Anesthetic Efficacy of a Combination of 0.5 M Mannitol Plus 36.8 mg of Lidocaine With 18.4 µg Epinephrine in Maxillary Infiltration: A Prospective, Randomized, Single-Blind Study

Kevin Younkin, DDS, MS,* Al Reader, DDS, MS,† Melissa Drum, DDS, MS,‡ John Nusstein, DDS, MS,§ and Mike Beck, DDS, MA||

*Former Graduate Student in Endodontics, The Ohio State University, Columbus, Ohio, Currently in private practice limited to endodontics, Westerville, Ohio, †Professor and Program Director, Division of Endodontics, ‡Associate Professor, Division of Endodontics, §Professor and Chair, Division of Endodontics, ||Emeritus Associate Professor, Division of Oral Biology, The Ohio State University, Columbus, Ohio

The purpose of this prospective, randomized, single-blind study was to determine the anesthetic efficacy of lidocaine with epinephrine compared to lidocaine with epinephrine plus 0.5 M mannitol in maxillary lateral incisor infiltrations. Forty-one subjects randomly received 2 maxillary lateral infiltrations consisting of a 1.84-mL solution of 36.8 mg lidocaine with 18.4 µg epinephrine (control solution) and a 2.90-mL solution of 36.8 mg lidocaine with 18.4 µg epinephrine (1.84 mL) plus 0.5 M mannitol (1.06 mL) in 2 separate appointments spaced at least 1 week apart. The maxillary lateral incisor was blindly electric pulp-tested in 2-minute cycles for 60 minutes postinjection. No response from the subject to the maximum output (a reading of 80) of the pulp tester was used as the criterion for pulpal anesthesia. Total percent pulpal anesthesia was defined as the total of all pulpal anesthesia readings (at output of 80) over the 60-minute test period. Pain during solution deposition and postoperative pain were also measured. The results demonstrated that a 2.90-mL solution of 36.8 mg lidocaine with 18.4 µg epinephrine (1.84 mL) plus 0.5 M mannitol (1.06 mL) was not statistically significantly superior to a 1.84-mL solution of 36.8 mg lidocaine with 18.4 µg epinephrine. The pain of solution deposition was lower with the lidocaine/mannitol formulation. Postoperative pain was not statistically significantly different between the lidocaine/mannitol formulation and the lidocaine formulation without mannitol. We concluded that adding 0.5 M mannitol to a lidocaine with epinephrine formulation was not significantly more effective in achieving a greater percentage of total pulpal anesthesia (as defined in this study) than a lidocaine formulation without mannitol in the maxillary lateral incisor.

Key Words: Anesthesia; Mannitol; Lidocaine; Infiltration; Maxillary.

Previous studies^{1–19} have evaluated the success (ie, never achieving 1 or 2 consecutive 80 readings with

the electric pulp tester) of maxillary infiltrations. When a volume of 1.8 mL or less was used with various anesthetic formulations, pulpal anesthetic success ranged from 62% to 100%.^{1–19} Therefore, an infiltration injection may not always be 100% successful because of individual variations in response to the drug administered, operator differences, and variations in anatomy as well as tooth position.

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Address correspondence to Dr Al Reader, Graduate Endodontics, College of Dentistry, The Ohio State University, 305 W. 12th Avenue, Columbus, Ohio 43210; reader.2@osu.edu.

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Previous studies by Wolf et al,²⁰ Smith et al,²¹ and Cohen et al²² demonstrated that lidocaine in combination with mannitol significantly improved the success of inferior alveolar nerve blocks (defined as the total of all the times of complete pulpal anesthesia as measured by the 80 readings, for each tooth, over 60 minutes) in asymptomatic subjects. Kreimer et al²³ found, for mandibular posterior teeth in patients with symptomatic irreversible pulpitis, that the addition of 0.5 M mannitol to 1.9 mL of lidocaine with epinephrine resulted in a statistically significantly higher success rate (success was defined as no or mild pain on a visual analog scale upon endodontic access or instrumentation) when compared to a lidocaine formulation without mannitol. The proposed mechanism of action is that mannitol opens the perineurial membrane to allow for enhanced penetration of lipophilic compounds,²⁴ and it may affect nerve conduction.²⁵ All previous studies have used combinations of lidocaine and mannitol for inferior alveolar nerve block anesthesia.^{20–23}

No objective study has yet evaluated the combination of lidocaine and mannitol for infiltration anesthesia. The purpose of this prospective, randomized, single-blind study was to determine the anesthetic efficacy of a lidocaine/epinephrine formulation and to compare it to a lidocaine/epinephrine formulation with 0.5 M mannitol for maxillary lateral incisor infiltration. Pain during the injection and postoperative pain were also studied.

