

Anesthetic Efficacy of a Combination of Hyaluronidase and Lidocaine With Epinephrine in Inferior Alveolar Nerve Blocks

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The purpose of this prospective, randomized, double-blind study was to determine the anesthetic efficacy of a buffered lidocaine with epinephrine solution compared to a combination buffered lidocaine with epinephrine plus hyaluronidase solution in inferior alveolar nerve blocks. Thirty subjects randomly received an inferior alveolar nerve block using 1 of the 2 solutions at 2 separate appointments using a repeated-measures design. Mandibular anterior and posterior teeth were blindly 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. Anesthesia was considered successful when 2 consecutive readings of 80 were obtained. A postoperative survey was used to measure pain and trismus. The results demonstrated 100% of the subjects had profound lip numbness with both solutions for inferior alveolar nerve blocks. The anesthetic success rates for individual teeth ranged from 20 to 80%. There were no significant differences ($P > .05$) between the 2 solutions. However, the combination lidocaine/hyaluronidase solution resulted in a significant increase in postoperative pain and trismus. It was concluded that adding hyaluronidase to a buffered lidocaine solution with epinephrine did not statistically increase the incidence of pulpal anesthesia in inferior alveolar nerve blocks and, because of its potential tissue damaging effect, it should not be added to local anesthetic solutions for inferior alveolar nerve blocks.

Key Words: Lidocaine; Hyaluronidase; Inferior alveolar nerve block; Local anesthesia.

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.¹⁻¹⁸ Failure rates of 8 to 67% have been reported in experimental studies.¹⁻¹⁴ Clinical studies in endodontics¹⁵⁻¹⁷ have found failure with

the IAN block occurring between 38 and 81% of the time.

The use of hyaluronidase as an adjunct to local anesthesia has been well documented in ophthalmological surgery.^{19,20} Hyaluronidase is an enzyme that hydrolyzes the hyaluronic component of the intercellular ground substance.²¹ Hence, the viscosity of the tissue is reduced, permitting a wider spread of injected fluids. Early studies in dentistry^{22,23} found that an IAN block was more easily attained and was more complete when hyaluronidase was added to a procaine/epinephrine solution. However, Eckenhoff and Kirby²⁴ found hyaluronidase did not increase the incidence of successful region-

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al nerve blocks. Recently, Malamed²⁵ reported, by way of Internet communications, that dentists had an increased interest in the use of hyaluronidase, although he cautioned that research trials should be completed before its widespread use.²⁵

Because hyaluronidase may increase success of an IAN block, the purpose of this prospective, randomized, double-blind study was to determine the anesthetic efficacy of buffered lidocaine (24 mg) with epinephrine (12 µg) compared with buffered lidocaine (24 mg) with epinephrine (12 µg) plus hyaluronidase (150 USP units) in IAN blocks.

MATERIALS AND METHODS

Thirty adult subjects participated in this study. The subjects were in good health and were not taking any medications that would alter pain perception. The Ohio State University Human Subjects Review Committee approved the study, and written informed consent was obtained from each subject.

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. The contralateral canine was used as the unanesthetized control to ensure that the pulp tester was operating properly and that the subject was responding appropriately during the experiment. Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease; none had histories of trauma or sensitivity.

Two appointments at least 1 week apart were scheduled for each of the 30 subjects. Through use of a repeated-measures design, each subject randomly received an IAN block at each of 2 successive appointments. The injections were an IAN block using a solution of buffered lidocaine with epinephrine and a solution of buffered lidocaine with epinephrine plus hyaluronidase. Before the experiment, the two anesthetic solutions were randomly assigned 5-digit numbers from a random number table. Each subject was randomly assigned to 1 of the 2 solutions to determine the sequence of the injections. Only the random numbers were recorded on the data collection and postoperative survey sheets to blind the experiment.

At the beginning of each appointment and before any injections were given, the experimental teeth and control contralateral canine were tested 3 times with the pulp tester (Analytic Technology Corp, Redmond, Wash) to record baseline vitality. After the tooth to be tested was isolated with cotton rolls and dried with gauze, toothpaste was applied to the probe tip, which was then placed midway between the gingival margin

and the occlusal/incisal edge of the tooth. The current rate was set at 25 seconds to increase from no output (0) to the maximum output (80). The number associated with the initial sensation was recorded. Trained personnel, blinded to the anesthetic solutions, administered all preinjection and postinjection tests.

