ORIGINAL CONTRIBUTION
anesthetic, local, administration

Pain Reduction in Local Anesthetic Administration Through pH Buffering

The effects of pH buffering on the pain of administration and efficacy of three local anesthetics (1% lidocaine, 1% lidocaine with 1:100,000 epinephrine, and 1% mepivacaine) were investigated in a randomized, prospective, double-blind study of 25 adult volunteers. Plain and buffered solutions of the three local anesthetics were prepared, and a 0.5 intradermal injection of each was administered. Pain of anesthetic infiltration was rated from zero to ten. The area of anesthetized skin surrounding each injection site was measured at time intervals following each injection. Buffering the local anesthetics significantly reduced the mean quantitative pain estimates compared to the nonbuffered controls: 1) 1% lidocaine compared with buffered 1% lidocaine, 4.9 ± 0.4 versus 1.1 ± 0.2 ($P < 10^{-6}$); 2) 1% lidocaine with epinephrine compared with buffered 1% lidocaine with epinephrine, 5.1 ± 0.4 versus 1.8 ± 0.4 ($P < 10^{-6}$); and 3) 1% mepivacaine compared with buffered 1% mepivacaine, 5.1 ± 0.4 versus 0.9 ± 0.2 ($P < 10^{-6}$). Onset, extent, and duration of skin anesthesia were not statistically altered by pH buffering. The pain of local anesthetic administration can be dramatically reduced by buffering the local anesthetic prior to its infiltration. Anesthetic efficacy is not compromised, and patient acceptance may be significantly increased. [Christoph RA, Buchanan L, Begalla K, Schwartz S: Pain reduction in local anesthetic administration through pH buffering. Ann Emerg Med February 1988;17:117-120.]

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Received for publication May 19, 1987. Revision received September 28, 1987. Accepted for publication November 16, 1987.

Presented at the University Association for Emergency Medicine Annual Meeting in Philadelphia, May 1987.

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INTRODUCTION

Lidocaine, a local anesthetic of the amide class, is one of the most commonly used local anesthetics in the United States today. It is available in a wide variety of concentrations and can be combined with varying concentrations of epinephrine to prolong its action, reduce toxicity, and afford improved hemostasis.[1]

Another amide local anesthetic, mepivacaine, is available for use in emergency departments across the country. It is similar to lidocaine in its activity, but has a slightly more rapid onset and longer duration of action.[1]

Lidocaine and mepivacaine share with other local anesthetics a characteristic discomfort associated with their use in infiltrative local anesthesia. It is known that very slow infiltration of the local anesthetic can reduce the pain associated with its infiltration,[2] but demands on the physician's time may preclude the very slow infiltration of local anesthetic. In addition, ED patients, especially children, are frequently agitated and fearful. Therefore, it would be desirable if a convenient method could be devised by which the infiltration of local anesthetic could be less painful.

The mechanism of action of local anesthetics has been clarified in several studies.[3-5] Local anesthetic solutions of the amide type are weak organic bases, comprised of charged and uncharged fractions when in solution. The relative percentage of each fraction is dependent on the pH of the solution, with less local anesthetic in the uncharged form as the acidity of the solution increases.

It is believed that only the uncharged form of the local anesthetic is capable of diffusion through interstitial tissues and transport across the nerve membrane.[3,4] The greater the concentration of the local anesthetic in its uncharged form, the more rapid might become its dispersion through the

tissues.

Once within the nerve axoplasm, Hille hypothesized, the uncharged local anesthetic reequilibrates into charged and uncharged fractions according to axoplasmal pH.[5] He suggested that the charged form blocked neurotransmission at the sodium channel.[5]

Most local anesthetic solutions currently marketed are quite acidic.[6] At the marketed pH of 5.0 to 7.0, the local anesthetic is more soluble and has a shelf-life of three to four years. If the pH of the anesthetic solution is adjusted toward its pKa (7.9 for lidocaine, 7.6 for mepivacaine), an increasing percentage of the product will be the uncharged base form. Most amines and amides are chemically unstable in this uncharged form, being subject to photodegradation, aldehyde formation, and other denaturing reactions. While the shelf-life of lidocaine and mepivacaine adjusted to a pH of 7.2 to 7.4 has not been measured precisely, it follows that raising their pH to this level would substantially reduce effective storage shelf-life and solubility.[7]

Therefore, it is rational to market local anesthetics within a pH range of 5.0 to 7.0 to enhance solubility and prolong shelf-life. On the other hand, raising the pH to 7.2 to 7.4 may have a positive impact on anesthetic efficacy by increasing the percentage of the local anesthetic in the uncharged form, enhancing soft tissue dispersion of the anesthetic.