MATERIALS AND METHODS

Forty-one adult subjects participated in this study. The subjects were in good health and were not taking any medications that would alter pain perception. Exclusion criteria were age under 18 years; allergies to mannitol, local anesthetics, or sulfites; current pregnancy; history of significant medical conditions (American Society of Anesthesiologists rating of Class III or higher); current use of any medications (over-the-counter pain-relieving medications, narcotics, sedatives, or antianxiety or antidepressant medications) that may affect pain assessment; active pathosis at the site of injection; and inability to give informed consent. The Ohio State University Human Subjects Review Committee approved the study, and written informed consent was obtained from each subject.

The study used a crossover design. Forty-one adult subjects received 2 infiltrations of the maxillary lateral incisor consisting of a 1.84-mL solution of 36.8 mg lidocaine with 18.4 µg epinephrine (the control solution) and a 2.90-mL solution of 36.8 mg lidocaine with 18.4 µg epinephrine (1.84 mL) plus 0.5 M mannitol (1.06

mL) (the test solution) at 2 separate appointments spaced at least 1 week apart.

Equal numbers of maxillary right and left sides were tested, with the lateral incisors chosen as the test tooth. With the crossover design, therefore, 82 infiltrations were administered, and each subject served as his or her own control. The side chosen for the first infiltration was used again for the second infiltration. The mandibular contralateral canine was used as a control to ensure that the pulp tester was operating properly and that the subject was responding appropriately. A visual and clinical examination was conducted to ensure that all tested teeth were free of caries, large restorations, crowns, and periodontal disease and that none had a history of trauma or sensitivity.

Before the injection at each of the 2 appointments, the experimental tooth and the contralateral mandibular canine (control) were tested 3 times with the electric pulp tester (Kerr, Analytic Technology Corp, Redmond, Wash) to ensure tooth vitality and obtain baseline information. The teeth were isolated with cotton rolls and dried with an air syringe. Toothpaste was applied to the probe tip, which was placed on the middle third of the labial surface of the lateral incisor. The value upon initial sensation was recorded. The current rate was set at 25 seconds, to increase from no output (0) to the maximum output (80). Trained personnel, who were blinded to the anesthetic formulations, administered all preinjection and postinjection tests.

Before the experiment, the 2 anesthetic formulations were randomly assigned 5-digit numbers from a random number table. Total percent pulpal anesthesia was defined as the total of all the times of complete pulpal anesthesia as measured by the 80 readings, for each tooth, over the 60 minutes. Only the random numbers were recorded on the data collection sheets to further blind the experiment.

The anesthetic formulations were prepared as follows. Under sterile conditions and using a tuberculin syringe (Becton-Dickinson & Co., Rutherford, NJ), 1.84 mL of 2% lidocaine with 1:100,000 epinephrine was drawn from standard dental cartridges (Astra Pharmaceuticals Products, Inc, Westborough, MA) into a 5-mL Luer-Lok disposable syringe (Becton-Dickinson & Co., Rutherford, NJ). All solutions used were checked to ensure that they had not expired. The 1.84-mL formulation therefore contained 36.8 mg of lidocaine and 18.4 µg epinephrine. For the second (test) formulation, 1.84 mL of 2% lidocaine with 1:100,000 epinephrine was drawn into a 5-mL syringe as described. Then, a 1-mL tuberculin syringe (Becton-Dickinson & Co., Rutherford, NJ) was used to add 1.06 mL of 0.5 M mannitol to the 5-mL syringe. The syringe was then inverted 20 times to mix the solution. The 1.06 mL of mannitol had been

withdrawn from a 50-mL vial of a 25% (12.5 g/50 mL) supersaturated mannitol solution (American Regent Laboratories, Inc., Shirley, NY). Each vial was used only once. Before the mannitol was added to the syringe containing the lidocaine with epinephrine, the 50-mL vial was heated in a water bath (Teledyne Hanau, Buffalo, NY) to 80°C for 15 minutes to dissolve any crystals that were present in the supersaturated solution. The vial was then allowed to cool to room temperature before use. The 2.90-mL formulation thus contained 36.8 mg of lidocaine with 18.4 µg of epinephrine (1.84 mL) plus 0.5 M mannitol (1.06 mL). No precipitate formed when the mannitol was combined with the lidocaine. Selected components and selected final anesthetic formulations had their pH values determined using a pH/millivolt meter (Orion Research Inc, Boston, MA).

