

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Reprints will not be available.

¶ Hodgkinson R, Husain FJ, Bluhm C: Reduced effectiveness of bupivacaine 0.5% to relieve labor pain after prior injection of chloroprocaine 2% (abstract). ANESTHESIOLOGY 57:A201, 1982.

TABLE 1. Maternal Characteristics

	Bicarbonate n = 31	Saline n = 31	*P*
Age (yr)*	23 ± 5	23 ± 4	NS
Parity			
Nulliparous	22	20	NS
Parous	9	11	
Race			
Caucasian	31	29	NS
Black	0	2	
Childbirth preparation class			
Lamaze	12	15	NS
Health Department/ University	8	11	
None	11	5	
Weight (kg)*	77 ± 16	81 ± 21	NS
Height (cm)*	167 ± 6	165 ± 7	NS
Gestational age (weeks)*	40 ± 1	40 ± 1	NS
Cervical dilation before epidural (cm)*	4.4 ± 1.2	4.4 ± 1.0	NS

NS = not significant.
* Mean ± SD.

contains 0.07% sodium bisulfite, but Nesacaine-MPF does not.)

Before beginning the protocol, we confirmed that the addition of 1 ml of 8.4% sodium bicarbonate to 30 ml of 2% Nesacaine-CE (n = 5) increased the *p*H from 3.81 ± 0.03 to 7.01 ± 0.004. Similarly, the addition of 1 ml of 8.4% sodium bicarbonate to 30 ml of 2% Nesacaine-MPF (n = 5) increased the *p*H from 3.35 ± .007 to 7.04 ± .004. One milliliter of saline did not affect the *p*H of Nesacaine-CE or Nesacaine-MPF. There was no effervescence or evidence of precipitation after the addition of bicarbonate or saline, and the two solutions of 2-chloroprocaine appeared identical.

Epidural 2-chloroprocaine and bupivacaine were given according to the following schedule: 0 min, 2 ml of 1.94% 2-chloroprocaine; 5 min, 5 ml of 1.94% 2-chloroprocaine; 7 min, 3 ml of 1.94% 2-chloroprocaine; 35 min, 5 ml of 0.25% bupivacaine; and 36 min, 5 ml of 0.25% bupivacaine.

The two 5-ml boluses of 0.25% bupivacaine were given just before the time when we expected the 2-chloroprocaine analgesia to regress.[5] Each dose of local anesthetic was given with the patient lying supine with a folded pillow beneath the right buttock to facilitate left uterine displacement. The study ended at the time the patient requested additional bupivacaine, *or* if no additional doses were required, at the time that the patient was noted to have full cervical dilation. After completion of the study, each patient received additional boluses of 0.25% bupivacaine as deemed appropriate by the anesthesiologist.

Each patient assessed the adequacy of her pain relief on a four-point scale (1 = no pain relief, 2 = a little pain relief, 3 = a lot of pain relief, 4 = complete pain relief) every 2 min, beginning at 8 min. The onset of analgesia was defined as the interval from time zero until the patient reported a pain relief score of 3 or 4. At 22 min, women who did not yet have a pain relief score of 3 or 4 received an additional 5 ml of 1.94% 2-chloroprocaine. (This 5-ml dose was obtained from the original 30-ml vial, which contained the 1 ml of study solution.) A patient was excluded if she was noted to have full cervical dilation before she reported a pain relief score of 3 or 4.

The anesthesiologist asked each patient to indicate her level of pain on an unmarked 100-mm visual analogue pain scale (0 = no pain, 100 = worst possible pain) at time zero, at 35, 45, and 55 min, and at 20-min intervals thereafter. The anesthesiologist also determined the level of sensory analgesia to pinprick and the extent of motor block[6] at 22 min and at 55 min. The duration of bupivacaine analgesia was defined as the interval from the injection of 0.25% bupivacaine at 35 min until the time that the patient requested additional analgesia, or the time that the patient was noted to have full cervical dilation.

Maternal blood pressure was determined with an automated blood pressure monitor at 1-min intervals for 20 min after each injection of local anesthetic. 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 by giving 5–10 mg of ephedrine intravenously. The duration of the active phase of the first stage of labor was defined as the interval between cervical dilation of 4 and 10 cm.

Maternal age, weight, height, gestational age, cervical dilation, durations of the first and second stages of labor, infant weight, and umbilical cord blood gas values were compared by Student's *t* test. Total dosage of bupivacaine, onset of 2-chloroprocaine analgesia, sensory levels, and pain scores were compared by the Wilcoxon rank sum test. Kaplan-Meier survival curves were constructed for the *duration* of epidural bupivacaine analgesia, and the two groups were compared by the Wilcoxon logrank test. The Kaplan-Meier method allowed us to include those women who were noted to have full cervical dilation before they lost analgesia from the first dose of bupivacaine. All other data were compared by chi-square or Fisher exact test as indicated. $P < .05$ was considered significant.

