Kovanaze Intranasal Spray vs Traditional Injected Anesthetics: a Study of Pulpal Blood Flow Utilizing Laser Doppler Flowmetry

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Objective: An ideal local anesthetic would be effective, minimally reduce pulpal blood flow (PBF), and not require injection. This study compared the effects of 3% tetracaine plus 0.05% oxymetazoline nasal spray (Kovanaze; KNS) and injections using 2% lidocaine with 1:100,000 epinephrine (LE) or 3% mepivacaine plain (MP) on PBF, anesthetic efficacy, and participant preference.

Methods: In a double-blind cross-over design, 20 subjects randomly received a test anesthetic and placebo at each of 3 visits (KNS/mock infiltration; mock nasal spray/LE; or mock nasal spray/MP). Nasal sprays and infiltration apical to a maxillary central incisor were delivered ipsilaterally. PBF was evaluated by laser Doppler flowmetry, and local anesthetic success was assessed with electric pulp testing. Postoperative pain levels, participant preference, and adverse events were also assessed.

Results: LE injections demonstrated significant reductions in PBF at all time intervals compared with baseline ($P < .05$), whereas KNS and MP did not. Pulpal anesthesia success rates were higher for LE (85%) compared with MP (35%) and KNS (5%). Participants reported significantly higher postoperative pain levels for KNS compared with LE and MP. Additionally, KNS was the least preferred of the anesthetics administered and resulted in more reported adverse events.

Conclusion: Although KNS showed no significant effect on PBF, it was not effective in achieving pulpal anesthesia as used in this study.

Key Words: Pulpal blood flow; Laser Doppler; Kovanaze; Local anesthesia.

Injectable local anesthetics are essential for eliminating pain during many dental procedures.[1] Disadvantages include patient anxiety and pain related to intraoral injections,[2] which can deter fearful patients and thus present barriers to dental care.[3] Phobic patients may be more accepting of alternative methods for administering local anesthetics that do not require use of a needle.

Epinephrine is often administered along with local anesthetics to prolong the duration of action. Although the vasoconstrictor addition has the potential to reduce pulpal blood flow (PBF), it does not create a damaging environment for pulp cells in teeth with no history of pulpitis.[4] The ability of the pulp to resist degradation is somewhat dependent on maintenance and integrity of the neurovascular supply.[5] As the dental pulp is contained within a low-compliance space, alterations in the microcirculation stemming from trauma may lead to detrimental changes. However, 2013 International Association of Dental Traumatology (IADT) Dental Trauma Guidelines reported a lack of strong evidence for avoiding vasoconstrictors in dental trauma cases. Despite the evidence, the IADT advocates for local anesthetics without vasoconstrictors if an alternative capable of providing the same level of anesthesia is available.[6] As with many physiologic events, tissue

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damage can be progressive, incremental, and difficult to temporally measure and quantify. If pulpal microcirculation is compromised and PBF is interrupted or altered due to a traumatic event, it stands to reason further PBF reductions from a vasoconstrictor should be avoided if possible. Accordingly, local anesthetic alternatives that do not reduce PBF may warrant evaluation for use in such cases.

Laser Doppler flowmetry (LDF) devices measure PBF within a tooth by assessing the detection of light scatter generated by moving erythrocytes. Flux describes the measured blood flow and is expressed as arbitrary perfusion units calculated by the product of blood cell speed and volume.[7] LDF is most beneficial for pulp vitality testing in young, traumatized teeth and those with large pulps that may not respond dependably to other forms of sensibility testing. It can also be used in mature teeth although restorations, caries, or significant pulp calcifications may interfere with the Doppler effect, decreasing LDF accuracy.[8] Previous studies utilizing LDF have shown a PBF decrease following the use local anesthetics in combination with sympathomimetic agents.[9–11]

In June 2016, the US Food and Drug Administration approved Kovanaze nasal spray (KNS) for clinical use in dentistry. It contains 3% tetracaine (an ester local anesthetic) and 0.05% oxymetazoline (a topical decongestant and sympathomimetic) and is designed for intranasal administration.[12–14] In otolaryngology practices, tetracaine has long been used for nasal local anesthesia.[15] Oxymetazoline is a direct-acting adrenergic α agonist with vasoconstrictive properties that slow systemic tetracaine absorption, prolonging the duration of anesthesia.[16] Multicenter studies concluded 3% tetracaine with 0.05% oxymetazoline used for maxillary nonmolar pulpal anesthesia was both safe and effective.[17] Because KNS is topically administered, it may potentially reduce dental anxiety related to injections and avoidance by needle-phobic patients.

