Anesthetic Efficacy of Combinations of 0.5 M Mannitol and Lidocaine With Epinephrine in Inferior Alveolar Nerve Blocks: A Prospective Randomized, Single-Blind Study

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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 inferior alveolar nerve (IAN) blocks. Forty subjects randomly received an IAN block in 3 separate appointments spaced at least 1 week apart using the following formulations: a 1.8 mL solution of 36 mg lidocaine with 18 µg epinephrine (control solution); a 2.84 mL solution of 36 mg lidocaine with 18 µg epinephrine (1.80 mL) plus 0.5 M mannitol (1.04 mL); and a 5 mL solution of 63.6 mg lidocaine with 32 µg epinephrine (3.18 mL) plus 0.5 M mannitol (1.82 mL). Mandibular teeth were blindly electric pulp tested at 4-minute cycles for 60 minutes postinjection. No response from the subject to the maximum output (80 reading) of the pulp tester was used as the criterion for pulpal anesthesia. Mean percent total pulpal anesthesia was defined as the total of all the times of pulpal anesthesia (80 readings) over the 60 minutes. Pain of solution deposition and postoperative pain were also measured. The results demonstrated that 2.84 mL of lidocaine with epinephrine plus 0.5 M mannitol was significantly better than 1.8 mL of lidocaine with epinephrine for the molars and premolars. The 5 mL of lidocaine with epinephrine plus 0.5 M mannitol was statistically better than 1.8 mL of lidocaine with epinephrine and 2.84 mL of lidocaine with epinephrine plus 0.5 M mannitol for all teeth except the central incisor. Solution deposition pain and postoperative pain were not statistically different among the mannitol formulations and the lidocaine formulation without mannitol. We concluded that adding 0.5 M mannitol to lidocaine with epinephrine formulations significantly improved effectiveness in achieving a greater percentage of total pulpal anesthesia compared with a lidocaine formulation without mannitol for IAN block.

Key Words: Inferior alveolar nerve block; Lidocaine; Mannitol.

The inferior alveolar nerve (IAN) block is the most frequently used injection technique for achieving local anesthesia for mandibular restorative and

surgical procedures. However, the IAN block does not always result in successful pulpal anesthesia.¹⁻⁶ Failure rates (never achieving two consecutive 80 readings with the electric pulp tester) of 10 to 39% have been reported.¹ A possible reason for failure is the perineurial barrier around the nerve may not allow complete diffusion of the anesthetic solution into the nerve trunk.

According to de Jong,⁷ "the perineurium's innermost layer, the perilemma, is lined with a smooth

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mesothelial membrane. Tight junctions in the perilemma turn the perineurium into a nerve's main diffusion barrier. Developmentally, the perilemma is a continuation of the pia-arachnoid membrane that covers brain and spinal cord, hence it is the blood/nerve equivalent of the central blood/brain barrier. These tough diffusion barriers lay waste to a substantial proportion of injected local anesthetic solution."

Under normal conditions, tight junctions along the inner layer of the perineurium maintain homeostasis in the endoneurial tissue containing peripheral neurons. These tight junctions act as a diffusion barrier not only for high molecular weight or hydrophilic substances,^{8–10} but also for lipophilic compounds.¹¹ This diffusion barrier is continuous along afferent somatic and autonomic nerve fibers to their peripheral endings.^{10,12} Inflammation causes a deficiency of the perineurial barrier and/or an enhanced permeability of endoneurial capillaries.^{8,13} A similar disruption of the perineurial barrier can be produced by the extraneural application of hyperosmolar solutions.^{14,15} Similar to what occurs at the blood brain barrier,¹⁶ the effects of hyperosmolar solutions have been linked to a transient shrinkage of perineurial cells with subsequent widening of zonulae occludens.^{8,17} Antonijevic et al¹⁴ found that a 0.5 M solution of mannitol was most effective in opening the perineurial membrane to allow for enhanced penetrability for macromolecules and/or ions. They demonstrated that the efficacy of both hydrophilic and lipophilic compounds could be improved dramatically by the concomitant alteration of perineurial permeability. This effect is short lived, reaching a maximum effect at certain concentrations of mannitol and declining at higher concentrations.^{14,16,18,19}

Additionally, there is some evidence that hyperosmolar solutions like mannitol delay or block action potential propagation in selective A-type neurons in rats.²⁰ However, the effects on neural conduction of a diluted mannitol-lidocaine formulation are unknown.

