Buffered Versus Non-Buffered Lidocaine With Epinephrine for Mandibular Nerve Block: Clinical Outcomes

James A. Phero, DDS, MD, * *Blake Nelson, BS, DDS,* † *Bobby Davis, BS,* ‡ *Natalie Dunlop, BS,* § *Ceib Phillips, PhD, MPH,* ‖ *Glenn Reside, DDS,* ¶ *Andrew P. Tikunov, PhD,* # *and Raymond P. White, Jr, DDS, PhD* **

Purpose: Outcomes for peak blood levels were assessed for buffered 2% lidocaine with 1:100,000 epinephrine compared with non-buffered 2% lidocaine with 1:100,000 epinephrine.

Patients and Methods: In this institutional review board–approved prospective, randomized, double-blinded, crossover trial, the clinical impact of buffered 2% lidocaine with 1:100,000 epinephrine (Anutra Medical, Research Triangle Park, Cary, NC) was compared with the non-buffered drug. Venous blood samples for lidocaine were obtained 30 minutes after a mandibular nerve block with 80 mg of the buffered or unbuffered drug. Two weeks later, the same subjects were tested with the alternate drug combinations. Subjects also reported on pain on injection with a 10-point Likert-type scale and time to lower lip numbness. The explanatory variable was the drug formulation. Outcome variables were subjects' peak blood lidocaine levels, subjective responses to pain on injection, and time to lower lip numbness. Serum lidocaine levels were analyzed with liquid chromatography-mass spectrometry. Statistical analyses were performed using Proc TTEST (SAS 9.3; SAS Institute, Cary, NC), with the crossover option for a 2-period crossover design, to analyze the normally distributed outcome for pain. For non-normally distributed outcomes of blood lidocaine levels and time to lower lip numbness, an assessment of treatment difference was performed using Wilcoxon rank-sum tests with Proc NPAR1WAY (SAS 9.3). Statistical significance was set at a P value less than .05 for all outcomes.

Results: Forty-eight percent of subjects were women, half were Caucasian, 22% were African American, and 13% were Asian. Median age was 21 years (interquartile range [IQR], 20-22 yr), and median body weight was 147 lb (IQR, 130-170 lb). Median blood levels (44 blood samples) at 30 minutes were 1.19 μg/L per kilogram of body weight. Mean blood level differences of lidocaine for each patient were significantly lower after nerve block with the buffered drug compared with the non-buffered agent ($P <$ .01). Mean score for pain on injection for nerve block (n = 46 scores) was 3.3 (standard deviation, 0.9). Seventy-eight percent of subjects reported lower or the same pain scores with the buffered drug; 61% of subjects reported a shorter time to lower lip numbness with the buffered drug.

Received from the School of Dentistry, University of North Carolina, Chapel Hill, NC.

*Resident, Department of Oral and Maxillofacial Surgery.

†Former Dental Student.

‡Dental Student.

§Dental Student.

‖Professor, Department of Orthodontics.

¶Clinical Associate Professor, Department of Oral and Maxillofacial Surgery.

#Research Associate, UNC/NCSU Joint Department of Biomedical Engineering.

**Dalton L. McMichael Distinguished Professor, Department of Oral and Maxillofacial Surgery.

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Address correspondence and reprint requests to Dr White: Department of Oral and Maxillofacial Surgery, School of Dentistry, University of North Carolina, Chapel Hill, NC 27599-7450; e-mail: ray_white@dentistry.unc.edu

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Conclusions: Buffering 2% lidocaine with epinephrine can produce clinical outcomes favorable for subjects and clinicians without clinically detrimental peak blood lidocaine levels.

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Local anesthetics have been a key component of dental treatment since the beginning of the 20th century. Based on the discovery of the anesthetic effects of the drug and the invention of the hypodermic syringe at the end of the 19th century, cocaine was rapidly adopted as a means of blocking painful sensory impulses during surgical procedures.[1] The discovery of procaine early in the 20th century led to this newer drug replacing cocaine to avoid its potential addictive properties. Lidocaine and its derivative products of the late 20th century, mepivacaine, bupivacaine, and articaine, are widely used to control pain with invasive oral procedures.[2] Local anesthetics are being administered in anesthesiology for pain control during and after orthopedic and head and neck procedures. In addition, for postprocedure pain control, longer-acting local anesthetics have been administered to produce long-term sensory nerve blockade, thus decreasing the need for analgesic drugs after procedures, particularly opioids.[3]