Results

Sixty-five women consented to participate. One woman in the bicarbonate group, and two women in the saline group, were excluded because they had full cervical dilation before they reported a pain relief score of 3 or 4. Of the remaining 62 women, there were 31 in the bicarbonate group and 31 in the saline group. The two groups were similar with regard to maternal characteristics (table 1) and conduct of labor and delivery (table 2). Eight

TABLE 2. Conduct of Labor and Delivery

	Bicarbonate n = 31	Saline n = 31	*P*
Duration of active phase of first stage of labor (min)*	249 ± 197	304 ± 199	NS
Duration of second stage of labor (min)*	73 ± 51	74 ± 56	NS
Method of delivery			
Spontaneous	18 (58%)	18 (58%)	NS
Forceps/vacuum	10 (32%)	12 (39%)	
Cesarean	3 (10%)	1 (3%)	
Infant weight (gm)*	3527 ± 537	3426 ± 418	NS
Meconium-stained amniotic fluid	5 (16%)	7 (23%)	NS
1-min Apgar ≥ 7	25 (81%)	26 (84%)	NS
5-min Apgar ≥ 7	31 (100%)	29 (94%)	NS
Umbilical venous blood analysis*			
*p*H	7.33 ± .06	7.33 ± .07	NS
P_{O_2} (mmHg)	25.4 ± 5.5	25.4 ± 4.8	NS
P_{CO_2} (mmHg)	37.8 ± 5.3	37.5 ± 6.7	NS
Base excess (mEq/L)	−4.7 ± 2.5	−5.1 ± 2.4	NS
Umbilical arterial blood analysis*			
*p*H	7.26 ± .06	7.24 ± .08	NS
P_{O_2} (mmHg)	14.8 ± 4.7	15.8 ± 3.8	NS
P_{CO_2} (mmHg)	46.6 ± 7.9	48.0 ± 8.8	NS
Base excess (mEq/L)	−5.7 ± 2.7	−6.2 ± 2.8	NS

NS = not significant.
* Mean ± SD.

TABLE 3. Analgesia After Epidural Injection of 2-Chloroprocaine

	Bicarbonate n = 31	Saline n = 31	*P*
Onset of analgesia with 2-chloroprocaine (min)*	12	14	<.05
Sensory level at 22 min†			
Left	T-10 ± 1	T-11 ± 2	.05
Right	T-10 ± 2	T-11 ± 2	NS
Motor block at 22 min			
None	24 (77%)	28 (90%)	NS
Partial	5 (16%)	3 (10%)	
Almost complete	1 (3%)	0 (0%)	
Complete	1 (3%)	0 (0%)	
Number of women who required an additional 5 ml of 2-chloroprocaine at 22 min	2 (6%)	10 (32%)	.01
Hypotension after injection of 2-chloroprocaine	2 (6%)	2 (6%)	NS

NS = not significant.
* Median (the onset of analgesia was defined as the interval from time zero until the patient reported a pain relief score of 3 or 4. The *mean* ± SD onsets were 13.3 ± 5.5 min for the bicarbonate group, and 17.9 ± 9.0 min for the saline group).
† Mean ± SD.

women in each group had received an intravenous bolus of nalbuphine ≥ 1 h before induction of epidural analgesia.

The onset of 2-chloroprocaine analgesia was slightly more rapid in the women in the bicarbonate group ($P < .05$) (table 3). Women in the bicarbonate group had a slightly higher left-sided sensory level at 22 min, a difference of borderline statistical significance ($P = .05$). Two women in the bicarbonate group, and ten in the saline group, required an additional 5 ml of 2-chloroprocaine at 22 min to achieve satisfactory analgesia ($P = .01$). These results were not affected by the change in formulation of 2-chloroprocaine midway through the study. For example, among the ten women in the saline group who required additional 2-chloroprocaine, five had received Nesacaine-CE, and five had received Nesacaine-MPF.

One woman in the bicarbonate group, and two in the saline group, were noted to have full cervical dilation *after* the onset of satisfactory analgesia but *before* the injection of bupivacaine. These three women were excluded from further analysis. Among the remaining 59 women, there was no significant difference between the two groups in sensory level or motor block at 55 min (table 4). Also there was no significant difference between groups in duration of bupivacaine analgesia or total dosage of bupivacaine during the first stage of labor (table 4; fig. 1). Finally, there was no significant difference between groups in pain scores over time (fig. 2).

