

# The efficacy of six local anesthetic formulations used for posterior mandibular buccal infiltration anesthesia

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**P**racticing dentists are continually searching for effective methods of delivering pain-free treatment for their patients. For most restorative and surgical procedures, dentists are able to manage operative pain and discomfort by using intraorally administered local anesthetics. Anesthetic administration techniques for intraoral anesthesia in dentistry commonly rely on either infiltration or nerve block injection. Agents commonly used in the United States include the following amide anesthetic formulations:

- 2 percent lidocaine with 1:100,000 epinephrine (L100);
- 4 percent articaine with 1:200,000 epinephrine (A200);
- 4 percent articaine with 1:100,000 epinephrine (A100);
- 4 percent prilocaine with 1:200,000 epinephrine (P200);
- 3 percent mepivacaine without vasoconstrictor (Mw/o);
- 0.5 percent bupivacaine with 1:200,000 epinephrine (B200).

The anesthetic formulation most often used for oral surgical procedures and considered the

## ABSTRACT

**Objective.** The authors conducted a randomized, double-blind clinical trial to evaluate pulpal anesthesia achieved after mandibular infiltration of five commonly marketed dental local anesthetic formulations as compared with a control formulation of lidocaine with epinephrine.

**Methods.** The authors evaluated 2 percent lidocaine with 1:100,000 epinephrine (L100) against 4 percent articaine with 1:100,000 epinephrine (A100), 4 percent articaine with 1:200,000 epinephrine (A200), 4 percent prilocaine with 1:200,000 epinephrine (P200), 3 percent mepivacaine without vasoconstrictor (Mw/o) and 0.5 percent bupivacaine with 1:200,000 epinephrine (B200). This repeated-treatment trial involved 18 healthy participants. The investigators administered mandibular infiltration injections (six sessions per participant) of 0.9 milliliters of anesthetic into the buccal fold adjacent to the distal root of the mandibular first molar. The authors determined anesthetic efficacy across a 20-minute period by measuring changes in sensory threshold to electrical pulp test (EPT) stimulation.

**Results.** Twelve female and six male participants (mean age, 24.9 years; range, 18-53 years) completed the study. The maximum mean increase from baseline of EPT measurements for the six formulations were 43.5 percent for L100, 44.8 percent for B200, 51.2 percent for P200, 66.9 percent for A200, 68.3 percent for Mw/o and 77.3 percent for A100 (A100 versus L100,  $P = .029$ ). Adverse reactions were minor and not formulation dependent.

**Conclusions and Clinical Implications.** The authors found that mandibular infiltration with 0.9 mL of the tested dental anesthetics could induce only partial pulpal anesthesia, a level likely to be inadequate for most dental procedures. When compared with L100, only the A100 induced statistically greater pulpal anesthesia after mandibular buccal infiltration.

**Key Words.** Local anesthetics; lidocaine; mandible; molar.  
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gold standard in the United States is L100.<sup>1</sup>

Practicing dentists have developed considerable interest in inducing mandibular pulpal anesthesia by means of administering buccal infiltration injections of anesthetic solutions adjacent to molars. Because the mandible has dense, thick cortical bone, the efficacy of infiltration anesthesia for mandibular molars for dental procedures traditionally has been considered inadequate.<sup>2-4</sup> Although practicing dentists have provided anecdotal reports of successful infiltration anesthesia for restorative procedures of mandibular molars with articaine, early clinical trials provided few scientific data to support their clinical impressions.<sup>5,6</sup>

In recent years, however, two separate investigative teams have published findings indicating that A100, when compared with L100, had statistically significant mandibular anesthetic properties when administered via buccal infiltration.<sup>7,8</sup> Researchers had not found this apparent advantage when comparing A200 with P200.<sup>5,6</sup> It is unclear if the differences reported are methodological or represent relative differences in the efficacy of the anesthetic formulations tested. The availability of several alternative local anesthetic formulations may lead to confusion among practicing dentists when they attempt to evaluate the agents' potential superiority and appropriate indications for dental infiltration anesthesia.