KNS has been shown to be effective for anesthetizing maxillary central incisors,[17] the most common site of traumatic dental injury.[18] Although the impact of KNS on PBF is unknown, it hypothetically should have minimal effects as it is delivered at an area farther from the pulpal tissues. If KNS minimally impacts PBF and provides effective pulpal anesthesia, it could be an ideal anesthetic for treating traumatized maxillary incisors.

This study's primary objective was to compare PBF measurements in maxillary incisors anesthetized with KNS vs 2 injectable anesthetics, 3% mepivacaine plain (MP) and 2% lidocaine with 1:100,000 epinephrine (LE). Other objectives included assessing pulpal anesthesia efficacy of each anesthetic, postoperative pain levels, participant preference between injection or intranasal spray delivery of the anesthetics, and adverse events associated with each anesthetic.

METHODS AND MATERIALS

The study was approved by the Louisiana State University Health Science Center Institutional Review Board (IRB: 9924) in New Orleans, LA (IRB: 9924), and informed consent and HIPAA authorization was obtained from all subjects. Adult patients were screened for study eligibility, which consisted of a health history review, dental history questionnaire, clinical examination, and intraoral periapical digital imaging of maxillary central incisors. Inclusion criteria were patients 18 to 30 years of age, American Society of Anesthesiology health classification I or II,[19] and maxillary anteriors with healthy periodontal and pulpal tissues. Exclusion criteria were patients currently pregnant or breastfeeding, a history of central incisor trauma, traumatic occlusion, fractured or carious teeth, existing restorations on central incisors, active orthodontic treatment, fixed maxillary orthodontic retainer, previous endodontic therapy of the maxillary central incisors, radiographic signs of pulp chamber and canal obliteration, pathologic discoloration, radiographic signs of root resorption, and any contraindications to KNS use including allergy.

A single-channel LDF unit (Moor VMS-LDF, Moor Instruments) measured PBF using emitted light with a wavelength of 785 nm +/− 10 nm, a 2.5-mW maximum output power, 1.0-second output time constant, and 20-Hz bandwidth. PBF was recorded using the Flux measurement in perfusion units. The VP3 probe used with the LDF unit had a fiber separation of 0.5 mm and an external diameter of 1.5 mm. LDF was calibrated per the manufacturer's instructions before each test visit. During all PBF data collections, participants were asked to limit movements, and precautions were taken to prevent probe or cord movement. Following a 2-minute period to allow a stable LDF recording, the Moor VMS-PC software was used to calculate mean PBF.

To ensure a reproducible LDF probe position at all visits, a custom polyvinyl siloxane (PVS) putty stent was fabricated for each participant. The stent extended bilaterally to the maxillary first premolars at a depth of the labial vestibule. A 1.5-mm diameter hole was cut through the PVS stent matching the external dimensions of the probe and positioned 3 mm coronal to the buccal gingival margin allowing the probe to be placed on the buccal middle third of the central incisor being evaluated.

An electric pulp tester (EPT; Analytic Technology Corp) was used to assess anesthetic efficacy. Pulpal