Discussion

There is evidence that the combination of a low *p*H with the presence of 0.2% sodium bisulfite was responsible for the neurotoxicity observed in cases of unintentional

TABLE 4. Analgesia After Epidural Injection of Bupivacaine

	Bicarbonate n = 30	Saline n = 29	*P*
Sensory level at 55 min*			
Left	T-10 ± 2	T-10 ± 2	NS
Right	T-9 ± 2	T-9 ± 2	NS
Motor block at 55 min			
None	26 (87%)	21 (72%)	NS
Partial	2 (7%)	7 (24%)	
Almost complete	1 (3%)	1 (3%)	
Complete	1 (3%)	0 (0%)	
Hypotension after injection of bupivacaine	6 (20%)	3 (10%)	NS
Duration of analgesia (min)†	60	60	NS
Total dosage of bupivacaine during first stage of labor (mg)*	64 ± 43	72 ± 57	NS

NS = not significant.
* Mean ± SD.
† Median (the mean ± SEM durations were 59 ± 3 min for the bicarbonate group, and 58 ± 4 min for the saline group).

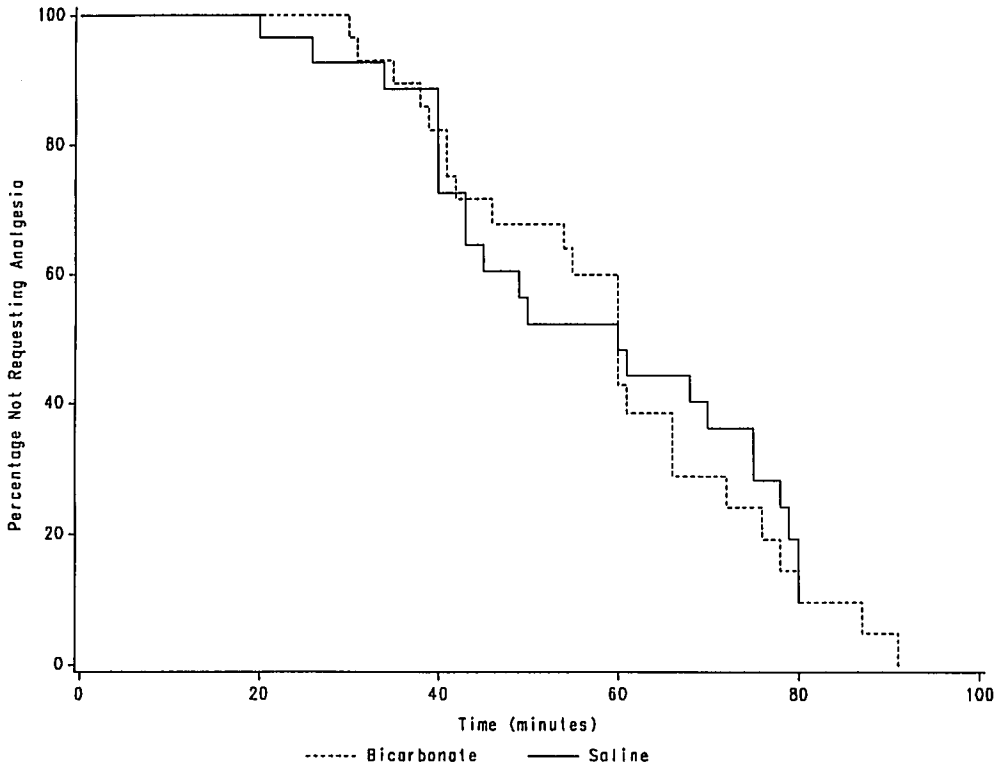
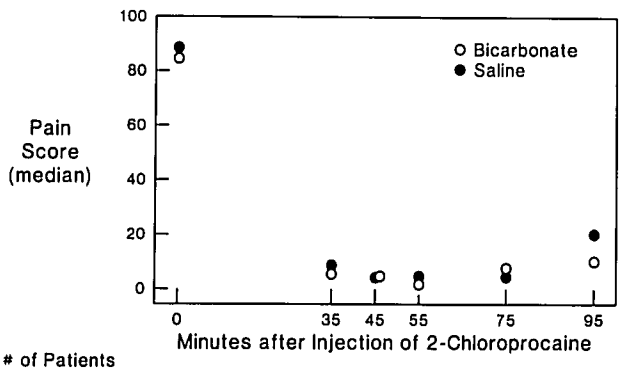


FIG. 1. Duration of analgesia after epidural injection of 0.25% bupivacaine. The duration of analgesia was defined as the interval from the injection of 0.25% bupivacaine at 35 min until the time that the patient requested additional analgesia, *or* the time that the patient was noted to have full cervical dilation. Survival curves for each group were calculated by the Kaplan-Meier method. There was no significant difference between the two groups.

intrathecal injection of 2-chloroprocaine.** Some clinicians prefer to increase the *p*H of 2-chloroprocaine to decrease the risk of neurotoxicity. The new formulation of 2-chloroprocaine (Nesacaine-MPF) retains a low *p*H but does not contain sodium bisulfite.