Several recent clinical studies have focused on enhanced anesthetic efficacy resulting from pH adjustment of the local anesthetic prior to use in regional anesthesia and major nerve block.[8-10] These studies did not, however, address the issue of the pain of anesthetic infiltration itself.

Our study was undertaken to investigate the effects of pH buffering on the pain of anesthetic infiltration and anesthetic efficacy of three commonly used local anesthetics: 1% lidocaine, 1% lidocaine with 1:100,000 epinephrine, and 1% mepivacaine.

MATERIALS AND METHODS

Healthy adult (18 to 40 years old) volunteers were enrolled into this randomized, prospective, double-blind study according to a protocol approved by the University of Virginia Human Investigation Committee.

Pregnant subjects, those with a history of allergic or other adverse reaction to lidocaine, mepivacaine, or epinephrine, or with a history of peripheral neuropathy, cardiovascular disease, or hypertension were excluded. Informed consent was obtained from 25 subjects, who were then enrolled and completed the study.

TABLE 1. *Prepared local anesthetic solution pH*

Local Anesthetic	pH
1% lidocaine	6.21
Buffered 1% lidocaine	7.22
1% lidocaine/epinephrine	5.98
Buffered lidocaine/epinephrine	7.16
1% mepivacaine	6.18
Buffered 1% mepivacaine	7.20

To minimize the incidence of adverse reactions to additives and preservatives, local anesthetic solutions free of adulterants were used for the study. These were obtained as solutions intended for use in epidural block. The local anesthetic solutions were prepared as 10:1 dilutions with either NaCl or $NaHCO_3$ as follows: 1) 20 mL 1% lidocaine + 2.0 mL NaCl (.9% NS); 2) 20 mL 1% lidocaine + 2.0 $NaHCO_3$ (1 mEq/mL); 3) 20 mL 1% lidocaine + 0.2 mL epinephrine (1:1,000) + 2.0 mL NaCl (.9% NS); 4) 20 mL 1% lidocaine + 0.2 mL epinephrine (1:1,000) + 2.0 mL $NaHCO_3$ (1 mEq/mL); 5) 15 mL 1% mepivacaine + 1.5 mL NaCl (.9% NS); and 6) 15 mL 1% mepivacaine + 1.5 mL $NaHCO_3$ (1 mEq/mL).

The pH of each resultant solution was measured using a Beckman 3560 pH meter (Beckman Instruments, Irvine, California).

Tuberculin syringes were used to draw 0.5-mL aliquots of each of the six local anesthetic solutions. For each subject, pairs of buffered and unbuffered local anesthetic solutions were assigned and labeled A to F, using a random number table. Injections were given intradermally by a blinded investigator over an interval of 2.5 seconds, timed by a metronome. A linear Visual Analogue Scale from 0 to 10, a device often used in pain analysis studies, was made available to each subject.[11] This device enabled subjects to assign a numerical value to the pain of anesthetic infiltration.

For each participant, the dorsum of the right hand was prepared with isopropyl alcohol and the entire contents of the syringe containing the local anesthetic labeled "unknown A" were administered intradermally using a 25-gauge needle. At the completion of the injection a stopwatch was started. Each participant then was asked to indicate on the Visual Analogue Scale the number that corresponded to his or her perception of the amount of pain associated with the infiltration of the anesthetic solution. The Visual Analogue Scale Pain Score was recorded.

Immediately thereafter, another investigator applied a 3-inch piece of cloth tape to the skin overlying the intradermal wheal raised by the local anesthetic injection. The edge of the tape was located over the center of the wheal, with the long axis situated at a 90° angle to the axis of the injecting needle. Thirty seconds after the injection, the diameter of the area of the skin anesthetized to pinprick was identified and marked on the tape. This procedure was repeated at one, 1½, 2½, 3½, and 4½ minutes after the injection, using different colored marking pens to indicate each time interval. The tape was removed and placed on an identifying paper for later measurement and recording.

The local anesthetic labeled "unknown B" then was injected intradermally in the dorsum of the left hand and the steps noted above were repeated. Local anesthetic "unknown C" was injected intradermally in the distal right volar forearm, local anesthetic "unknown D" in the distal left volar forearm, "unknown E" in the proximal right volar forearm, and "unknown F" in the proximal left volar forearm.