A few calculations are necessary to explain the molarity for the final volume of the lidocaine/mannitol formulation. Molarity (M), or molar concentration, is defined as the ratio of the number of moles of a solute per liter of solution. The mole of a compound is the amount of the compound in grams equal to its molecular weight. Therefore, the number of moles in 12.5 g of mannitol would be: moles of mannitol = 12.5 g (per 50-mL vial) $\times$ 1 mol/182.17 g (molecular weight of mannitol) = 0.0686 M. The molarity of the mannitol solution used in this study would therefore be: molarity = 0.0686 M mannitol/0.05 L solution = 1.372 M. Because the solutions were diluted by the lidocaine/epinephrine solution, the final molarity must be calculated from the molarity after dilution using the following formula: $(M_i)(V_i) = (M_f)(V_f)$, where M_i is the initial molarity multiplied by V_i (the initial volume) = equal to M_f (the final molarity) multiplied by V_f (the final volume). Therefore, for the mannitol formulation, the calculated molarity of 0.5 M mannitol would require the following volumes: $(1.372 \text{ M})(X) = (0.5 \text{ M})(2.90 \text{ mL}) = 1.06 \text{ mL}$ of mannitol. For a total volume of 2.90 mL of a 0.5 M mannitol solution, 1.84 mL of lidocaine would be combined with 1.06 mL of mannitol.

A standard infiltration was administered with a 27-gauge 1-inch needle (Monoject, Sherwood Medical, St Louis, MO) attached to the Luer-Lok syringe using the 2 anesthetic formulations. Following needle penetration, the needle was advanced to the target site and aspiration was performed; 1 minute was used to deposit the lidocaine formulation and 1.5 minutes were used for the lidocaine/mannitol formulation. The subject was asked to rate the pain of solution deposition. The pain scale ranged from 0 to 3: 0 indicated no pain, 1 indicated mild pain (recognizable but not discomforting), 2 indicated moderate pain (uncomfortable but bearable), and 3 indicated severe pain (pain that caused considerable

discomfort and was difficult to bear). The principal investigator (KY) performed all infiltrations.

At 1 minute after the infiltration was complete, the maxillary lateral incisor was pulp tested. At 2 minutes, the mandibular control canine was tested. This cycle of testing was repeated every 2 minutes for 60 minutes. At every fourth cycle, the control tooth (the contralateral mandibular canine) was tested with a pulp tester without batteries to determine the reliability of the subject. If the subject responded positively to an inactivated pulp tester, then they were not considered reliable and could not be used in the study. All testing was stopped at 60 minutes postinjection.

All subjects completed postinjection surveys after each infiltration administered. The subjects rated pain in the injection area using the previous pain scale (none, mild, moderate, severe) immediately after the numbness wore off and again each morning upon arising for 3 days.

No response from the subject at the maximum output (80) of the pulp tester was used as the criterion for pulpal anesthesia. Total percent pulpal anesthesia was defined as the total of all ratings of pulpal anesthesia over the 60-minute test period. With a nondirectional alpha risk of 0.05 and assuming an SD of the differences to be 20%, a sample size of 40 pairs would be required to obtain a power of 0.85 to demonstrate a difference of $\pm 10\%$.

Between-solution discomfort ratings for both solution deposition and postinjection ratings, as well as total percent pulpal anesthesia, were assessed using the Wilcoxon matched-pairs signed-ranks test. Comparisons were considered significant at $P < .05$.

RESULTS

Twenty-nine men and 12 women ranging in age from 21 to 33 years, with an average age of 26 years, participated in this study.

The discomfort ratings for solution deposition for the 2 formulations are presented in Table 1. There was a significant difference ($P = .0161$) between the formulations. The pH values of the solutions were 6.99 for the mannitol, 5.59 for the 2% lidocaine with 1:100,000 epinephrine, and 5.47 for the final formulation of lidocaine/mannitol.

Total percent pulpal anesthesia is presented in Table 2. The 1.84-mL solution of 36.8 mg of lidocaine with 18.4 µg epinephrine was statistically significantly better in providing anesthesia than the 2.90-mL formulation of 36.8 mg lidocaine with 18.4 µg of epinephrine (1.84 mL) plus 0.5 M mannitol (1.06 mL) ($P = .0004$). The incidence of pulpal anesthesia for the 2 formulations is presented in the Figure.