The addition of a vasopressor, usually epinephrine, to lidocaine and other injected local anesthetics serves to prolong the anesthetic effect by decreasing blood flow to the anatomic area and the diffusion of the drug away from the anatomic site of injection. To prolong the shelf life of the vasopressor, the drug combination must be formulated with a low pH (~3.5) for lidocaine with epinephrine. When lidocaine with epinephrine is injected, the combination of the needle penetration of tissue and the low pH of the solution causes an unpleasant or painful sensation often reported by subjects. Buffering the drug to a neutral pH could make the injection more comfortable for the patient.

By current consensus of clinicians and biological scientists, to be effective, a local anesthetic drug must penetrate the nerve membrane blocking the voltage-gated sodium channel preventing depolarization.[4] No longer is this considered an action only at the surface of the targeted nerve. Because only the unionized form of the drug penetrates the affected nerve membrane, a local anesthetic drug should be more effective in onset and potency if the pH is closer to the drugs' acidity constant (pKa) when more of the drug is in the unionized form. For lidocaine, the pKa is approximately 8.0, with minor variation dependent on temperature.[5] The drug injected at a neutral pH decreases the need and time lag for buffering by tissue fluid and makes the maximum unionized form of the drug immediately available while retaining the desired qualities of the vasopressor.[6] Until recently, buffering the drug combination with bicarbonate just before injection was impractical for many of the more complicated, protracted procedures in dentistry. However, a kit capable of efficiently buffering an adequate volume of lidocaine with epinephrine for any procedure immediately before injection became available in 2015 (Anutra Medical, Research Triangle Park, Cary, NC).

Investigators have reported less pain on injection of buffered lidocaine with epinephrine into skin when the pH of the drug is closer to 7.4.[7-9] Previous clinical studies in dentistry, not all from peer-reviewed journals, have reported similar but not universally consistent results.[10-13] Subjects injected intraorally for mandibular nerve block with buffered lidocaine tended to have a faster onset of lower lip numbness, with differences no greater than 5 minutes, and less pain on injection, but not always.

Mean maximum blood levels of local anesthetic occur approximately 30 minutes after oral injection.[14] Buffering local anesthetics might alter peak blood lidocaine levels compared with the non-buffered drug. Blood lidocaine levels could be similar, lower, or higher. However, no data have been published on peak blood levels for buffered lidocaine anesthetics used in dental and oral surgical procedures.

This study, with a crossover design with each patient also serving as a control, was planned to determine relative blood levels of buffered lidocaine after oral injection for mandibular nerve block compared with the unbuffered combination. This useful information to clinicians on the metabolism and potential systemic toxicity of lidocaine could be important for subjects with dosage limitations because of body weight or health issues. In addition, the study was designed to substantiate previous reports of less pain on injection and earlier onset of anesthesia with the buffered drug.

Patients and Methods

Twenty-four subjects were recruited with a protocol approved by the institutional review board of the University of North Carolina (UNC; Chapel Hill, NC), and treated in 2 sessions at the UNC Oral and Maxillofacial Surgery Clinic; 23 subjects completed the 2 study sessions. According to the protocol, subjects served as their own controls in a crossover study design. The sample size in this pilot study was chosen to provide

estimates for the calculation of the number of subjects that would be required in larger studies with a more diverse population.

A block randomization was used to randomize subjects to sequence 1: 4 mL of non-buffered 2% lidocaine (80 mg) with 1:100,000 epinephrine given in period 1 and 4 mL of buffered 2% lidocaine (80 mg) with 1:100,000 epinephrine given in period 2; or to sequence 2: 4 mL of buffered 2% lidocaine (80 mg) with 1:100,000 epinephrine given in period 1 and 4 mL of non-buffered 2% lidocaine (80 mg) with 1:100,000 epinephrine given in period 2. The buffered local anesthetics were adjusted to a neutral pH with bicarbonate just before injection for nerve block (Anutra Medical). The syringe for the buffered drug in each period had an added volume of 8.4% sodium bicarbonate 0.4 mL to compensate for the bicarbonate added to the lidocaine. The same investigator loaded the syringes with the local anesthetic drugs for the 2 clinical study sessions.