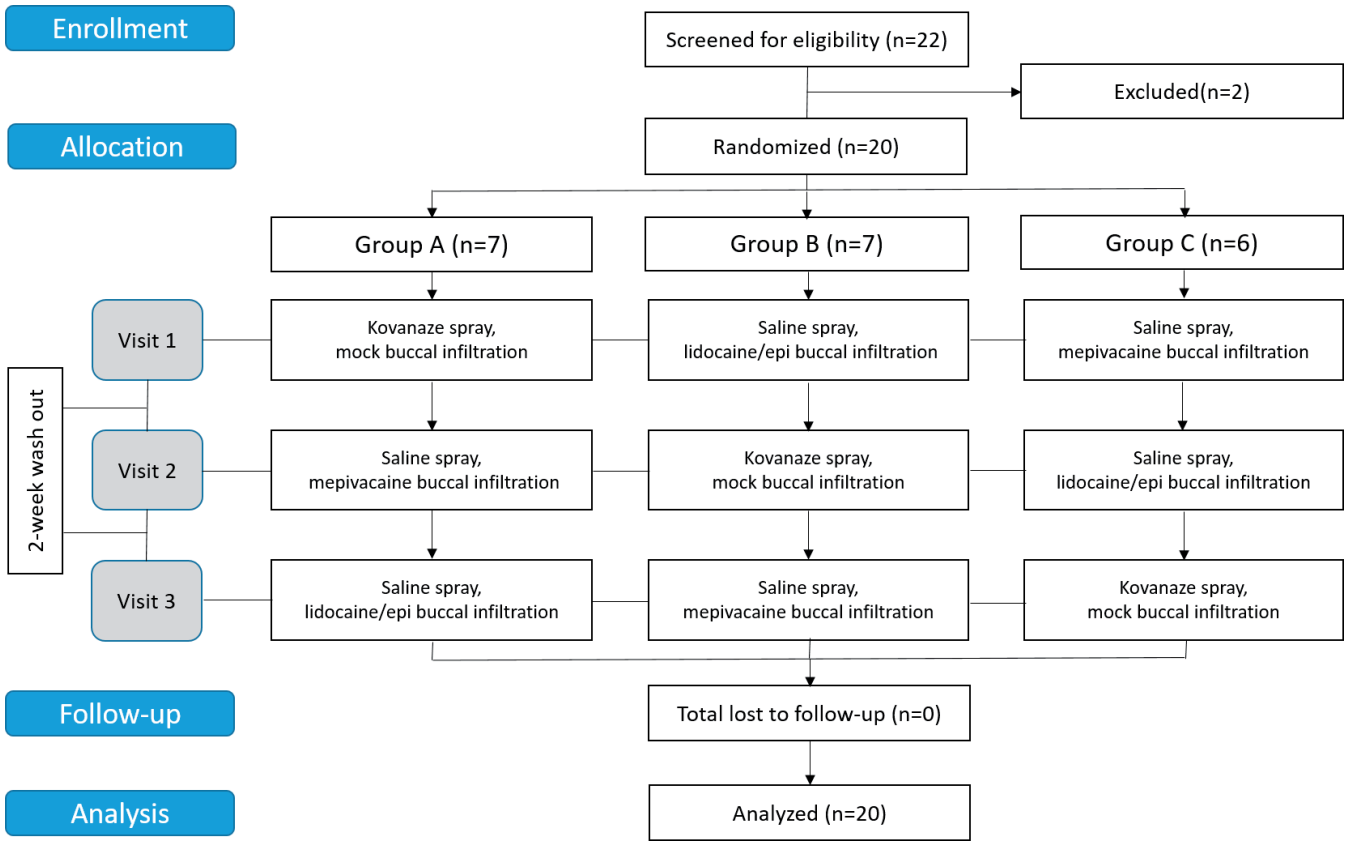

Figure 1. Study flowchart.

anesthesia success was defined as attaining 2 consecutive EPT readings of 80 within a 15-minute period. Before testing, each tooth was dried with a sterile 2 × 2-inch gauze, and a conducting medium (Colgate Total toothpaste; Colgate-Palmolive Company) was applied to the EPT tip, which was then placed on the incisal third of the central incisor. Participants were instructed to let go of the probe once a sensation was felt. The voltage change rate was set to 5 for all recordings.

Anesthetics evaluated were Kovanaze (St. Renatus), MP (Cook-Waite), and LE (Cook-Waite). Injections were performed with a standard dental anesthetic syringe and cartridge. All anesthetics and atomizers were masked and marked so only the researcher administering the anesthetics and placebo (MO) knew the contents.

Test Visit Protocol

In this double-blind cross-over design, participants received a different test anesthetic and saline placebo combination at each visit (Figure 1). To eliminate carry-over effects, a 2-week washout period was completed between each test session. Participants were randomly assigned into 3 groups by a third-party blind draw. Participants were blinded to group assignment and anesthetics, and the data collector (ST) was blinded to subject identification and group assignment. Prior to the administration of each anesthetic, baseline (T0) measurements for PBF and EPT readings were recorded. EPT and LDF measurements were then completed at designated time intervals labeled T1, T2, T3, T4, T5, and T6, respectively. Following the injection, EPT was completed at 5, 10, 15, 30, 45, and 60 minutes, whereas LDF measurements were recorded at 7, 12, 17, 32, 47, and 62 minutes. At the completion of each visit, participants were asked to document pain using a printed Heft-Parker Visual Analog Scale (HP-VAS) diagram on a questionnaire 1, 4, and 24 hours later.[20] Additionally, participants were instructed to record any adverse events and indicate their personal preference for either the nasal spray or the injection. Questionnaires were returned to researcher ST 24 hours after the test visit.