Clinicians would benefit from knowing the relative efficacy of the commonly available local anesthetic formulations for achieving pulpal anesthesia after mandibular buccal infiltration. Therefore, we initiated a study to evaluate the pulpal anesthetic characteristics of five commonly used local anesthetic formulations when used for mandibular infiltration anesthetic injections and compare their efficacy with that of L100. We also assessed side effects and adverse drug reactions.

#### **PARTICIPANTS, MATERIALS AND METHODS**

To characterize the pulpal anesthetic properties resulting from mandibular infiltration of common dental local anesthetic formulations, we performed a randomized, double-blind, controlled clinical trial comparing L100 with five other marketed local anesthetic formulations: A200, A100, P200, Mw/o and B200. Using posted announcements within the University of Pittsburgh School of Dental Medicine clinics, we recruited and enrolled 18 healthy male and female participants

in this repeated-treatment study.

For each participant, the trial consisted of a one-hour screening visit and six 90-minute treatment visits, with a follow-up by telephone 24 hours after each visit. Participants who met the inclusion criteria at the screening were scheduled for their first treatment visit within eight days. Subsequent treatment sessions were scheduled at intervals no shorter than one week and no longer than three weeks. No dental care was provided as part of this investigation.

We used the following inclusion criteria for enrollment in the study: age of 18 to 65 years, a mandibular first molar without a dental restoration or detectable caries, a normal electrical pulp test (EPT) sensitivity value between 10 and 50 units, the ability to sign an informed consent form before undergoing any study procedures and the ability to understand and agree to cooperate with study requirements. Participants were not eligible for participation if they met any of the following exclusion criteria: evidence of soft-tissue infection near the proposed injection site; known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics; history of significant cardiac, neurological or psychiatric disorders; treated or untreated hypertension equal to or greater than 140 millimeters of mercury (Hg) systolic or 90 mm Hg diastolic; bronchial asthma; lactation or pregnancy; or current use of  $\beta$ -blockers, monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressors or ergot-type oxytocic drugs. We also excluded potential participants who had taken acetaminophen, nonsteroidal anti-inflammatory drugs, opioids or other analgesic agents within 24 hours of administration of study medication; had taken an investigational drug or participated in another study within the preceding four weeks; or required sedation therapy to tolerate the injection procedure. We asked female participants of child-bearing age to verify the specific birth control method they or their partner had used (such as

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**ABBREVIATION KEY.** **A100:** 4 percent articaine with 1:100,000 epinephrine. **A200:** 4 percent articaine with 1:200,000 epinephrine. **B200:** 0.5 percent bupivacaine with 1:200,000 epinephrine. **EPT:** Electrical pulp test. **Hg:** Mercury. **L100:** 2 percent lidocaine with 1:100,000 epinephrine. **Mw/o:** 3 percent mepivacaine without vasoconstrictor. **pK<sub>a</sub>:** Acid dissociation constant. **P200:** 4 percent prilocaine with 1:200,000 epinephrine. **VAS:** Visual analog scale.

abstinence, use of oral contraceptives or use of other devices or methods) for at least one month before and during participation in the study. We required that female participants of childbearing potential receive negative results on a urine pregnancy test before receiving test medications.

**Screening phase.** We obtained approval of this clinical trial through the University of Pittsburgh Biomedical Institutional Review Board and informed consent for study participation before conducting all screening procedures. At the screening visit, participants provided a medical history and underwent a brief physical examination that included checking and recording of vital signs (blood pressure, pulse rate, respiratory rate, body weight). We performed a tooth pulp vitality test by using electrical pulp stimulation to select the tooth (either no. 19 or no. 30) to be evaluated during subsequent treatment sessions.

**Experimental phase.** At the first treatment visit, we randomly assigned participants to one of six treatment sequence allocations (6 × 6 Latin square design). One of the authors (S.B.) removed the manufacturers' labels from the dental cartridges containing the six study formulations so that they were identical in appearance. He placed cartridges in coded envelopes numbered for treatment sequence. To ensure blinding, neither the research assistant, the administrator nor the patient had knowledge of the formulation used.