Mannitol is a 6-carbon sugar alcohol ($C_6H_{14}O_6$) with a molecular weight of 182.17.^{21,22} Mannitol occurs naturally in fruits and vegetables and is an osmotic diuretic.^{21,22} After intravenous injection, mannitol is confined to the extracellular space, metabolized only slightly and excreted rapidly by the kidneys.^{21,22} Approximately 80% of a 100 g dose appears in the urine within 3 hours. Mannitol is freely filtered by the glomeruli with less than 10% tubular reabsorption.^{21,22} It induces diuresis by elevating the osmolarity of the glomerular filtrate and thereby hinders tubular reabsorption of water. Mannitol is used in medicine to reduce the risk of perioperative renal failure and to treat cerebral edema.^{21,22} Mannitol is also used to enable chemotherapeutic agents to cross the

blood brain barrier.²² Studies have shown that mannitol is an inert substance.^{14,22}

Since mannitol opens the perineurial membrane to allow for enhanced penetrability for macromolecules (and/or ions)¹⁴ and may effect nerve conduction,²⁰ it may also increase the success of an IAN block when administered concurrently with a local anesthetic solution. 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 IAN blocks. Pain of injection and postoperative pain were also studied.

MATERIALS AND METHODS

Forty 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 as follows: younger than 18 years of age; allergies to mannitol, local anesthetics, or sulfites; pregnancy; history of significant medical conditions (ASA Class II or higher); taking any medications (over-the-counter pain-relieving medications, narcotics, sedatives, antianxiety, or antidepressant medications), which 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.

Using a crossover design, 40 adult subjects received 3 IAN blocks in 3 separate appointments spaced at least 1 week apart. These blocks consisted of: a 1.8 mL solution of 36 mg lidocaine with 18 μ g epinephrine (control solution); a 2.84 mL solution of 36 mg lidocaine with 18 μ g epinephrine (1.80 mL) plus 0.5 M mannitol (1.04 mL); and a 5 mL solution of 63.6 mg lidocaine with 32 μ g epinephrine (3.18 mL) plus 0.5 M mannitol (1.82 mL).

Equal numbers of mandibular right and left sides were tested, with the first and second molars, first and second premolars, and lateral and central incisors chosen as the test teeth.

With the crossover design, 120 IAN blocks were administered and each subject served as his or her own control. The same side chosen for the first IAN block was used again for the second and third IAN blocks. The mandibular contralateral canine was used as the 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 teeth were free of caries, large

restorations, crowns, periodontal disease, and that none had a history of trauma or sensitivity.

Before the injection at each of the 3 appointments, the experimental tooth and the contralateral 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 in the middle third of the buccal or labial surface of the tooth being tested. The value at the 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 3 anesthetic formulations were randomly assigned 5-digit numbers from a random number table. Each subject was randomly assigned to each of the 3 anesthetic formulations to determine which formulation was to be administered at each appointment. Only the random numbers were recorded on the data collection sheets to further blind the experiment.

The anesthetic formulations were prepared immediately prior to injection as follows. Under sterile conditions, 1.8 mL of 2% lidocaine with 1 : 100,000 epinephrine was drawn from standard dental cartridges (Astra Pharmaceuticals Products Inc, Westborough, Mass) 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 1.8 mL formulation contained 36 mg of lidocaine with 18 μ g epinephrine. For the second formulation, 1.8 mL of 2% lidocaine with 1 : 100,000 epinephrine was drawn into a 5 mL syringe as described above. Using a 1 mL tuberculin syringe (Becton-Dickinson), 1.04 mL of 0.5 M mannitol was withdrawn from a 50 mL vial of a 25% (12.5 g/50 mL) supersaturated mannitol solution (American Regent Laboratories Inc, Shirley, NY) and was added to the 5 mL syringe. The syringe was then inverted 20 times to mix the solution. Each vial of mannitol solution 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 present in the supersaturated solution. The vial was then allowed to cool to room temperature before use. The 2.84 mL formulation contained 36 mg of lidocaine with 18 μ g of epinephrine (1.8 mL) plus 0.5 M mannitol (1.04 mL). For the third formulation, 3.18 mL of 2% lidocaine with 1 : 100,000 epinephrine was drawn into a 5 mL syringe as described above. Added to this same syringe was 1.82 mL of the 0.5 M mannitol. The syringe was then inverted 20 times to mix the solution. The 5 mL formulation con-

tained 63.6 mg of lidocaine with 32 μ g epinephrine (3.18 mL) plus 0.5 M mannitol (1.82 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, Mass).