The anesthetic solutions were prepared as follows. Under sterile conditions, 0.1 mL of 1:1000 epinephrine (American Regent Laboratories, Inc, Shirley, NY) was withdrawn from a 1-mL ampule using a 1-mL tuberculin syringe and added to a 10-mL single-dose ampule of plain 2% lidocaine (Abbott Laboratories, North Chicago, Ill). This produced a final concentration of 1:100,000 epinephrine. The ampule was inverted 20 times to mix the solutions. One and two-tenths milliliters of the solution were drawn from the ampule and placed in a 3-cm³ Leur-Lok syringe. The 1.2-mL volume of solution contained 24 mg of lidocaine and 12 µg of epinephrine. Because higher success rates have been observed with a buffered hyaluronidase solution,^{26,27} 0.6 mL of sodium bicarbonate was drawn from a vial containing 50 mL of 8.4% sodium bicarbonate (Abbott Laboratories) using a 1-mL tuberculin syringe. The 0.6 mL of the sodium bicarbonate was added to the lidocaine solution (24 mg of lidocaine and 12 µg of epinephrine) to produce a final volume of 1.8 mL buffered with 0.33 mEq/mL of sodium bicarbonate. For the lidocaine/hyaluronidase solution, a 1-mL vial containing 150 USP units of lyophilized hyaluronidase (Wydase, Wyeth Laboratories, Philadelphia, Pa) was added to the lidocaine with epinephrine solution. The lyophilized form was used in order to not change the volume of the solution injected. The anesthetic solutions administered were blinded by masking the Leur-Lok syringes containing the anesthetic solutions with white, opaque tape and labeling the syringes with random 5-digit numbers. The opaque tape did not cover the syringe area next to the needle attachment, which allowed evaluation of aspiration during the IAN blocks. Sample solutions of each anesthetic solution were tested to determine pH values using an Orion pH meter (Orion Research Inc, Boston, Mass).

Because hyaluronidase may cause a hypersensitivity reaction,²¹ each subject received a preliminary mucosal test. The mucosa just inside the vermilion border of the lip was injected with approximately 0.2 mL of a freshly prepared test solution the subjects were to receive at that appointment. Therefore, only half the injections contained hyaluronidase. The contralateral lip was used in order to not interfere with determining lip numbness from the IAN block. Each subject was observed for 5 to 10 minutes to see if a positive reaction consisting of a wheal with pseudopods developed. The site was also

Table 1. Percentages and Discomfort Ratings of Solution Deposition

Solution	None	Mild	Moderate	Severe
Solution deposition*				
Lidocaine	27% (8/30)	53% (16/30)	13% (4/30)	7% (2/30)
Lidocaine with hyaluronidase	30% (9/30)	47% (14/30)	23% (7/30)	0% (0/30)

* There were not significant differences ($P > .05$) between the solutions.

checked at the end of the appointment. No patient had a positive reaction.

The standard IAN block²⁸ was administered with a 27-gauge 1 1/2-inch needle (Monoject; Sherwood Medical, St Louis, Mo) using each of the anesthetic solutions. After the target area was reached and aspiration was performed, 1 minute was used to deposit the anesthetic solution 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.

At 1 minute after the IAN block, the first and second molars were pulp tested. At 2 minutes, the first and 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. At every fourth cycle, the control tooth, ie, the contralateral canine, was tested by a pulp tester without batteries to test the reliability of the subject. Each subject was asked if his or her lip/tongue were numb every minute for 5 minutes and at every fourth minute during pulp testing. If profound lip numbness was not recorded within 20 minutes, the block was considered unsuccessful; the subject was then reappointed. Two 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 also recorded any other problems such as difficulty in opening.

No response from the subject at the maximum output (80 reading) of the pulp tester was used as the criterion for pulpal anesthesia. Anesthesia was considered successful when 2 consecutive 80 readings were obtained. Anesthesia was considered a failure if the subject never achieved 2 consecutive 80 readings.

Comparisons between the buffered lidocaine solution and the buffered lidocaine plus hyaluronidase solution for anesthetic success and incidence of trismus were analyzed nonparametrically using Bonferroni-adjusted McNemar tests. Between-group comparisons on solution deposition discomfort and postinjection discomfort were made using Bonferroni-adjusted Wilcoxon, matched-pairs, signed-ranks test. Comparisons were considered significant at $P < .05$.

RESULTS

Twenty-three males and 7 females from age 19 to 43 years (average 24 years) participated in this study. One hundred percent of the subjects had subjective lip and tongue anesthesia with the IAN blocks. The discomfort ratings of solution deposition for the IAN blocks are presented in Table 1. There were no significant differences ($P > .05$) between the solutions.