A midlevel oral and maxillofacial surgical resident and a full-time faculty member shared the task of administering the mandibular nerve block. The clinicians and the subjects were masked to the drug administered at each clinical session.

In week 1, each patient received an anesthetic to block the inferior alveolar and lingual nerves with the Halstead techniques. No buccal nerve block was administered to avoid the chance of pain from stimulation of the periosteum covering the coronoid process. At least 1 week later, sufficient to exceed the washout period for the drug, the nerve block involved the alternate local anesthetic combination.

Venous blood samples were drawn from the antecubital fossa 30 minutes after the injection of the local anesthetic at each of the 2 clinical sessions and assayed for serum lidocaine levels with a Sciex TripleTOF liquid chromatography-mass spectrometry (LC-MS; Sciex, Framingham, MA) equipped with a C18 Hypersil (10 × 2.1 mm, 3.0 μm) using methods previously described by Dal Bo et al.[15]

At each visit, assessment for pain level on injection was reported by each patient to a clinical investigator based on a 10-point Likert-type scale anchored by no pain and worst pain imaginable. A timed assessment was performed after the anesthetic for clinical onset of anesthesia by the patient reporting to the same clinical investigator when the lower lip was numb on the injected side.

The explanatory variable was the drug formulation. Outcome variables were the LC-MC–assessed values for blood lidocaine levels, subjects' subjective responses to pain on injection, and time to lower lip numbness. Statistical analyses were performed using Proc TTEST (SAS 9.3; SAS Institute, Cary, NC), with the crossover option for a 2-period crossover design, to analyze the normally distributed continuous outcome for pain. For non-normally distributed continuous outcomes for blood lidocaine levels and time to lower lip numbness, an assessment of treatment difference was performed using Wilcoxon rank-sum tests with Proc NPAR1WAY (SAS 9.3).[16] Statistical significance was set at a P value less than .05 for all outcomes.

Results

Forty-eight percent of the 23 subjects completing the protocol were women, half were Caucasian, 22% were African American, and 13% were Asian (Table 1). Median age was 21 years (interquartile range [IQR], 20-22 yr) and median body weight was 147 lb (IQR, 130-170 lb).

The median blood lidocaine level at 30 minutes after injection for 22 subjects (44 blood samples) was 70 μg/L (IQR, 62-87 μg/L). Compared by body weight, the median blood level of lidocaine at 30 minutes for all subjects was 1.19 μg/L per kilogram of body weight. Median blood lidocaine levels were significantly higher (15 μg/L) for the injected non-buffered lidocaine than for the buffered lidocaine (95% confidence interval [CI], 5.8-34.6; P = .006; Fig 1). Conversely, the outcomes suggested that blood lidocaine values were markedly lower when the injected drug was buffered. When subjects received non-buffered lidocaine, 16 of 22 subjects (73%) had a blood lidocaine concentration that was higher than with the buffered lidocaine, 3 (13%) had the same level calculated as less or equal to 1.6 μg/L, and 3 (13%) had a blood lidocaine concentration that was lower.

Based on all responses on the 10-point Likert scale, the mean score for pain on injection for nerve block

Table 1. DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS, SERVING AS THEIR OWN CONTROLS, RANDOMLY RECEIVING BUFFERED AND NON-BUFFERED 2% LIDOCAINE WITH 1:100,000 EPINEPHRINE (N = 23)

Men, n (%)	12 (52)
Women, n (%)	11 (48)
Weight (lb), median (IQR)	147 (130-170)
Age (yr), median (IQR)	21 (20-22)
Ethnicity or race, n (%)	
Caucasian	12 (52)
African American	5 (22)
Asian	3 (13)
Other	3 (13)

Abbreviation: IQR, interquartile range.