The postoperative pain ratings are summarized in Table 3. There was no significant difference ($P > .30$) between the formulations.

Table 1. Percentages and Discomfort Ratings of Solution Deposition

<i>Solution Deposited*</i>	<i>None</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
1.84 mL of lidocaine (36.8 mg) with epinephrine (18.4 µg)	10% (4/41)	54% (22/41)	32% (13/41)	5% (2/41)
2.90 mL of lidocaine (36.8 mg) with epinephrine (18.4 µg) plus 0.5 M mannitol	29% (12/41)	44% (18/41)	27% (11/41)	0% (0/41)

* There was a significant difference ($P = .0161$) between the formulations.

DISCUSSION

The use of maximum-output readings (80) as a criterion for pulpal anesthesia was based on the studies of Dreven et al²⁶ and Certosimo and Archer.²⁷ These studies^{26,27} showed that no patient response to a reading of 80 with the electric pulp tester ensured pulpal anesthesia in vital asymptomatic teeth. Additionally, Certosimo and Archer²⁷ demonstrated that electric pulp test readings under 80 resulted in pain during operative procedures in asymptomatic teeth.

Total percent pulpal anesthesia with the lidocaine/mannitol formulation was statistically significantly lower than the formulation of lidocaine (Table 2). While there was a difference, the Figure shows that neither formulation achieved 100% pulpal anesthesia; also, after 30 minutes both formulations had a declining rate of anesthesia. Previous studies of maxillary anesthesia using 2% lidocaine with 1:100,000 epinephrine and a similar methodology have shown comparable results.^{11,13–15,17–19} While there is good evidence that these combined lidocaine/mannitol formulations significantly improved the success of inferior alveolar nerve block,^{20–22} this effect was not seen with maxillary lateral incisor infiltration. Perhaps the lidocaine/mannitol formulation has little effect on the perineurium, since the covering is nonexistent or reduced with a terminal nerve complex (infiltration anesthesia). Because we studied a young adult population, the results of this study may not apply to children or older patients.

In the formulation with mannitol, both the lidocaine and epinephrine concentrations were diluted. It is possible that diluting the formulations with mannitol decreased the efficacy of the lidocaine with epinephrine. Studies by Mikesell et al¹⁴ and Mason et al¹⁸ in maxillary lateral incisors showed that increasing the volume of

lidocaine or increasing the epinephrine concentration provided better pulpal anesthesia over a 60-minute period. While we could have included additional formulations in the study by increasing the total injected volume of lidocaine with epinephrine without mannitol (by adding normal saline or a similar solution), we felt that dilution would not increase the success rate of the infiltration.

We chose a hyperosmolar solution of mannitol since it is inert²⁴ and it has been used extensively in medicine.²⁸ Antonijevic et al²⁴ demonstrated that the injection of 0.5 M mannitol into rat plantar subcutaneous paw tissue was without ill effect. The hypertonic solution of mannitol did not induce an inflammatory cell infiltrate when the tissues were examined histologically.²⁴

To keep the mannitol concentration at 0.5 M, the final volume of the solution has to be calculated based on the formula for molarity (see Materials and Methods). The result is a higher volume of solution than would be used if only lidocaine with epinephrine was administered. The 25% (12.5 g/50 mL) solution of mannitol was chosen for this study because it was the highest commercially available concentration. Therefore, when the mannitol was combined with the lidocaine/epinephrine, the final volume of the solution could still be kept to a clinically acceptable amount. When mannitol was combined with the lidocaine solution, no precipitate formed. Because mannitol is inert,²⁴ we would not expect it to chemically combine or react with the lidocaine or epinephrine. The pH values of the lidocaine and lidocaine/mannitol formulations were similar (5.59 and 5.47, respectively). It is unlikely that pH would affect the success rate of the infiltration.

Moderate pain upon solution deposition was experienced by 27% to 32% of participants, with 2 reports of severe pain, for the 2 formulations (Table 1). Previous

Table 2. Mean Percent Total Pulpal Anesthesia

<i>Tooth</i>	<i>Mean Percent ± SD Total Pulpal Anesthesia for Each Formulation (n = 41 Subjects)</i>		<i>P*</i>
	<i>1.84 mL of 36.8 mg Lidocaine with 18.4 µg Epinephrine</i>	<i>2.9 mL of 36.8 mg Lidocaine with 18.4 µg Epinephrine Plus 0.5 M Mannitol</i>	
Lateral incisor	58% ± 29.2%	46% ± 29.5%	.0004

* Statistically significant.