Anesthetic success is presented in Table 2. Success rates for the lidocaine solution ranged from 20 to 81%, and for the lidocaine solution with hyaluronidase success ranged from 23 to 70%. There were no significant differences ($P > .05$) between the two solutions. The incidence of pulpal anesthesia for the two techniques is presented in Figures 1 through 6.

The postoperative pain ratings and subjects reporting postoperative trismus are summarized in Table 3 and 4. The lidocaine solution with hyaluronidase had significantly ($P < .05$) higher pain ratings and percentage of patients reporting trismus.

The pH of the solutions were 7.78 for buffered lido-

Table 2. Percentages and Number of Subjects Who Experienced Anesthetic Success

Tooth	Anesthetic Success	
	Lidocaine	Lidocaine With Hyaluronidase
Second molar	70% (21/30)	70% (21/30)*
First molar	50% (15/30)	67% (20/30)*
Second premolar†	52% (15/29)	59% (17/29)*
First premolar†	81% (21/26)	61% (16/26)*
Lateral	30% (9/30)	30% (9/30)*
Central	20% (6/30)	23% (7/30)*

* There were no significant differences ($P > .05$) between the solutions.

† Premolars were missing due to orthodontic treatment.

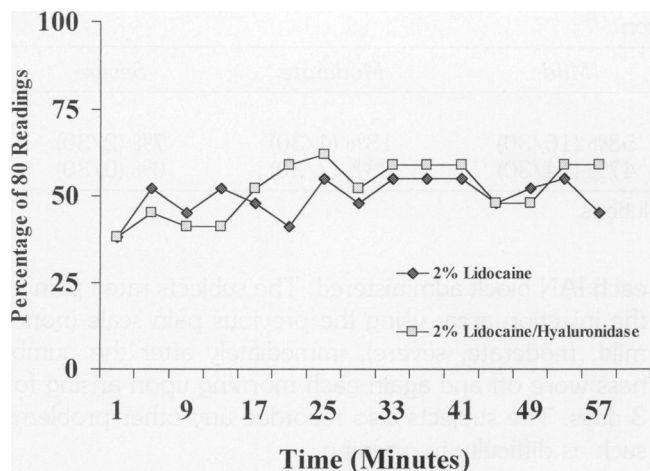


Figure 1. Incidence of second molar anesthesia as determined by lack of response to electrical pulp testing at the maximum setting (percentage of 80/80s) at each postinjection time interval for the 2 anesthetic solutions.

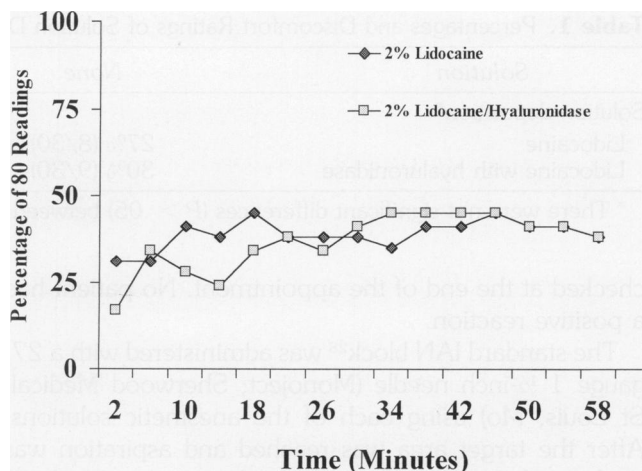


Figure 3. Incidence of second premolar anesthesia as determined by lack of response to electrical pulp testing at the maximum setting (percentage of 80/80s) at each postinjection time interval for the 2 anesthetic solutions.

caine with epinephrine and 7.86 for buffered lidocaine with epinephrine plus hyaluronidase.

DISCUSSION

The use of the 80 reading as a criterion for pulpal anesthesia was based on the studies of Dreven et al²⁹ and Certosimo and Archer.³⁰ These studies showed that no patient response to an 80 reading ensured pulpal anesthesia in vital asymptomatic teeth. Additionally, Certosimo and Archer³⁰ demonstrated that EPT readings less than 80 resulted in pain during operative procedures in asymptomatic teeth.