KNS Visit. KNS (12 mg tetracaine and 02 mg oxymetazoline total) was administered according to the manufacturer's instructions. The first 0.2 mL spray was delivered directed 90 degrees to the inferior meatus

intranasally on the same side as the tested central incisor. After 4 minutes, a second 0.2 mL nasal spray was delivered, directed 45 degrees to the middle meatus. Nasal sprays were administered in 0.5 seconds or less. Immediately following the second KNS spray, 20% benzocaine topical anesthetic (3D-Dental) was applied with a cotton-tipped applicator to dried mucosa in the labial vestibule above the same central incisor. Two minutes after the second administration of KNS, a 30-gauge short dental needle was inserted in the mucosa at the apex of the test tooth, and 0.5 mL of sterile saline was administered over 20 seconds. The syringe was held in position for a total of 60 seconds.

Traditional Anesthetic Visits. During appointments in which LE or MP was the test anesthetic, the same protocol was followed, but KNS was replaced with two 02 mL saline nasal spray placebos. For the buccal infiltration injection, 1.7 mL of either LE or MP was administered using a 30-gauge short dental needle over a 60-second period.

Statistical Analysis

An a priori power analysis was performed using a difference in PBF measurements of 0.95 as the effect size, based on a previous study by Odor[9] (Power Analysis and Sample Size Software 2020, NCSS, LLC). Using a 90% power and .05 significance level, a total sample size of 18 subjects (6 per group) was calculated. A total of 22 adult subjects were initially screened to compensate for expected subject dropout.

To determine significance for PBF at each interval compared with the baseline, a repeated measures analysis of variance (ANOVA) was used to test within-subject effects. A paired *t* test was used to assess each pair of anesthetics. Bonferroni adjustment was used to control the overlap type 1 error in multiple comparisons. Anesthetic efficacy was documented as frequency of "yes" or "no," giving a percentage of success or failed pulpal anesthesia. Cochran Q test was used to assess pulpal anesthesia between all groups. McNemar test was used to assess pulpal anesthesia between each pair of anesthetics.

Repeated measures ANOVA was used to assess HP-VAS scores. A paired *t* test was used to assess each pair of different anesthetics. If "No Preference" was chosen for anesthetic preference, it was considered as 50%/50% preference for injection and nasal spray. In such cases, a 0.5-count to both was added to the frequency table. The Cochran Q test was used to evaluate whether all 3 groups had the same probability of achieving pulpal anesthesia. The McNemar test was used to assess whether the probability is different between each pair of anesthetic groups. All statistical analyses were performed using SAS (Version 9.4) with a P value set to .05.

RESULTS

Of the 22 screened participants, 2 were excluded, 1 due to presence of a fixed maxillary orthodontic retainer and 1 due to recent nasal surgery, resulting in a total of 20 study participants (Figure 1). The participants included 10 males and 10 females with an average age of 26.8 years. Of these participants, tooth #8 was tested on 17 people, whereas tooth #9 was tested on 3 people.

Pulpal Blood Flow

Within each test group, only the LE group demonstrated a statistically significant decrease in PBF at each time interval (T1-6) compared with baseline (T0) values ($P < .05$), whereas PBF changes in the MP and KNS groups both lacked any statistical significance. Intergroup comparison of PBF changes from baseline (T0) to all time points (T1-6) demonstrated statistical significance only for the LE group vs both the KNS and MP groups. Comparison between the KNS and MP PBF data lacked any significance differences (Table 1).

Other Objectives

Figure 2 presents the overall success rates for pulpal anesthesia. LE produced a significantly higher percentage of successful pulpal anesthesia compared with MP (85% vs 35%; $P = .0016$) and KNS (85% vs 5%; $P < .0001$). The difference in efficacy between MP and KNS was also statistically significant (35% vs 5%; $P = .0143$). Figure 3 depicts the percentage patients with EPT readings of 80, or pulpal anesthesia, as it relates to each test anesthetic over 60 minutes.

Participants' postoperative HP-VAS pain scores demonstrated statistically higher ratings recorded at 1, 4, and 24 hours after KNS compared with either LE or MP (Table 2). Significantly more participants preferred receiving a traditional injection with LE or MP compared with KNS ($P = .0143$ and $P = .0108$, respectively), whereas there was no significant difference in preference between the traditional injected anesthetics ($P = .8383$; Figure 4). Participants reported more adverse events after KNS administration. The most reported side effects were a runny nose, intranasal

Table 1. Pulpal Blood Flow†

	Pulpal Blood Flow					
Test Groups	*T1*	*T2*	*T3*	*T4*	*T5*	*T6*
Change in PBF at time intervals compared with baseline (T0)						
LE	−3.15 ± 2.61*	−3.94 ± 2.09*	−4.22 ± 2.56*	−4.44 ± 2.68*	−3.79 ± 2.65*	−3.44 ± 3.01*
MP	0.22 ± 1.43	1.03 ± 2.20	1.66 ± 3.82	1.21 ± 3.41	0.38 ± 2.96	0.64 ± 3.06
KNS	0.32 ± 1.03	1.25 ± 2.38	0.39 ± 2.00	0.22 ± 1.91	0.09 ± 2.07	−0.37 ± 1.89
Paired statistical analysis of PBF changes at time intervals compared with baseline (T0)						
LE vs MP	.001*	<.0001*	<.0001*	<.0001*	.0003*	.0007*
LE vs KNS	<.0001*	<.0001*	<.0001*	<.0001*	<.0001*	.0002*
MP vs KNS	.8108	.7404	.1407	.3036	.7394	.237

* $P < .05$.