The following calculations were utilized to determine the molarity for the final volumes of the lidocaine/mannitol formulations. Molarity (M), or molar concentration, is defined as a ratio between 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 moles. The molarity of the mannitol solution used in this study was: molarity = 0.0686 moles mannitol/0.05 L solution = 1.372 M. Because the solutions were diluted by the lidocaine with epinephrine solution, the final molarity was calculated from the molarity after dilution using the following formula: $(M_i)(V_i) = (M_f)(V_f)$ where M_i was the initial molarity multiplied by V_i (the initial volume), which was equal to M_f (the final molarity) multiplied by V_f (the final volume). Therefore, for the second formulation the calculated molarity of 0.5 M mannitol required the following volumes: $(1.372 \text{ M})(X) = (0.5 \text{ M})(2.84 \text{ mL}) = 1.04 \text{ mL}$ of mannitol. For the total volume of 2.84 mL of a 0.5 M mannitol formulation, 1.8 mL of lidocaine was combined with 1.04 mL of mannitol. For the third formulation, the calculated molarity of 0.5 M mannitol required the following volumes: $(1.372 \text{ M})(X) = (0.5 \text{ M})(5.00 \text{ mL}) = 1.82 \text{ mL}$ of mannitol. For the total volume of 5 mL of a 0.5 M mannitol formulation, 3.18 mL of lidocaine was combined with 1.82 mL of mannitol.

A standard IAN block²³ was administered with a 27-gauge 1 1/2-inch needle (Monoject; Sherwood Medical, St Louis, Mo) using each anesthetic formulation. Following needle penetration, and as the needle was advanced during placement, 0.2 mL of solution was deposited. After the target area was reached and aspiration was performed, 1 minute was used to deposit all anesthetic formulations, and the subject was asked to rate the pain of solution deposition. The pain scale was from 0 to 3. Zero indicated no pain. One indicated mild pain, pain that was recognizable but not discomforting. Two indicated moderate pain, pain that was discomforting but bearable. Three indicated severe pain, pain that caused considerable discomfort and was difficult to bear. The principal investigator (R.W.) performed all IAN injections.

At 1 minute after the IAN block, the first and second molars were pulp tested. At 2 minutes, the first and

Table 1. Percentages and Discomfort Ratings of Solution Deposition

<i>Solution</i>	<i>None</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
Solution deposition*				
1.8 mL of lidocaine (36 mg) with epi (18 µg)	17% (7/40)	50% (20/40)	30% (12/40)	3% (1/40)
2.84 mL of lidocaine (36 mg) with epi (18 µg) plus 0.5 M mannitol	12% (5/40)	45% (18/40)	40% (16/40)	3% (1/40)
5 mL of lidocaine (63.6 mg) with epi (32 µg) plus 0.5 M mannitol	7% (3/40)	55% (22/40)	35% (14/40)	3% (1/40)

* There were no significant differences ($P > .05$) among the formulations.

second premolars were tested. At 3 minutes, the central and lateral incisors were tested. At 4 minutes, the control canine was tested. This cycle of testing was repeated every 4 minutes for 60 minutes. At every fourth cycle the control tooth (the contralateral canine) was tested with a pulp tester without batteries to test the reliability of the subject. If the subject responded positively to an inactivated pulp tester, then they were not reliable and could not be used in the study. Subjects were asked if their lips and tongues were numb every minute for 5 minutes and at every fourth minute during pulp testing. If profound lip numbness was not recorded within 5 minutes, the block was considered unsuccessful and the subject was then reappointed. Two of 120 (1.7%) IAN blocks were unsuccessful in this study and these subjects required an additional appointment. All testing was stopped at 60 minutes postinjection.