Anesthetic success with the lidocaine IAN block occurred from 20 to 81% of the time. The success rates are similar to those seen in previous studies¹⁻¹⁴ in which a similar method was used. Therefore, even after a clinically successful block (lip numbness), pulpal anesthesia may not be guaranteed. Theories of anesthetic failure for the IAN block have included accessory innervation,^{11,31,32} accuracy of needle placement,^{12,33,34} anesthetic solution migration along the path of least resistance,³⁴ central core theory,³ and anxiety and psychological factors.³⁵

The buffered lidocaine/hyaluronidase solution did not result in a statistically ($P > .05$) higher success rate compared with the lidocaine solution (Table 2). Nordqvist³⁶

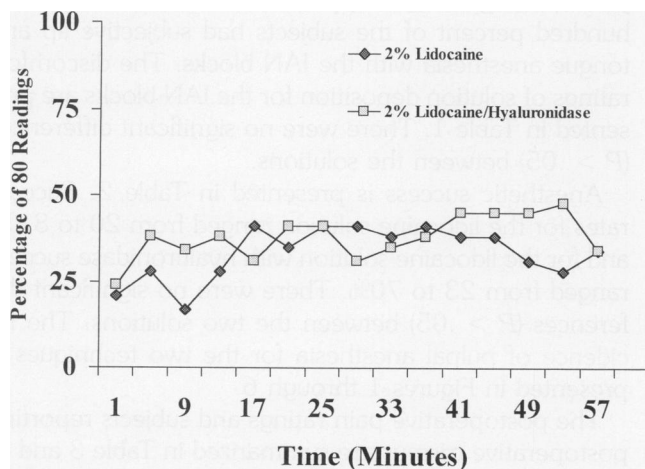


Figure 2. Incidence of first molar anesthesia as determined by lack of response to electrical pulp testing at the maximum setting (percentage of 80/80s) at each postinjection time interval for the 2 anesthetic solutions.

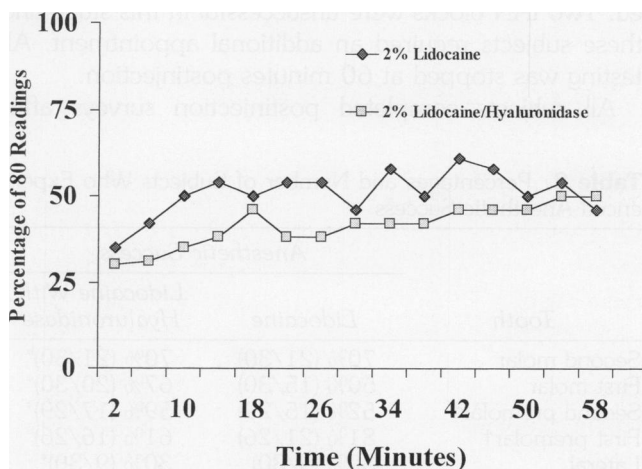


Figure 4. Incidence of first premolar anesthesia as determined by lack of response to electrical pulp testing at the maximum setting (percentage of 80/80s) at each postinjection time interval for the 2 anesthetic solutions.

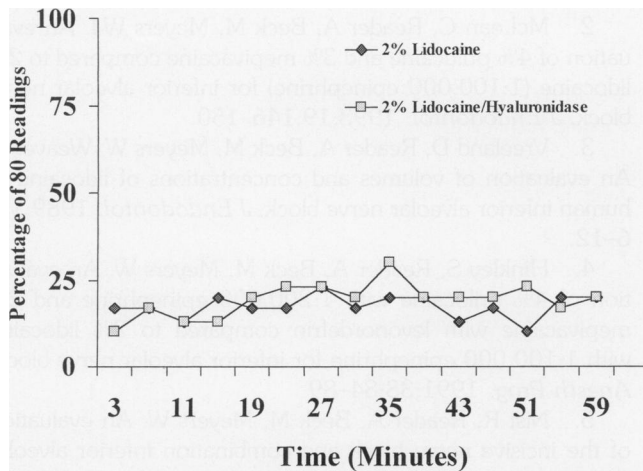


Figure 5. Incidence of lateral incisor anesthesia as determined by lack of response to electrical pulp testing at the maximum setting (percentage of 80/80s) at each postinjection time interval for the 2 anesthetic solutions.

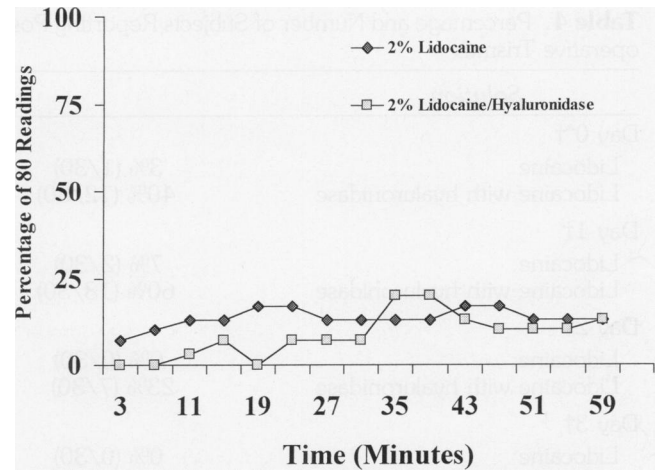


Figure 6. Incidence of central incisor anesthesia as determined by lack of response to electrical pulp testing at the maximum setting (percentage of 80/80s) at each postinjection time interval for the 2 anesthetic solutions.