The clinician administered a mandibular infiltration into the buccal fold adjacent to the distal root of the mandibular first molar on the same side of the mouth for all treatments. The same investigator administered all injections given to a particular participant to provide consistency of the location of needle insertion with respect to the tooth. He or she recorded baseline EPT values before administering the injection of one half-cartridge (0.9 milliliter) by using an aspirating dental syringe and a 30-gauge short disposable needle. The clinician injected solution slowly across 30 seconds into the mandibular vestibule adjacent to the distal root of the mandibular first molar with frequent aspirations. Participants were requested to rate the pain experience induced by the injection procedure using a 100-millimeter visual analog scale (VAS) on which 0

indicated no pain and 100 indicated worst pain ever. No topical anesthetics were applied before injection.

During each treatment session, the clinician recorded the participant's supine blood pressure and heart rate before injection of the study formulation, five minutes after injection and at completion of the treatment session (90 minutes). He or she determined the anesthetic's efficacy by measuring changes in the sensory threshold of the dental pulp after performing electrical tooth stimulation with a commercially available EPT (Kerr Vitality Scanner 2006, SybronEndo, Orange, Calif.). The investigator assessed only the mandibular first molar on the anesthetized side.

The site of tooth contact for the EPT was the midpoint of the occlusal one-third of the buccal surface. The investigator applied the pulp tester during the screening phase to ensure that the tooth being tested was healthy and not hyperalgesic (in other words, had an EPT score in the range of 10 to 50 units). After administration of an anesthetic, the EPT stimulation was increased to a maximum of 80 units. Before testing a tooth, the investigator isolated it with cotton rolls and air dried it. He or she ensured contact with the electrode by applying fluoride gel toothpaste to the probe tip. He or she administered the EPT every minute for the first 20 minutes.

To verify the presence of anesthesia, the investigator asked the participant to provide a descriptive self-report of soft-tissue anesthesia characteristics. At baseline and immediately after the EPT, the investigator asked the participant to select one of the following categories of sensory function:

- no change in sensation;
- slight feeling of numbness;
- moderate but not complete feeling of numbness;
- complete numbness on one side of the mouth.

At the conclusion of the testing session, the investigator recorded any adverse reactions that occurred.

**Follow-up phase.** One of the investigators contacted participants by telephone approximately 24 hours after each treatment session to determine if any adverse reactions had occurred after discharge. Investigators elicited information about adverse events by asking each participant, "Have you noticed any changes in your health

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**Adverse reactions to the mandibular molar infiltration testing were minor and not dependent on local anesthetic formulation.**  
 .....

since yesterday's testing session?" A positive response was followed by a series of specific questions regarding location and description of the effect or effects. The investigators also elicited information about specific oral symptoms or complaints previously reported<sup>9</sup> as being associated with local anesthetic injections (such as swelling, headache, infection, pain, gingivitis, numbness or tingling). Participants received \$40 for each visit; they made seven visits in all.

We calculated an estimated sample size of 18 participants to be large enough to detect a 15 percent difference in EPT-quantified anesthesia between the formulations at a .05 significance level with .90 power. We created tables summarizing participants' characteristics, including age, sex, weight and screening EPT values. We assessed significant differences in pain level during injection (VAS value) by using one-way repeated-measures analysis of variance (ANOVA). We assessed pulpal EPT changes for drug formulations (six) across time (20 tests and one base reading) by using within-cases ANOVA. We reported EPT values as change from baseline to a maximum of 80 units. Subsequently, we compared the standard control local anesthetic (L100) with each of the five other tested formulations by using least significant difference (LSD) pairwise tests. We tested the maximum percentage of participants achieving an EPT value of 80 for significant difference in proportions by using the Cochran *Q* test. We summarized vital signs as recorded at baseline, five minutes and completion of testing by using descriptive statistics. All adverse reactions, reported either immediately after testing or during the follow-up telephone call 24 hours later, are described below.