All subjects completed postinjection surveys after each IAN block 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. The subjects were also asked to record subjectively any additional comments or side effects not relating to pain.

No response from the subject at the maximum output (80 reading) of the pulp tester was used as the criterion for pulpal anesthesia. Mean percent total pulpal anesthesia was defined as the total of all the times of pulpal anesthesia (80 readings) over the 60 minutes. With a nondirectional alpha risk of 0.05 and assuming a standard deviation of 32 and a correlation of 0.60, a sample size of 40 subjects was required to demonstrate a difference in anesthetic success of ± 15 percentage points with a power of 0.85.

Comparisons between the 3 formulations regarding mean percent total pulpal anesthesia were assessed using multiple Wilcoxon, matched-pairs, and signed rank tests adjusted using the step-down Bonferroni method of Holm. Comparisons between the 3 formulations regarding solution deposition pain and postinjection pain were made using the Friedman statistic. Comparisons were considered significant at $P < .05$.

RESULTS

Twenty-eight women and 12 men, ranging in age from 18 to 49 years, with an average age of 22 years, participated in this study.

One hundred percent of the subjects used for the data analysis had subjective lip and tongue anesthesia with the IAN blocks. The discomfort ratings of solution deposition for the 3 formulations are presented in Table 1. There were no significant differences ($P > .05$) among the formulations. The pH of the solutions was: 7.0 for mannitol, 5.6 for the 2% lidocaine with 1 : 100,000 epinephrine, and 5.7 for the final formulation of lidocaine/mannitol.

Mean percent total pulpal anesthesia is presented in Table 2. The posterior teeth had higher values of total pulpal anesthesia than the anterior teeth. The results demonstrated that 2.84 mL of lidocaine with epinephrine plus 0.5 M mannitol was significantly better than 1.8 mL of lidocaine with epinephrine for the molars and premolars. The 5 mL of lidocaine with epinephrine plus 0.5 M mannitol was statistically better than 1.8 mL of lidocaine with epinephrine and 2.84 mL of lidocaine with epinephrine plus 0.5 M mannitol for all teeth except the central incisor. The incidence of pulpal anesthesia for the 3 solutions is presented in the Figure.

The postoperative pain ratings are summarized in Table 3. There were no significant differences ($P > .05$) among the formulations. Table 4 summarizes the number of subjects reporting trismus for the 3 formulations.

DISCUSSION

The use of the 80 reading (signaling maximum output) as a criterion for pulpal anesthesia was based on the studies of Dreven et al²⁴ and Certosimo and Archer.²⁵ These studies^{24,25} showed that no patient response to an 80 reading with the electric pulp tester ensured pulpal anesthesia in vital asymptomatic teeth. Additionally, Certosimo and Archer²⁵ demonstrated that electric pulp test readings less than 80 resulted

Table 2. Mean Percent and SD Total Pulpal Anesthesia (N = 40 Subjects)

Tooth	Formulations					
	1.8 mL of Lidocaine	2.84 mL of Lidocaine With 0.5 M Mannitol		5 mL of Lidocaine With 0.5 M Mannitol		
		<i>P</i> *		<i>P</i> ** <i>P</i> ***		
2nd Molar	75% ± 32	84% ± 25	.0187	93% ± 17	.0016	.0016
1st Molar	48% ± 35	64% ± 32	.0016	80% ± 28	.0016	.0016
2nd Premolar	54% ± 40	66% ± 34	.0187	72% ± 35	.0016	.0408
1st Premolar	50% ± 41	66% ± 36	.0187	73% ± 31	.0016	.0408
Lateral	27% ± 36	28% ± 37	1.0000	42% ± 39	.0187	.0408
Central	12% ± 25	14% ± 29	1.0000	20% ± 32	.5040	.3912

* *P* value represents the comparison of 1.8 mL of 36 mg lidocaine with 18 µg epinephrine versus 2.84 mL of 36 mg lidocaine with 18 µg epinephrine plus 0.5 M mannitol.

** *P* value represents the comparison of 1.8 mL of 36 mg lidocaine with 18 µg epinephrine versus 5 mL of 63.6 mg lidocaine with 32 µg epinephrine plus 0.5 M mannitol.