The Visual Analogue Scale quantifications of pain (pain scores) for each of the six local anesthetic solutions were averaged. The mean pain scores associated with the buffered and unbuffered solutions of each local

TABLE 2. *Surface area of skin anesthetized to pinprick (cm^2 ± standard error)*

Local Anesthetic	Time After Anesthetic Infiltration					
	½ Min	1 Min	1½ Min	2½ Min	3½ Min	4½ Min
1% lidocaine	3.5 ± 1.6	4.4 ± 2.4	4.7 ± 2.3	5.6 ± 3.4	6.6 ± 3.8	6.9 ± 4.5
1% lidocaine-buffered	3.5 ± 1.8	4.9 ± 2.6	5.7 ± 3.1	6.4 ± 3.6	7.4 ± 4.1	7.8 ± 4.1
1% lidocaine/epinephrine	3.3 ± 2.1	4.2 ± 2.9	4.7 ± 4.2	5.7 ± 5.1	6.8 ± 7.0	7.0 ± 5.4
1% lidocaine/epinephrine-buffered	3.0 ± 1.7	3.9 ± 1.8	4.7 ± 2.6	5.3 ± 3.1	6.4 ± 4.1	6.5 ± 4.1
1% mepivacaine	3.3 ± 1.8	4.4 ± 2.4	4.6 ± 2.4	5.8 ± 3.1	7.2 ± 3.6	8.0 ± 4.9
1% mepivacaine-buffered	3.3 ± 1.7	4.1 ± 2.1	5.1 ± 3.2	6.3 ± 3.6	7.3 ± 5.1	7.9 ± 4.3

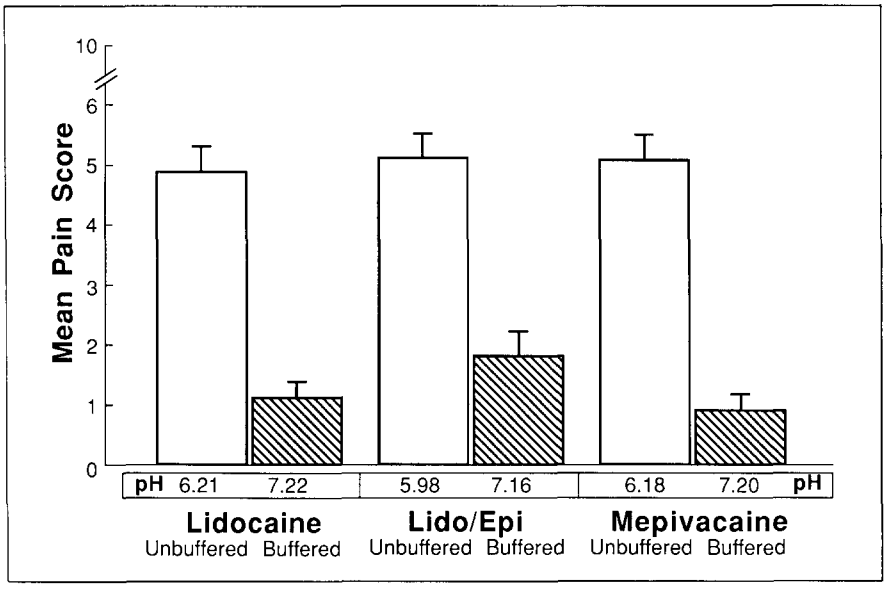

FIGURE. *Mean pain scores associated with intradermal infiltration of pain and pH buffered local anesthetic solution.*

anesthetic were compared using the Student's *t* test for paired samples.[12]

Assuming that the intradermal wheal created by the local anesthetic approximated the shape of a circle, and that the interstitial dispersion of anesthetic would follow a pattern of enlarging concentric circles, the surface area of anesthetized skin was calculated in cm^2 at each time interval.