## RESULTS

The 18 enrolled participants, six men and 12 women, completed all six of the testing sessions. Their mean age was 24.9 years, with a range of 18 to 53 years. Baseline EPT screening of the vitality of the mandibular first molar (10 left and eight right) yielded a mean score of 34.4 ( $\pm$  4.5 standard deviation) and a range of 24 to 42 units. Changes in vital signs between readings at baseline, five minutes after injection and 30 minutes after injection were minimal. Overall, mean blood pressures, pulse rates and respiration rates were within normal limits and remained essentially unchanged from baseline values when monitored at five and 30 minutes after injection.

TABLE

Participants achieving complete pulpal anesthesia.*			
ANESTHETIC†	PARTICIPANTS ACHIEVING COMPLETE PULPAL ANESTHESIA (N = 18)		TIME TO PEAK ONSET (MINUTES)
	No.	%	
L100	3	16.7	8
A100	7	38.9	14
A200	6	33.3	10
P200	4	22.2	12
Mw/o	6	33.3	11
B200	2	11.1	9

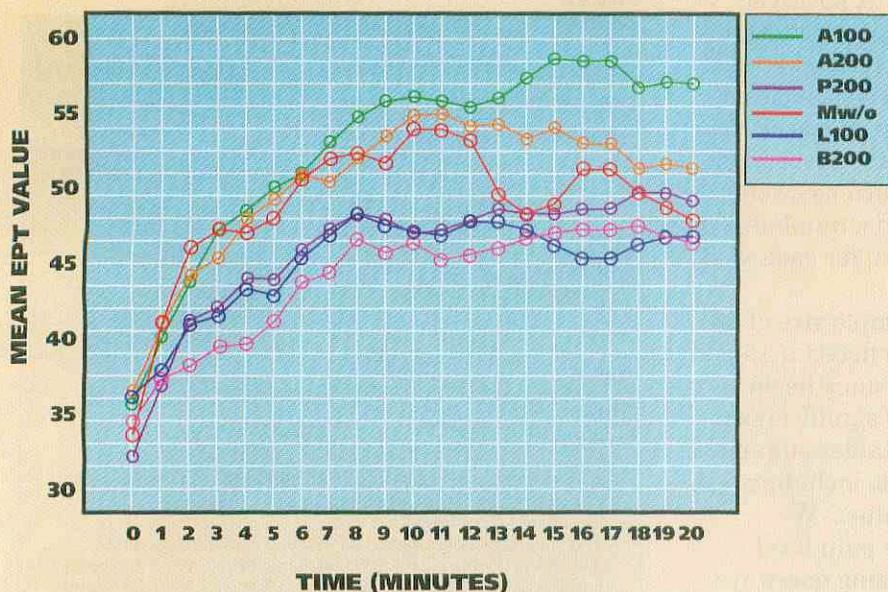
\* The maximum percentage of participants achieving an electrical pulp test value of 80 at any time during the testing session ( $P = .29$ , not significant).

† L100: 2 percent lidocaine with 1:100,000 epinephrine. A100: 4 percent articaine with 1:100,000 epinephrine. A200: 4 percent articaine with 1:200,000 epinephrine. P200: 4 percent prilocaine with 1:200,000 epinephrine. Mw/o: 3 percent mepivacaine without vasoconstrictor. B200: 0.5 percent bupivacaine with 1:200,000 epinephrine.

Pain-at-injection ratings using the 100-mm VAS were similar for all test anesthetic formulations as compared with those for the standard L100 (ANOVA,  $P = .19$ ). We calculated mean VAS pain ratings for injection pain as follows: 32.2 for B200, 27.6 for L100, 26.2 for A100, 24.1 for A200, 22.9 for Mw/o and 21.0 for P200.