*** *P* value represents the comparison of 2.84 mL of 36 mg lidocaine with 18 µg epinephrine plus 0.5 M mannitol versus 5 mL of 63.6 mg lidocaine with 32 µg epinephrine plus 0.5 M mannitol.

in pain during operative procedures in asymptomatic teeth.

Mean percent total pulpal anesthesia with 1.8 mL of 36 mg of lidocaine with 18 µg of epinephrine for the IAN block occurred from 12 to 75% of the time (Table 2) (Figure). The addition of 0.5 M mannitol to 36 mg of lidocaine with 18 µg of epinephrine resulted in a statistically higher mean percent total pulpal anesthesia for the molars and premolars when compared to 36 mg of lidocaine with 18 µg epinephrine (Table 2). In these teeth, the increase in mean percent total pulpal anesthesia, over the 36 mg of lidocaine with 18 µg of epinephrine, ranged from 9 to 16% (Table 2). This would seem to confirm the study by Antonijevic et al¹⁴ who demonstrated that the efficacy of lipophilic compounds could be improved by the concomitant alteration of perineurial permeability using a 0.5 M solution of mannitol, or based on the findings of Matsuka and Spigelman,²⁰ the mannitol possibly delayed or blocked action potential propagation in selective neurons.²⁰

Further enhancement of pulpal anesthesia was achieved when the amount of lidocaine and epinephrine was increased to 63.6 mg with 32 µg of epinephrine plus 0.5 M mannitol (Table 2). In the posterior teeth, the increase in mean percent total pulpal anesthesia, over the 36 mg of lidocaine with 18 µg of epinephrine, ranged from 18 to 32% (Table 2). We can speculate that the higher amount of lidocaine with epinephrine and 0.5 M mannitol caused more of the lidocaine to penetrate the perineurium, or blocked the nerves more effectively,²⁰ resulting in better pulpal anesthesia. The effect of 0.5 M mannitol when combined with lidocaine with epinephrine in the lateral incisor, while statistically significant, was less pronounced. That is, clinically, the 20 to 42% total pulpal

anesthetic success rate in the lateral and central incisors with 63.6 mg of lidocaine with 32 µg of epinephrine plus 0.5 M mannitol would not result in clinically acceptable pulpal anesthesia. We can speculate that the opening of the perineurium by mannitol, or the amount of mannitol to help block conduction, did not allow complete penetration of the anesthetic solution, in a minimum inhibitory concentration, to the inner core of the nerve fibers supplying the anterior teeth. Because pulpal anesthesia was not 100% in the posterior teeth with any of the 3 formulations, practitioners should consider supplemental techniques (such as intraosseous,^{26–29} periodontal ligament injections,³⁰ or a buccal infiltration of 4% articaine with 1 : 100,000 epinephrine^{31,32}) when an IAN block, with or without mannitol, fails to provide pulpal anesthesia for a particular tooth. Because we studied a young adult population, the results of this study may not apply to children or the elderly.

In the two formulations with mannitol, both the lidocaine and epinephrine concentrations were diluted. While we could have added additional formulations to the study by increasing the total injected volume of lidocaine with epinephrine to 3.17 mL or 5 mL without mannitol (by adding normal saline or a similar solution), we felt that dilution would not increase the success of the IAN block. Increasing the amount of lidocaine with epinephrine from 36 mg to 63.6 mg in an additional formulation alone would not increase success of the IAN block as shown by Nusstein et al.¹ Additionally, increasing the epinephrine concentration to 32 µg in an additional formulation alone would not increase the success of the IAN block as shown by Wali et al.⁶ In the current study, combining mannitol with the lidocaine with epinephrine formulations did statistically increase success. Therefore, diluting the

Second Molar

First Molar

Second Premolar

First Premolar

Lateral Incisor

Central Incisor

Incidence of pulpal anesthesia for the molars, premolars, lateral and central incisors as determined by lack of response to electrical pulp testing at the maximum setting (percentage of 80/80s), at each postinjection time interval, for the 3 anesthetic formulations.

formulations with mannitol increased the efficacy of the lidocaine with epinephrine.