Incidence of lateral incisor pulpal anesthesia as determined by lack of response to electrical pulp testing at the maximum setting (percentage of 80/80's), at each postinjection time interval, for the two anesthetic formulations.

studies of maxillary lateral incisor infiltration deposition pain using 2% lidocaine with 1:100,000 epinephrine reported incidences of 23% to 34% moderate pain and 3% severe pain.^{14,17} Therefore, based on the current study and previous studies, there is a potential for moderate/severe pain with anterior infiltration. Previous studies performed by Wolf et al²⁰ and Smith et al²¹ found no statistically significant difference between lidocaine/mannitol formulations and a lidocaine formulation in minimizing solution deposition pain during an inferior alveolar nerve block. In the current study, the lidocaine formulation was statistically significantly more painful for solution deposition than the lidocaine/mannitol formu-

lation. Two factors could have accounted for the lower pain with the lidocaine/mannitol formulation. The lidocaine with epinephrine formulation was diluted by the addition of mannitol, and the larger volume of lidocaine/mannitol was deposited over a longer period of time.

Moderate postinjection pain, at the time subjective numbness wore off, occurred 3% of the time, with no reports of severe pain (Table 3). A previous study of maxillary anterior infiltration, using 2% lidocaine with 1:100,000 epinephrine, reported faint to weak postoperative pain (using a visual analog scale) at the time subjective numbness wore off.¹⁵ For both formulations, moderate pain decreased to 0% to 3% by day 1, with no reports of moderate pain on days 2 and 3 (Table 3). A similar result was reported for postoperative pain following maxillary anterior infiltration.¹⁵ There were no significant differences between the formulations (Table 3). Therefore, the addition of 0.5 M mannitol was not found to result in any more postoperative pain than the control solution (1.84 mL of 36.8 mg lidocaine with 18.4 µg epinephrine) (Table 3). Because studies have found that 0.5 M mannitol is inert,²⁴ we would not expect an increased incidence of moderate postoperative pain.

CONCLUSIONS

We concluded that adding 0.5 M mannitol to a lidocaine/epinephrine formulation was not significantly more effective in achieving a greater percentage of total

Table 3. Percentages and Discomfort Ratings for Postinjection Survey†

Solution	None	Mild	Moderate	Severe
Day 0*,‡				
1.84 mL of lidocaine (36.8 mg) with epinephrine (18.4 µg)	78% (29/39)	23% (9/39)	3% (1/39)	0% (0/39)
2.9 mL of lidocaine (36.8 mg) with epinephrine (18.4 µg) plus 0.5 M mannitol	82% (31/38)	16% (6/38)	3% (1/38)	0% (0/38)
Day 1*				
1.84 mL of lidocaine (36.8 mg) with epinephrine (18.4 µg)	95% (37/39)	5% (2/39)	0% (0/39)	0% (0/39)
2.9 mL of lidocaine (36.8 mg) with epinephrine (18.4 µg) plus 0.5 M mannitol	89% (34/38)	8% (3/38)	3% (1/38)	0% (0/38)
Day 2*				
1.84 mL of lidocaine (36.8 mg) with epinephrine (18.4 µg)	97% (38/39)	3% (1/39)	0% (0/39)	0% (0/39)
2.9 mL of lidocaine (36.8 mg) with epinephrine (18.4 µg) plus 0.5 M mannitol	97% (37/38)	3% (1/38)	0% (0/38)	0% (0/38)
Day 3*				
1.84 mL of lidocaine (36.8 mg) with epinephrine (18.4 µg)	97% (38/39)	3% (1/39)	0% (0/39)	0% (0/39)
2.9 mL of lidocaine (36.8 mg) with epinephrine (18.4 µg) plus 0.5 M mannitol	100% (38/38)	0% (0/38)	0% (0/38)	0% (0/38)

† n = 39 for the lidocaine solution (one subject did not return the postoperative pain questionnaire); n = 38 subjects for the lidocaine/mannitol formulation (two subjects did not return the postoperative pain questionnaire).

‡ Rating at time subjective numbness wore off.

* There was no significant difference ($P > .05$) between the formulations.

pulpal anesthesia than a lidocaine formulation without mannitol for maxillary anterior infiltration.

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