felt that hyaluronidase loosened the structure of the connective tissue, thereby allowing the anesthetic solution easier access to the nerve fibers. Studies in the field of ophthalmology have shown that combining hyaluronidase with local anesthetic solutions significantly improves peribulbar infiltrations or retrobulbar blocks.³⁷⁻⁴⁰ However, other studies have found hyaluronidase did not improve the success of intraocular surgery.^{41,42} It seems that the addition of hyaluronidase to a lidocaine solution, as used in this study, had little effect on the success of the IAN block. Practitioners should consider supplemental techniques (such as intraosseous^{8-10,13,14,16-18} or periodontal ligament injections^{6,15}) when an IAN block fails to provide pulpal anesthesia for a particular tooth.

Solution deposition had an incidence of around 20% moderate/severe pain ratings (Table 1). The ratings in-

dicade that an IAN block has the potential to be painful even though the solution was deposited slowly over 1 minute. Other studies^{3,5} of the IAN block have reported similar findings. There were no significant differences between the solutions. Therefore, the addition of hyaluronidase was not found to be any more irritating on injection than the solution without hyaluronidase (Table 1).

The postinjection survey showed there was a much higher incidence of moderate/severe pain and trismus with the hyaluronidase solution (Tables 3 and 4). Hyaluronidase is an enzyme that breaks down the components of the connective tissue. The manufacturer²¹ found that the breakdown of dermal tissue appeared to peak in 5 minutes, remained constant for the first hour, and then declined slowly over 5 hours. Further studies²¹

Table 3. Percentages and Discomfort Ratings for Postinjection Survey

Solution	None	Mild	Moderate	Severe
Day 0*†				
Lidocaine	40% (12/30)	47% (14/30)	7% (2/30)	7% (2/30)
Lidocaine with hyaluronidase	20% (6/30)	37% (11/30)	37% (11/30)	10% (3/30)
Day 1†				
Lidocaine	47% (14/30)	43% (13/30)	10% (3/30)	0% (0/30)
Lidocaine with hyaluronidase	20% (6/30)	37% (11/30)	33% (10/30)	10% (3/30)
Day 2†				
Lidocaine	80% (24/30)	17% (5/30)	3% (1/30)	0% (0/30)
Lidocaine with hyaluronidase	47% (14/30)	30% (9/30)	20% (6/30)	3% (1/30)
Day 3†				
Lidocaine	93% (28/30)	7% (2/30)	0% (0/30)	0% (0/30)
Lidocaine with hyaluronidase	57% (17/30)	37% (11/30)	7% (2/30)	0% (0/30)

* Rating at time subjective numbness wore off.

† There were significant differences ($P < .05$) between the solutions.

Table 4. Percentage and Number of Subjects Reporting Postoperative Trismus

Solution	
Day 0*†	
Lidocaine	3% (1/30)
Lidocaine with hyaluronidase	40% (12/30)
Day 1†	
Lidocaine	7% (2/30)
Lidocaine with hyaluronidase	60% (18/30)
Day 2†	
Lidocaine	0% (0/30)
Lidocaine with hyaluronidase	23% (7/30)
Day 3†	
Lidocaine	0% (0/30)
Lidocaine with hyaluronidase	17% (5/30)

* Rating at time subjective numbness wore off.

† There were significant differences ($P < .05$) between the solutions.

showed that reconstitution of the dermal barrier was incomplete at 24 hours, but at 48 hours, the barrier was completely restored. While the pterygomandibular space is different from dermal connective tissue, the high postoperative pain ratings and incidence of trismus clearly show that some adverse effects on the tissue occurred with the injection of hyaluronidase. The postoperative pain ratings and trismus showed improvement by the third day (Tables 3 and 4), demonstrating that the tissue damage was somewhat limited. We recommend that hyaluronidase not be added to local anesthetic solutions for IAN blocks due to its tissue-damaging potential.

CONCLUSIONS

We conclude that adding hyaluronidase to a buffered lidocaine solution with epinephrine did not significantly increase the incidence of pulpal anesthesia in IAN blocks and, because of its potential tissue-damaging effects, it should not be added to local anesthetic solutions for inferior alveolar nerve blocks.

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