The table reports the complete pulpal anesthesia frequency (EPT score of 80) and time to peak onset for each drug. The figure depicts the changes in EPT recordings after injection of each of the six formulations. We found all formulations increased EPT values across time ( $P < .001$ , ANOVA). Maximum mean increases from baseline EPT were 43.5 percent for L100, 44.8 percent for B200, 51.2 percent for P200, 66.9 percent for A200, 68.3 percent for Mw/o and 77.3 percent for A100. In comparison with the lidocaine control formulation, only A100 was significantly different ( $P = .029$ , LSD). We saw a similar pattern of anesthetic efficacy when assessing the percentages of complete (EPT = 80) recordings (Cochran *Q*,  $P = .29$ ); the table shows the maximum percentages of an EPT score of 80 and the times of the peak onsets for each of the formulations.

Participants' mean self-reports of soft-tissue numbness during the 20-minute testing sessions reveal a similar pattern of relative efficacy ( $P = .31$ , ANOVA). Peak numbness was recorded as occurring between seven and 15 minutes after



**Figure.** Mean changes in electrical pulp test (EPT) scores after mandibular infiltration with 4 percent articaine with 1:100,000 epinephrine (A100), 4 percent articaine with 1:200,000 epinephrine (A200), 4 percent prilocaine with 1:200,000 epinephrine (P200), 3 percent mepivacaine without vasoconstrictor (Mw/o), 2 percent lidocaine with 1:100,000 epinephrine (L100) and 0.5 percent bupivacaine with 1:200,000 epinephrine (B200). Alone among the formulations, A100 yielded a significantly greater change in EPT values than did L100 ( $P = .029$ , least significant difference).

injection for the six formulations. We found A100 to provide the highest degree of numbness and B200 to provide the lowest. When compared with the lidocaine control, B200 was significantly less effective in providing soft-tissue anesthesia ( $P = .039$ , LSD).

Adverse reactions to the mandibular molar infiltration testing were minor and not dependent on local anesthetic formulation. Three reactions, reported by two participants, occurred during the testing sessions (one instance of pain or soreness and two instances of swelling). At the follow-up 24 hours after testing, six participants reported a total of 11 adverse reactions. These included six instances of pain or soreness at the injection site, two instances of swelling at the injection site, one headache, one instance of tooth sensitivity and one fissure at the corner of the lip. All reported reactions were transient and resolved within seven days.

## DISCUSSION

We designed this study to evaluate five commonly used dental formulations of local anesthetics to determine if any of the agents were superior to L100, the anesthetic formulation most commonly administered by U.S. dentists.<sup>1</sup> We selected a relatively small volume of anesthetic (0.9 mL) for

this investigation, in part to avoid causing the soft-tissue trauma that might occur after repeated injections during the six testing sessions. In addition, we expected the use of minimal volumes to help differentiate efficacies by avoiding loss of assay sensitivity associated with highly effective therapeutic agents.<sup>10,11</sup>

The use of EPT is essential to any quantitative clinical trial of dental anesthetics. As previously observed, the EPT criteria for complete anesthesia (EPT = 80) are a stringent test that may not be required for many restorative and cosmetic procedures.<sup>12</sup> Although the EPT is a precise assess-

ment of pulpal anesthesia, clinically adequate anesthesia for some restorative procedures may not necessitate complete pulpal anesthesia. The pulpal anesthesia achieved with A100 in our trial according to EPT scores was limited to a 77.3 percent increase from baseline, a level of anesthesia likely to be inadequate for most dental procedures. Notably, the results demonstrated by Robertson and colleagues<sup>8</sup> and by Kanaa and colleagues<sup>7</sup> using a volume of 1.8 mL of A100 demonstrated greater levels of anesthesia than those we found and may support the use of a full cartridge of A100 in clinical dental practice.

Buccal infiltration injection of local anesthetics has been shown to be less painful than lingual infiltration.<sup>13</sup> Although we found no statistical differences in pain at injection, our findings suggest that the bupivacaine injection was the most painful and the prilocaine injection was the least painful (mean VAS scores of 32.2 and 21.0, respectively). Bupivacaine injections cause more discomfort than those of prilocaine, according to a published report.<sup>14</sup> A difference in the pH of the formulations has been implicated as a possible cause of the pain responses to local anesthetic injections.<sup>15</sup>