† The change in PBF (mean ± SD) at each data collection point (T1-6) compared with baseline (T0). Paired statistical analysis compared each test group to another with respect to PBF change at each time interval (T1-6) compared with baseline (T0). KNS, Kovanaze; LE, 2% lidocaine with 1:100,000 epinephrine; MP, 3% mepivacaine plain; PBF, pulpal blood flow.

burning, sore throat, nasal congestion, and postnasal drip. When either LE or MP was administered, most subjects reported no adverse events (Table 3).

DISCUSSION

Like MP, KNS did not substantially reduce PBF at any timepoint. Evidence is lacking on the long-term effects of altered PBF in cases of dental trauma, but studies have postulated the importance of preserving the integrity of the neurovascular bundle to maintain vitality of traumatized teeth.[5] The IADT continues to advocate for using local anesthetics without a vasoconstrictor if an alternative capable of providing the same level of anesthesia is available.[6] The findings in this study demonstrate that KNS failed to provide pulpal anesthesia equivalent to LE or MP. These findings agree with Capetillo et al,[21] who found success rates with KNS for the maxillary lateral incisor and first premolars to be 22% and 37%, respectively.

Both the current study and Capetillo et al[21] defined success as the percentage of subjects who achieved 2 consecutive EPT readings of 80 within 15 minutes as described by Nusstein.[22] This endpoint has been established as clinically relevant because an 80 EPT reading ensures pulpal anesthesia on asymptomatic teeth,[23,24] and EPT readings <80 can result in pain during dental procedures.[24] This standard has been used in multiple endodontic studies on local anesthesia.[23–26] Comparatively, a clinical study utilizing KNS for single tooth restorative dental treatment defined anesthetic success as completion of the dental procedure and demonstrated a success rate of 88%, likely reflecting differences in defining success.[27]

The relatively low success rate for MP (35%) is also of interest. Previous EPT studies of incisors anesthetized with MP found the mean duration of profound anesthesia to be 11.3 minutes.[28] Mason et al[29] found

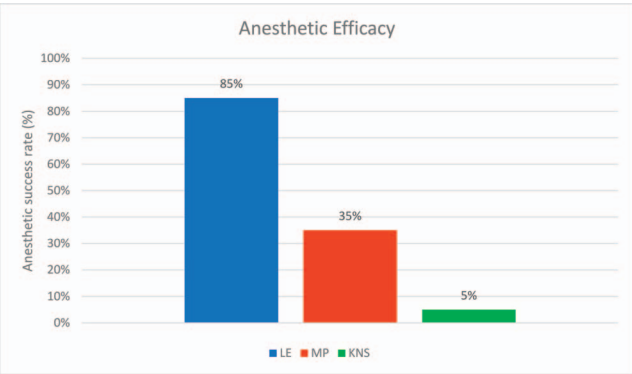

Figure 2. Anesthetic efficacy. Paired statistical analysis showed significant statistical difference between each of the anesthetics; LE and MP ($P = .0016$), MP and KNS ($P = .0143$), and LE and KNS ($P < .0001$). KNS, Kovanaze; LE, 2% lidocaine with 1:100,000 epinephrine; MP, 3% mepivacaine plain.

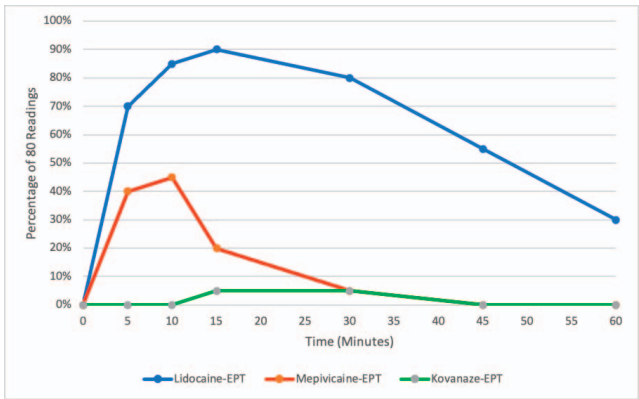

Figure 3. Pulpal anesthesia. Percentage (%) of participants with profound pulpal anesthesia, as determined by an EPT reading of 80, for each anesthetic over 60 minutes. EPT, electric pulp tester.