Antonić et al¹⁴ found that a hyperosmolar solution of 0.5 M mannitol caused a transient, artificial opening of the perineurium. While their study focused on the effects of peripherally applied opioids in an experimental animal, the opening of the perineurium by mannitol would be applicable to any peripheral nerve. Our results would support the findings of Antonić et al¹⁴ for an IAN block. We chose a hyperosmolar solution of mannitol since studies^{14,22} have shown it is inert and it has been used extensively in medicine.³³ Antonić et al¹⁴ demonstrated the injection of 0.5 M mannitol into rat plantar subcutaneous paw tissue was without effect. The hypertonic solution of mannitol did not induce an inflammatory cell infiltrate when the tissues were examined histologically.¹⁴

In order 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 the lidocaine solution was

administered. The 25% (12.5 g/50 mL) solution of mannitol was chosen for this study because it was the highest concentration available commercially. Therefore, when combining the mannitol with lidocaine, the final volume of the solution could still be kept to a clinically acceptable amount—5 mL. When mannitol was combined with the lidocaine solution, no precipitate formed. Because mannitol is inert,^{14,22} 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, 5.6 and 5.7, respectively. It is unlikely that pH caused differences in success rates of the IAN blocks.

Moderate solution deposition pain ranged from 30 to 40% and 3% for severe pain for the 3 solutions (Table 1). Other studies^{2,4,5} of the IAN block, using 2% lidocaine with 1 : 100,000 epinephrine, have reported a 20 to 25% incidence of moderate/severe pain. Therefore, the IAN block has the potential to be painful even though the solution was deposited slowly over 1 minute. There were no significant differences among the formulations. Therefore, the addition of 0.5 M

Table 3. Percentages and Discomfort Ratings for Postinjection Survey

<i>Solution</i>	<i>None</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
Day 0*†				
1.8 mL of lidocaine (36 mg) with epi (18 µg)	3% (1/40)	62% (25/40)	35% (14/40)	0% (0/40)
2.84 mL of lidocaine (36 mg) with epi (18 µg) plus 0.5 M mannitol	5% (2/40)	70% (28/40)	25% (10/40)	0% (0/40)
5 mL of lidocaine (63.6 mg) with epi (32 µg) plus 0.5 M mannitol	3% (1/40)	72% (29/40)	25% (10/40)	0% (0/40)
Day 1*				
1.8 mL of lidocaine (36 mg) with epi (18 µg)	30% (12/40)	68% (27/40)	3% (1/40)	0% (0/40)
2.84 mL of lidocaine (36 mg) with epi (18 µg) plus 0.5 M mannitol	30% (12/40)	65% (26/40)	5% (2/40)	0% (0/40)
5 mL of lidocaine (63.6 mg) with epi (32 µg) plus 0.5 M mannitol	35% (14/40)	62% (25/40)	3% (1/40)	0% (0/40)
Day 2*				
1.8 mL of lidocaine (36 mg) with epi (18 µg)	68% (27/40)	32% (13/40)	0% (0/40)	0% (0/40)
2.84 mL of lidocaine (36 mg) with epi (18 µg) plus 0.5 M mannitol	70% (28/40)	30% (12/40)	0% (0/40)	0% (0/40)
5 mL of lidocaine (63.6 mg) with epi (32 µg) plus 0.5 M mannitol	75% (30/40)	25% (10/40)	0% (0/40)	0% (0/40)
Day 3*				
1.8 mL of lidocaine (36 mg) with epi (18 µg)	80% (32/40)	20% (8/40)	0% (0/40)	0% (0/40)
2.84 mL of lidocaine (36 mg) with epi (18 µg) plus 0.5 M mannitol	82% (33/40)	18% (7/40)	0% (0/40)	0% (0/40)
5 mL of lidocaine (63.6 mg) with epi (32 µg) plus 0.5 M mannitol	82% (33/40)	18% (7/40)	0% (0/40)	0% (0/40)

* There were no significant differences ($P > .05$) among the formulations.

† Rating at time subjective numbness wore off.

mannitol, or an increase in the amount of lidocaine with epinephrine plus 0.5 M mannitol, was not found to be any more painful on injection than the control solution—1.8 mL of 36 mg lidocaine with 18 µg epinephrine (Table 1).