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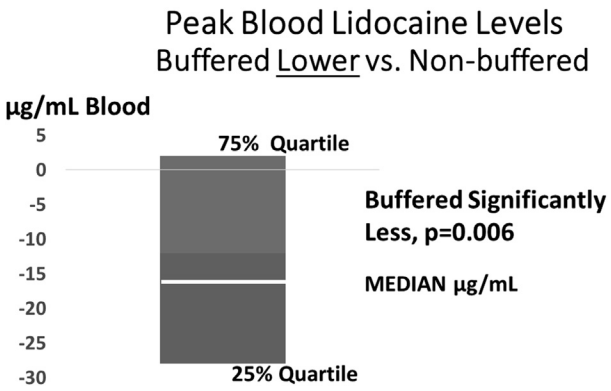

FIGURE 1. Subjects' (n = 22) peak venous blood levels of lidocaine in samples taken 30 minutes after injection comparing differences for the same patient between buffered 2% lidocaine with 1:100,000 epinephrine and non-buffered 2% lidocaine with 1:100,000 epinephrine.

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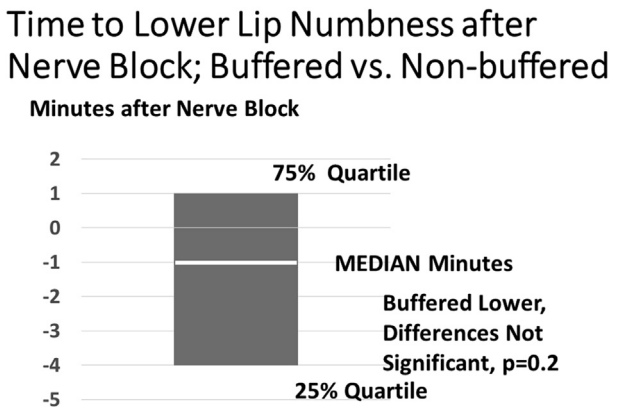

FIGURE 2. Subjects' (N = 23) reporting time to a numb lower lip after injection comparing differences for the same patient between buffered 2% lidocaine with 1:100,000 epinephrine and non-buffered 2% lidocaine with 1:100,000 epinephrine.

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(n = 46 scores) was 3.3 (standard deviation, 0.9). Although not statistically significant, on average, slightly lower scores, approximately two thirds of 1 U (95% CI, −1.46 to 0.13), were reported with the buffered lidocaine (P = .096). Of 23 subjects, 17 (78%) reported the same or lower pain scores with the buffered drug combination compared with the non-buffered lidocaine.

Median time to lower lip numbness after nerve block (n = 46 scores) was 3 minutes (IQR, 2-4 minutes). The difference in time between the 2 drug formulations was not statistically significant (P = .23). Subjects' median time to lip numbness for the buffered lidocaine compared with the non-buffered drug was −1 minute (IQR, −4 to +1; 95% CI, −18 to 6.6; Fig 2). Time to lip numbness with the buffered lidocaine was shorter for 14 subjects (61%). For 8 subjects (35%), time to lip numbness was shorter for the non-buffered lidocaine.

Discussion

The present data on peak lidocaine blood levels markedly favor outcomes after the buffered lidocaine with epinephrine; blood levels at 30 minutes after injection for three fourths of subjects were lower for the buffered lidocaine. These comparative data on blood lidocaine levels with buffered and non-buffered lidocaine with epinephrine have not previously been reported in the literature. This suggests to clinicians that the buffered lidocaine does not increase systemic toxicity after injection of the buffered lidocaine with epinephrine compared with the same dosages of the unbuffered drug. The lidocaine dosage in this study (80 mg) is often administered to adequately perform a procedure in 1 quadrant of the mandible requiring pulpal and periosteal anesthesia. For subjects in this study whose weight averaged 147 lb (67 kg), the dosage of 80 mg is well below a conservative suggested maximum dosage of lidocaine (5 mg/kg or 335 mg). If results with the buffered drug had been marginally higher compared with the non-buffered drug, then it likely would not have posed a clinical problem with most dental procedures. However, for subjects with much lower body weight or those with compromised liver function, a higher blood lidocaine level even with low dosages might be problematic. If these data suggesting lower peak venous blood levels of lidocaine with the buffered lidocaine with epinephrine can be substantiated with larger volumes of the drug in future clinical trials, choosing the buffered drug combination might be preferred for pediatric and other select subjects, particularly those with compromised liver function.