Table 2. Postoperative HP-VAS Pain Scores†

Test Groups	*1 Hour*	*4 Hours*	*24 Hours*
Postoperative HP-VAS pain scores after test visit			
LE	24.40 ± 23.3	5.00 ± 13.5	2.70 ± 12.1
MP	14.60 ± 14.3	1.15 ± 5.1	0.00 ± 0.0
KNS	52.40 ± 39.8	28.75 ± 38.0	10.65 ± 21.0
Paired statistical analysis comparing HP-VAS scores			
LE vs MP	.1299	.1968	.3299
LE vs KNS	.003*	.0103*	.0119*
MP vs KNS	.0005*	.0053*	.0351*

* $P < .05$.

† Postoperative HP-VAS scores (mm; mean ± SD) reported 1, 4, and 24 hours after each test visit. Paired statistical analysis compared each test group to another with respect to HP-VAS scores at each time interval. HP-VAS, Heft-Parker Visual Analog Scale; KNS, Kovanaze; LE, 2% lidocaine with 1:100,000 epinephrine; MP, 3% mepivacaine plain.

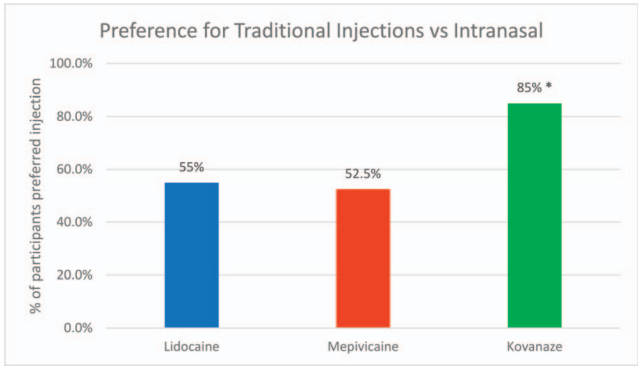

Figure 4. Preference for traditional injections vs intranasal. Percentage (%) of participants who preferred traditional injections compared with intranasal administration when each test anesthetic was given. Paired statistical analysis showed no significant difference in preference comparing LE to MP ($P = .8383$), whereas there was a significant difference comparing LE to KNS ($P = .0143$) and MP to KNS ($P = .0108$). *$P < .05$. KNS, Kovanaze; LE, 2% lidocaine with 1:100,000 epinephrine; MP, 3% mepivacaine plain.

higher success rates of 73% for the lateral incisor 20 minutes after infiltration with MP, but this decreased to 30% at 30 minutes and 0% at 47 minutes. Our protocol evaluated pulpal anesthesia at 5, 10, 15, 30, 45, and 60 minutes following anesthetic administration. There may have been an improved success rate for MP if pulpal anesthesia was evaluated at closer intervals after the 15-minute mark.

It may not be suitable to utilize KNS during dental appointments where profound pulpal anesthesia is needed, but it may be feasible for limited restorative treatment. The binary success and failure categorization used in this study is consistent with the current endodontic literature. Furthermore, the more stringent standard of 2 consecutive EPT readings of 80 were deemed appropriate because this study investigated the feasibility for endodontic treatment. Although this definition was used for success and failure, a practitioner may consider KNS acceptable when the depth and duration of anesthesia is not critical such as with a simple direct restoration.

Study participants frequently reported adverse events and higher recorded pain values following KNS administration. Participants also stated a preference for traditional injectable local anesthetics over intranasal delivery. One study assessing patient preference for anesthesia delivery types comparing lidocaine injection to oxymetazoline nasal spray also found that patients preferred local anesthetic injections.[21] A previous clinical trial evaluated the use of KNS, a tetracaine-only spray, and a placebo and noted more nasal region pain with KNS compared with the tetracaine-only group (25% vs 11%, respectively).[17] The adverse effects found in this study are similar to the manufacturer's listed potential side effects for over-the-counter nasal decon-

Table 3. Adverse Events

	Adverse Events As Reported by Test Group		
	LE	*MP*	*KNS*
Reported adverse events (n)	Pain at injection site (5) Runny nose (3)	Pain at injection site (2)	Runny nose (13) Burning sensation (8) Sore throat (7) Postnasal drip (6) Headache (4) Sinus drainage (4) Difficulty swallowing (4) None (3) Altered taste (1) Gag reflex (1)
Totals (n)	8	2	51