Moderate postinjection pain, at the time subjective numbness wore off, ranged from 25 to 35% for the 3 formulations (Table 3). The percentages were higher for the lidocaine with epinephrine formulation than other studies^{2,4,5} using 2% lidocaine with 1 : 100,000 epinephrine, in which a 14 to 17% incidence of moderate/severe pain was reported at the time subjective numbness wore off. Perhaps population variation would account for the differences among studies. Judging from this study and others,^{2–5} the IAN block has the potential to result in moderate postoperative pain. For all 3 solutions, moderate pain decreased to 2 to 5% by day 1 with no reports of moderate pain for days 2 and 3 (Table 3). Similar results have been reported in other studies^{2,4,5} of postoperative pain for the IAN block. Therefore, moderate postoperative pain is somewhat limited to the time subjective numbness wears off. There were no significant differences among the formulations (Table 3). Therefore, the addition of 0.5 M mannitol or an increase in the amount of lidocaine with epinephrine plus 0.5 M mannitol was not found to result in any more postoperative pain than the control solution—1.8 mL of 36 mg lidocaine with 18 µg epinephrine (Table 3). Because studies have found that 0.5 M mannitol is inert,^{14,22} we would not expect an increased incidence of moderate postoperative pain.

In medicine, treatment of elevated intracranial or intraocular pressure requires a 1.5–2 g/kg dose of mannitol intravenously.³³ To treat oliguria, 50 to 100 g of mannitol is infused intravenously over 90 minutes.³³ Using these large amounts of mannitol results in a number of precautions (renal dysfunction, heart failure, or pulmonary congestion) in its use.³³ The total amount of grams administered for the IAN blocks, in the current study, were 0.26 g (1.04 mL of mannitol) and 0.45 g (1.82 mL of mannitol). Therefore, the small amount administered and the inertness of the 0.5 M mannitol would negate the cautions and contraindications associated with mannitol for medical treatment.

The small number of patients experiencing trismus postoperatively (2 to 5%) (Table 4) would indicate that there is a small potential for this to occur after an IAN block. Previous studies of the IAN block using 2% lidocaine with 1 : 100,000 epinephrine recorded a 3 to 9% incidence of trismus postoperatively.^{4,5} Because the solutions containing mannitol had a similar number of subjects reporting trismus compared to the control solution of lidocaine with epinephrine, the mannitol did not contribute to an increased incidence of trismus. Again, since 0.5 M mannitol is inert,^{14,22} we would not expect more trismus postoperatively.

We concluded that adding 0.5 M mannitol to lidocaine with epinephrine formulations was significantly more effective in achieving a greater percentage of total pulpal anesthesia than a lidocaine formulation without mannitol. Injection pain and postoperative pain were not statistically different among the mannitol formulations and the lidocaine formulation without mannitol.

Table 4. Percentage and Number of Subjects Reporting Postoperative Trismus

Day 0†	
1.8 mL of 36 mg lidocaine with 18 µg epinephrine	5% (2/40)
2.84 mL of 36 mg lidocaine with 18 µg epinephrine plus 0.5 M mannitol	5% (2/40)
5 mL of 63.6 mg lidocaine with 32 µg epinephrine plus 0.5 M mannitol	5% (2/40)
Day 1	
1.8 mL of 36 mg lidocaine with 18 µg epinephrine	3% (1/40)
2.84 mL of 36 mg lidocaine with 18 µg epinephrine plus 0.5 M mannitol	5% (2/40)
5 mL of 63.6 mg lidocaine with 32 µg epinephrine plus 0.5 M mannitol	3% (1/40)
Day 2	
1.8 mL of 36 mg lidocaine with 18 µg epinephrine	0% (0/40)
2.84 mL of 36 mg lidocaine with 18 µg epinephrine plus 0.5 M mannitol	0% (0/40)
5 mL of 63.6 mg lidocaine with 32 µg epinephrine plus 0.5 M mannitol	3% (1/40)
Day 3	
1.8 mL of 36 mg lidocaine with 18 µg epinephrine	0% (0/40)
2.84 mL of 36 mg lidocaine with 18 µg epinephrine plus 0.5 M mannitol	0% (0/40)
5 mL of 63.6 mg lidocaine with 32 µg epinephrine plus 0.5 M mannitol	0% (0/40)

† Reported at time subjective numbness wore off.

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