The mean anesthetized skin surface areas for the buffered and unbuffered pairs of each local anesthetic solution were compared at each time interval using the Student's *t* test for paired samples.[12]

RESULTS

The effect of the buffering of the local anesthetic solutions was a raising of the pH toward a more physiologic range of 7.0 to 7.4 (Table 1). This was accomplished without a rise in pH above 7.4, which would have increased the risk of precipitation of local anesthetic out of solution.[1,7]

The amount of pain associated with the infiltration of the local anesthetic solutions was dramatically reduced by buffering (Figure). The infiltration of the 1% lidocaine was 4.5 times more painful than buffered 1% lidocaine; 1% lidocaine with epinephrine was 2.8 times more painful than buffered 1% lidocaine with epinephrine; and 1% mepivacaine was 5.7 times more painful than buffered 1% mepivacaine. These results were statistically highly significant with $P < 10^{-6}$ in all cases.

Buffering these local anesthetic solutions did not compromise their anesthetic efficacy, as indicated by the surface area of skin that was anesthetized to pinprick (Table 2). While the comparisons of anesthetized skin surface area for buffered compared with nonbuffered 1% lidocaine did indicate a trend toward enhanced interstitial dispersion by the buffered 1% lidocaine, the results were not statistically significant except for the 1½-minute time interval. At that time the buffered 1% lidocaine did anesthetize a larger surface area of skin than did the nonbuffered 1% lidocaine ($P = .03$). For the comparisons of buffered compared with nonbuffered 1% lidocaine with epinephrine and buffered compared with nonbuffered 1% mepivacaine, there were no statistically significant differences in surface area of anesthetized skin.

DISCUSSION

This study of 25 adult volunteers demonstrated a dramatic reduction in the pain of anesthetic infiltration of three local anesthetics commonly used in the ED. This was accomplished by buffering the pH of the local anesthetic toward a more physiologic range of 7.0 to 7.4 without risk of anesthetic precipitation or denaturing of the compound. Many of the subjects indicated that infiltration of pH-adjusted local anesthetics was painless.

The alleviation of pain associated with infiltration of buffered local anesthetic could hypothetically be attributed to two processes: the adjustment of local anesthetic pH toward the physiologic range of 7.0 to 7.4 reduces the direct tissue irritation caused by the infiltration of a more acidic compound; and by increasing the pH of the local anesthetic to 7.0 to 7.4, the relative concentration of local anesthetic in the uncharged form is increased, thus enhancing interstitial dispersion of the local anesthetic. The result might be sensory nerve blockade occurring almost instantaneously.

The reduction in pain of infiltration of the buffered local anesthetic solu-

tion is not due to either a dilutional effect or reduced dosage of local anesthetic, as all subjects received the same volume and dosage.

Adjustment of pH does not adversely affect local anesthetic efficacy. The onset of skin anesthesia was at least as rapid for the buffered local anesthetic compared with the unbuffered anesthetic. Measures of skin anesthesia were carried out for 4½ minutes. Multiple studies on nerve preparations,[4] major nerve block,[9,10] and regional nerve block[8] have shown that the duration of anesthetic effect is unchanged by local anesthetic buffering. In our ED, we have noted no clinically significant alterations of anesthetic duration when using buffered solutions for infiltrative local anesthesia.

The findings of this study have multiple applications in the ED. The pediatric patient, already fearful and anxious, will likely be much more cooperative through a minor surgical procedure if the local anesthetic is nearly painless. Local anesthesia can be provided without spending an inordinate amount of physician time slowly infiltrating the anesthetic. As the pain of digital nerve blockade is primarily related to the pain of anesthetic infiltration, it may be that this form of regional anesthesia would also be more readily tolerated by buffering the local anesthetic prior to use.

To facilitate the incorporation of local anesthetic buffering into clinical practice, an ampule of $NaHCO_3$ can be stored in the minor procedure room specifically for admixture with local anesthetic solutions. The buffering of the local anesthetic should be done immediately prior to its use, as adjusting the pH upward would be expected to decrease the shelf-life of the anesthetic.[1,7]

CONCLUSION

The pain of infiltration of 1% lidocaine, 1% lidocaine with epinephrine, and 1% mepivacaine can be dramatically reduced by buffering their pH to 7.0 to 7.4. In a volunteer study, the infiltration of the anesthetic became almost painless. Buffering can be easily and safely accomplished by the addition of $NaHCO_3$ so that the resultant ratio of local anesthetic to $NaHCO_3$ equals 10:1. In doing so, the efficacy of the local anesthetic is not compromised. It is recommended that local anesthetic buffering occur immediately prior to the use of the local anesthetic, so as to eliminate concerns regarding shortened shelf-life of the anesthetic caused by the buffering.

The authors thank Robert D Powers, MD, and Joseph F Chance, MD, for editorial assistance in the preparation of this manuscript.

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