* Reported adverse events broken down by test group (n = number of participants who reported each event). KNS, Kovanaze; LE, 2% lidocaine with 1:100,000 epinephrine; MP, 3% mepivacaine plain.

gestants with 0.05% oxymetazoline, which includes burning or stinging sensations, sneezing, increased nasal discharge, and temporary discomfort.[33] These noted side effects could also explain the higher reported pain scores with KNS. Oxymetazoline is presumed to be a likely source of these reported side effects. Furthermore, although phobias related to local anesthetic injections may be curtailed using intranasal administration, the potential side effects and discomfort associated with KNS may not be acceptable to some patients. Future studies should consider incorporating patients with needle phobias as they may have altered preferences.

Limitations

The low success rate for profound pulpal anesthesia when using KNS could be attributed to nonadherence to the manufacturer's recommendations regarding administration of a third intranasal spray if failed anesthesia is determined 10 minutes following the second spray.[34] For this study, only 2 sprays were administered to maintain participant blinding. It is possible that administering a third KNS dose may increase pulpal anesthesia success. In addition, the efficacy of both MP and LE were less than reported in previous studies.[32] It is likely that participants were closely monitoring for sensations and reported those that would otherwise be imperceptible during restorative treatment when other noise and vibration stimuli are present. However, as new anesthetics are being evaluated, use of EPT is preferred over completion of restorative treatment alone as the measure of success when anesthetic efficacy is unknown, otherwise subjects may be put at risk for pain and a need for rescue anesthesia. The sham injections did not contain the same volume of solution as the MP or LE injection. This protocol was intended to simulate the pain of an injection, and the additional volume was not deemed necessary as no difference in discomfort was expected. Other trials have used mock injections where no tissue penetration was performed.[21] Because the smallest volume of saline was injected when the KNS was the active drug, this would expectedly bias the study to have reduced pain responses during this visit; however, the opposite was found.

CONCLUSION

When administered to provide local anesthesia of a maxillary central incisor, LE injection produced significant decreases in PBF while both KNS nasal spray and MP injection had no significant effects. However, KNS and MP produced significantly lower rates of local anesthetic success compared with LE. Patients had a significantly higher preference for traditional dental injections using MP and LE compared to KNS nasal spray. Also, KNS had substantially more reported side effects than either of the traditional injected anesthetics.

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REFERENCES

1. Haas DA. An update on local anesthetics in dentistry. *J Can Dent Assoc*. 2002;68:546–551.
2. Kaufmann E, Epstein JB, Naveh E, et al. A survey of pain, pressure, and discomfort induced by commonly used oral local anesthesia injections. *Anesth Prog*. 2005;52:122–127.
3. Milgrom P. Four dimensions of fear of dental injections. *J Am Dent Assoc*. 1997;128:756–762.
4. Kim S, Edwall L, Trowbridge H, et al. Effects of local anesthetics on pulpal blood flow in dogs. *J Dent Res*. 1984;63:650–652.
5. Yu CY, Abbott PV. Responses of the pulp, periradicular and soft tissues following trauma to the permanent teeth. *Aust Dent J*. 2016;61(1 suppl):39–58.
6. Dental trauma guidelines. International Association of Dental Traumatology. Accessed April 10, 2019. https://www.iadt-dentaltrauma.org/1-9%20%20iadt%20guidelines%20combined%20-%20lr%20-%2011-5-2013.pdf
7. Basic theory and operating principles of laser doppler blood flow monitoring and imaging (LDF & LDI), Issue 1. Moor Instruments. Accessed September 7, 2020. https://www.moor.co.uk/wp-content/uploads/2018/10/Moor_Laser_doppler_theory_Issue_1.pdf
8. Ghouth N, Duggal M, BaniHani A, et al. The diagnostic accuracy of laser doppler flowmetry in assessing pulp blood flow in permanent teeth: a systematic review. *Endod Dent Traumatol*. 2018;34:311–319.
9. Eleazer PD, Glickman GN, McClanahan SB, et al. *Glossary of Endodontic Terms*. 9th ed. Chicago, IL: American Association of Endodontists; 2015.
10. Odor TM, Pitt Ford TR, McDonald F. Adrenaline in local anaesthesia: the effect of concentration on dental pulpal circulation and anaesthesia. *Endod Dent Traumatol*. 1994;10:167–173.
11. Ahn J, Pogrel MA. The effects of 2% lidocaine with 1:100, 000 epinephrine on pulpal and gingival blood flow. *Oral*

Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85:197–202.