Villa and Marx[1] first advocated the use of a 2-chloroprocaine-bupivacaine sequence for epidural analgesia in laboring women. Cohen *et al.*[7] and De Campo *et al.*[8] noted that epidural injection of a 2-chloroprocaine-bupivacaine mixture produced analgesia of less duration than that produced by injection of bupivacaine alone. Hodgkinson *et al.*¶ confirmed that epidural injection of 2-chloroprocaine adversely affected the subsequent onset, quality, and duration of epidural bupivacaine analgesia in laboring women. Others[9–12] then reported that epidural administration of 2-chloroprocaine decreased the subsequent efficacy of epidural morphine[9,10] and fentanyl[11,12] analgesia after cesarean section. They speculated that 2-chloroprocaine may lower the *p*H in the epidural space to such an extent that subsequently injected local anesthetic or narcotic remains highly ionized.[9–12] Using a rat sciatic nerve preparation, Galindo and Witcher[2] observed that a mixture of 2-chloroprocaine and bupivacaine resulted in nerve blockade that resembled that produced by 2-chloroprocaine alone. However, increasing the *p*H of the mixture from 3.60 to 5.56 resulted in a nerve blockade that resembled that produced by bupivacaine alone. In the present study, *p*H-adjustment of 2-chloroprocaine did *not* improve the quality or the duration of subsequent epidural bupivacaine analgesia. The epidural injection of bupivacaine occurred 13–28 min after the last epidural injection of 2-chloroprocaine, and it is likely that the *p*H of the 2-chloroprocaine had been buffered to body *p*H



# of Patients						
Bicarbonate	31	30	29	28	23	14
Saline	31	29	28	28	22	13

FIG. 2. Median pain scores over time. The first 2 ml of 2-chloroprocaine were injected at time zero. The first 5 ml of bupivacaine were injected at 35 min. There were no significant differences between the two groups.

** Gissen AJ, Datta S, Lambert D: The chloroprocaine controversy II. Is chloroprocaine neurotoxic? Regional Anesth 9:135–145, 1984

by that time.[11] Another possible mechanism to explain the interaction of 2-chloroprocaine and bupivacaine was suggested by Corke *et al.*,[13] who suggested that a metabolite of 2-chloroprocaine, 4-amino-2-chlorobenzoic acid, remains in the nerve after recovery from 2-chloroprocaine blockade and interferes with the subsequent blockade by bupivacaine.

We may be criticized for giving the two 5-ml boluses of 0.25% bupivacaine before the 2-chloroprocaine analgesia had regressed. But, in clinical practice, the anesthesiologist typically gives the first dose of bupivacaine just before he/she expects the 2-chloroprocaine analgesia to regress. This practice prevents the patient from experiencing a sudden recurrence of pain. (When 2-chloroprocaine analgesia begins to regress, it regresses very quickly.) In the present study, we gave the 0.25% bupivacaine just before the time when we expected the 2-chloroprocaine analgesia to dissipate.

In the present study, *p*H-adjustment of 2-chloroprocaine slightly hastened the onset of epidural analgesia and decreased the number of women who required additional 2-chloroprocaine to achieve satisfactory analgesia. Others noted earlier that *p*H-adjustment of lidocaine[14] and bupivacaine[15,16] hastened the onset of epidural analgesia in pregnant women. Furthermore, DiFazio *et al.*[14] observed that *p*H-adjustment of lidocaine decreased the number of women who required additional lidocaine to achieve adequate analgesia. In contrast, Ross *et al.*[17] and Glosten *et al.*[18] did not observe a significantly faster onset of analgesia after epidural injection of *p*H-adjusted 2-chloroprocaine during labor[17] and before tubal ligation.[18] We are unable to provide a definitive explanation for the difference in results. However, we note that Ross[17] and Glosten[18] determined the onset of analgesia according to each patient's response to pinprick, whereas we defined the onset of analgesia according to each patient's assessment of the onset of pain relief.

We conclude that, under the conditions of the present study, *p*H-adjustment of 2-chloroprocaine slightly hastened the onset of epidural analgesia during labor. Second, *p*H-adjustment of 2-chloroprocaine significantly decreased the number of women who required additional 2-chloroprocaine to achieve satisfactory analgesia. Third, *p*H-adjustment of 2-chloroprocaine did *not* significantly affect the quality or the duration of subsequent epidural bupivacaine analgesia during labor. We also note that the mixing of drugs (*e.g.*, the addition of sodium bicarbonate to 2-chloroprocaine) introduces the potential for error and contamination. Therefore, we do not consider the present results sufficiently compelling to recommend *routine* *p*H-adjustment of 2-chloroprocaine.

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