In addition to investigations of the volume and formulation used, further investigations of rela-

tive efficacy associated with the site of injection and technique need to be conducted. For example, researchers have found that the combination of labial and lingual infiltration may be superior for attaining pulpal anesthesia in mandibular permanent central incisors.<sup>16</sup> The use of mandibular infiltration anesthesia to improve success rates of the standard inferior alveolar nerve block also should be investigated. It is conceivable that the proper combination of formulation, technique and site will maximize the efficacy of mandibular infiltration techniques and possibly eliminate the need for the routine use of inferior alveolar block anesthesia for restorative procedures in the mandible.<sup>13</sup>

It is interesting to note that the A100 formulation appeared to maintain anesthesia for a longer period than did the standard L100 formulation (Figure and Table). Kanaa and colleagues<sup>7</sup> also found this to be the case. It is unclear whether the higher EPT scores after administration of articaine are due to the drug's greater anesthetic potency or to its favorable tissue-diffusion properties.<sup>17,18</sup> Although the duration of mandibular infiltration anesthesia likely is shorter than would be expected with an inferior alveolar nerve block, greater anesthesia was achieved when investigators used A100 throughout the testing session. Investigators in future studies of mandibular infiltration should extend assessments to at least one hour to allow for full determination of the effective duration of this technique. Haas and colleagues<sup>5,6</sup> reported that A200 was not superior to P200 after mandibular infiltration. However, they did note a slight but statistically insignificant improvement in pulpal anesthesia with articaine versus prilocaine. Our results support their finding, in that the A200 formulation was minimally more effective than the P200 formulation. In addition, the comparator Haas and colleagues<sup>5,6</sup> selected was not L100 but P200. The prilocaine formulation's anesthetic infiltration properties may be slightly greater than those of L100. Because the effects of mandibular infiltration anesthesia are minimal, further study is indicated.

A100 and L100 usually demonstrate similar efficacy in maxillary infiltration or in mandibular inferior alveolar nerve blocks.<sup>19-22</sup> In the case of maxillary infiltrations, this may be because of the high rates of success of both anesthetic formulations.

The participants' mean self-reported ratings of

soft-tissue anesthesia for the various local anesthetics were to some extent similar to those for L100. The exception was for soft-tissue anesthesia after administration of B200. This may be best explained by bupivacaine's less favorable dissociation properties—having a higher acid dissociation constant ( $pK_a$ ) of 8.1—when compared with the dissociation properties of other local anesthetic agents we tested ( $pK_a$  7.6-7.9). When injected into normal tissue, local anesthetics with higher  $pK_a$ s have a larger ratio of charged-to-uncharged anesthetic, therefore limiting the drugs' diffusion through the lipid cell membrane of the nerve.

## CONCLUSIONS

Our study findings indicate that all of the local anesthetic formulations studied provide partial, albeit nominal, pulpal anesthesia after mandibular infiltration with one half-cartridge of anesthetic. This degree of anesthesia is likely to be inadequate for most dental procedures. Additionally, it appears that the efficacy of anesthetic delivered via mandibular infiltration depends on the local anesthetic formulation administered. When comparing anesthetic formulations with L100, we found only the A100 formulation to provide a greater level of pulpal anesthesia after mandibular infiltration, as measured by means of EPT. Future investigations involving A100 to determine the optimal volume, technique and site of injection may maximize the efficacy of mandibular infiltration anesthetic techniques. ■

**Disclosures.** Within the last five years, Dr. Moore has served as medical director, a research consultant or both to pharmaceutical companies regarding development of new anesthetics for dentistry. These companies include Dentsply Pharmaceutical, York, Pa.; Kodak Dental Systems by Carestream Health, Atlanta; Novocol Pharmaceutical of Canada, Cambridge, Ontario, Canada; and Septodont USA, New Castle, Del. He and Dr. Boynes also have served as investigators for U.S. Food and Drug Administration—required Phase II and Phase III clinical research contracts awarded to the University of Pittsburgh by Novalar Pharmaceuticals, San Diego; Novocol Pharmaceutical of Canada; and Wyeth Consumer Healthcare, Madison, N.J.

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