The outcome of this study, less pain on injections into skin with buffered lidocaine, has been reported consistently. In 25 adult volunteers, less pain was reported after intradermal 0.5-mL injections of the buffered drug compared with the non-buffered drug.[7] Masters[8] reported similar results with the buffered local anesthetic administered in skin for plastic surgery procedures. Of the 40 subjects in that study, half the procedures were performed on the face. Similarly, Lee et al[9] reported less pain with buffered lidocaine than with non-buffered lidocaine in hand surgery, a traditionally painful anatomic site for injections. These results were noted after a topical anesthetic cream was applied to the skin according to the protocol to minimize the impact of needle puncture in the 2 groups of subjects.

The present data on pain with injection for nerve block mirror outcomes from previous clinical studies

in dentistry, not all from peer-reviewed journals. In contrast to injections of the skin, a field block for local anesthesia, the data for pain from intraoral injections for nerve block are not uniformly predictable.[10-13] Although not always statistically relevant, subjects injected intraorally for mandibular nerve block generally have less or the same pain on injection with buffered lidocaine, but not always. Other factors than the pH of the drug formulation are involved, including needle penetration of the mucosa, the volume and speed of the solution injected, the variable potential of penetration of the periosteum during injection, and the anatomic proximity of the injected drug to the targeted nerve trunk. These differences compared with a field block for anesthesia in the skin could explain the different outcomes.

Although not consistent across all subjects in the study, a faster onset of lower lip numbness was reported by two thirds of subjects when lidocaine with epinephrine was buffered just before administration. Kashyap et al[11] and Malamed et al[12,13] suggested an earlier onset of anesthesia for most, but not all, subjects with buffered lidocaine with 1:100,000 epinephrine compared with non-buffered drugs. The rationale for an earlier onset of anesthesia, usually a difference in minutes, for buffered preparations of local anesthetic drugs with epinephrine compared with non-buffered drugs is based on the time lag after injection for tissue fluids to buffer the lower pH levels of 3.5 of commercial preparations to 7.4. After buffering lidocaine with epinephrine with bicarbonate, the commercial preparation has a pH closer to the drug's pKa (for lidocaine, the pKa is ~8.0), making more of the unionized form of the drug more rapidly available to the targeted nerve trunk, resulting in a faster onset of anesthesia.

Clinicians should consider that the present data have limitations. Administered drug dosages were low and not close to maximum recommended dosages by body weight. Thus, peak blood levels were low overall. Although blood lidocaine levels usually are reported at 30 minutes after injection, the beneficial outcomes reported for the buffered lidocaine could differ if peak blood levels occur within less than 30 minutes. Although the experimental design uniquely compared outcomes for the same patient 2 weeks apart and numerical values were assigned to the outcomes for pain on injection and onset of lip numbness, the data were subjective, relying on the subjects' interpretation and responses. All subjects studied were young healthy adults. Potential patients with a more compromised health status or different dental experiences might report other responses. Although it was clear that the drug buffered just before injection was associated with less or the same pain for most subjects on injection of the local anesthetic for nerve block, a clear benefit, pain levels on a 10-point Likert-type scale overall were low (average, 3 of 10). Although the buffered lidocaine did result in many of the subjects having a numb lip more rapidly than occurred with the non-buffered drug, an indication of a more rapid impact on the targeted sensory nerves, the differences generally were only a few minutes. This benefit must be weighed by the practice of the respective clinicians. For example, general dentists might gain by a rapid onset of the drug, whereas surgeons planning a more protracted procedure might not see the same advantages.

The present data suggest that lidocaine with epinephrine buffered just before injection for nerve block for mandibular procedures has positive benefits for patients. Similar studies should be conducted for outcomes after field block in the upper jaw, which might be different. Based on current concepts of the pharmacology of the effect of local anesthetics on targeted nerves, buffering commercial preparations of local anesthetics with epinephrine, making the unionized form of the injected drug more rapidly available to the targeted nerves, could allow clinicians to use a lower concentration by volume of the local anesthetic. For example, buffered 1% lidocaine with epinephrine could be as effective as non-buffered 2% lidocaine with epinephrine. This potential should be studied for nerve block in the mandible and field block in the maxilla, with possible outcomes having obvious clinical benefits, particularly to pediatric patients who have lower weight-determined dosage limits. The recently available buffering kit for this study has practical benefits for clinicians; volumes of the administered buffered drug can be as large as the capacity of the syringe chosen by the clinician. In addition, studies should be conducted with a wide range of patients with different health statuses who might require a variety of dental and oral procedures.

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