12. Active pharmaceutical ingredients. St. Renatus. Accessed July 30, 2017. http://www.kovanaze.com/kovanaze-needle-free-anesthesia-mist/active-pharmaceuticalingredients-api/

13. Noorily A, Noorily S, Otto R. Cocaine, lidocaine, tetracaine: which is best for topical nasal anesthesia? *Anesth Analg*. 1995;81:724–727.

14. Drug facts. Bayer Corporation. Accessed May 10, 2019. http://labeling.bayercare.com/omr/online/Afrin-Original_Pump_Mist-001.pdf

15. Ogle OE, Mahjoubi G. Local anesthesia: agents, techniques, and complications. *Dent Clin North Am*. 2012;56:133–148.

16. Shanler SD, Ondo AL. Successful treatment of the erythema and flushing of rosacea using a topically applied selective α1-adrenergic receptor agonist, oxymetazoline. *Arch Dermatol*. 2007;143:1369–1371.

17. Ciancio SG, Marberger AD, Ayoub F, et al. Comparison of 3 intranasal mists for anesthetizing maxillary teeth in adults. *J Am Dent Assoc*. 2016;147:339–347.

18. Zerman N, Cavalleri G. Traumatic injuries to permanent incisors. *Endod Dent Traumatol*. 1993;9:61–64.

19. Keats AS. The ASA classification of physical status – a recapitulation. *Anesthesiology*. 1978;49:233–236.

20. Heft MW, Parker SR. An experimental basis for revising the graphic rating scale for pain. *Pain*. 1984;19:153–161.

21. Capetillo J, Drum M, Reader A, et al. Anesthetic efficacy of intranasal 3% tetracaine plus 0.05% oxymetazoline (Kovanaze) in maxillary teeth. *J Endod*. 2019;45:257–262.

22. Nusstein J, Reader A, Drum M. Local anesthesia strategies for the patient with a "hot" tooth. *Dent Clin North Am*. 2010;54:237–247.

23. Dreven LJ, Reader A, Beck M, Meyers WK, Weaver J. An evaluation of an electric pulp tester as a measure of analgesia in human vital teeth. *J Endod*. 1987;13:233–238.

24. Certosimo AK, Archer RD. A clinical evaluation of the electric pulp tester as an indicator of local anesthesia. *Oper Dent*. 1986;21(1):25–30.

25. Vreeland D, Reade A, Beck M, et al. An evaluation of volumes and concentrations of lidocaine in human inferior alveolar nerve block. *J Endod*. 1989;15:6–12.

26. McLean C, Reader A, Beck M, et al. An evaluation of 4% prilocaine and 3% mepivacaine compared with 2% lidocaine (1:100,000 epinephrine) for inferior alveolar nerve block. *J Endod*. 1993;19:146–150.

27. Chaney M, Kerby R, Reader A, et al. An evaluation of lidocaine hydrocarbonate compared with lidocaine hydrochloride for inferior alveolar nerve block. *Anesth Prog*. 1991;38:212–216.

28. Hinkley S, Reader A, Beck M, et al. An evaluation of 4% prilocaine with 1:200,000 epinephrine and 2% mepivacaine with 1:20,000 levonordefrin compared with 2% lidocaine with 1:100,000 epinephrine for inferior alveolar nerve block. *Anesth Prog*. 1991;38:84–89.

29. Burns Y, Reader A, Nusstein J, Beck M, Weaver J. Anesthetic efficacy of the palatal-anterior superior alveolar injection. *J Am Dent Assoc*. 2004;135:1269–1276.

30. Hersh EV, Pinto A, Saraghi M, et al. Double-masked, randomized, placebo-controlled study to evaluate the efficacy and tolerability of intranasal K305 (3% tetracaine plus 0.05% oxymetazoline) in anesthetizing maxillary teeth. *J Am Dent Assoc*. 2016;147:278–287.

31. Peterson JK, Luck H, Kristensen F, Mikkelsen L. A comparison of four commonly used local analgesics. *Int J Oral Surg*. 1977;6:51–59.

32. Mason R, Drum M, Reader A, Nusstein J, Beck M. A prospective, randomized, double-blind comparison of 2% lidocaine with 1:100,000 and 1:50,000 epinephrine and 3% mepivacaine for maxillary infiltrations. *J Endod*. 2009;35:1173–1177.

33. FAQs plus tips for using Afrin nasal sprays. Bayer Corporation. Accessed February 20, 2019. https://www.afrin.com/how-to-and-faq/

34. Use and training. St. Renatus. Accessed Jan 6, 2019. http://www.kovanaze.com/use-and-training/