Anesthetic Efficacy of Intranasal 3% Tetracaine plus 0.05% Oxymetazoline (Kovanaze[®]) in Maxillary Teeth

Thesis

Presented in Partial Fulfillment of the Requirements for the Degree of Master of
Science in the Graduate School of The Ohio State University

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2018

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Abstract

Introduction: The high success achieved in maxillary local anesthesia is unfortunately impossible in needle-phobic patients who avoid their dental appointments, which is approximately 10% of the U.S. population. Needle-free alternatives to local anesthesia would therefore be beneficial. The purpose of this study was to determine the patient preference for and pulpal anesthetic efficacy of a 3% tetracaine plus 0.05% oxymetazoline (Kovanaze[®]) nasal spray in maxillary lateral incisors and first premolars.

Methods: Fifty adult subjects randomly received a 3% tetracaine plus 0.05% oxymetazoline (Kovanaze[®]) nasal spray and mock injection or a mock nasal spray and 2% lidocaine with 1:100,000 epinephrine injection at the maxillary lateral incisor or first premolar in two appointments spaced at least 1 week apart in a single-blind cross-over design. Pulpal anesthesia was evaluated with an electric pulp tester. Side effects and subject preferences were also recorded.

Results: Anesthetic success was significantly lower for the Kovanaze[®] nasal spray and mock injection (22-37%) than for the mock nasal spray and lidocaine injection (89-91%). Subjects reported more side effects and pain after the Kovanaze[®] nasal spray and mock injection appointment than the control. All subjects (100%) preferred the injection after experiencing both routes of administration.

Conclusions: The 3% tetracaine plus 0.05% oxymetazoline (Kovanaze[®]) nasal spray and mock injection was less preferable, caused more side effects, and had significantly less anesthetic success than the mock nasal spray and 2% lidocaine with 1:100,000 epinephrine injection in maxillary lateral incisors and first premolars.

Dedication

To Julia, Cora, and Helen: I love you each very much and I appreciate all of your patience and support during the last couple of years while I completed this residency and wrote this Master's thesis. I look forward to the next chapter in our life and I promise I won't write any more books. Let's go play!

Acknowledgments

To Drs. Drum, Reader, Nusstein, Fowler, and Beck: Thank you so much for all the support and guidance you've provided over the last couple of years, both personally and professionally. I am now ready to go out into the world as a well-prepared endodontist. I will always be grateful to be accepted into the best endodontic program in the world.

To Steve, Jake, and Kathryn: I can't imagine experiencing all the highs and lows we encountered during this program with anyone else. You are all awesome and I obviously think we are the best class ever. We should get together again sometime.

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Chapter 1: Introduction

Several studies (1-3) have shown that many dental patients have anxiety and fear of needles, and even though local anesthesia in maxillary teeth is successful 62-100% of the time (4-7), that high success rate cannot be achieved in needle-phobic patients when they avoid their appointments. Between 15% and 59% of survey populations reported at least some dental fear and avoided the dentist, and approximately 25% of patients had not visited their dentist in two years (1-3). Overall, an estimated 10% of the U.S. population has a condition called needle phobia and is not receiving the dental care needed to maintain a healthy dentition (8). Alternatives to traditional needle-based approaches for inducing local anesthesia would benefit these needle-phobic patients and all dental patients greatly.

The United States Food and Drug Administration has approved a nasal spray (Kovanaze®) for clinical use. Kovanaze® is a 3% tetracaine plus 0.05% oxymetazoline solution intended for local anesthesia of maxillary anterior and first premolar teeth. The major advantage of Kovanaze® is that it can reduce fear, anxiety, and avoidance of treatment in needle-phobic patients. Kovanaze® also has the potential to reduce inadvertent needle-stick injuries, which complies with several government initiatives (9, 10) to use needle-free systems whenever possible. Cleveland et al. (10) found that

approximately 25% of needle-stick injuries were from anesthetic syringe needles and that more than half of those injuries could have been prevented with safer handling practices or re-capping systems. In an educational review, Blanton and Jeske (11) discussed safe injection practices for dental local anesthesia to prevent iatrogenic injuries due to a poor understanding of normal head and neck anatomy. Although these complications are rare, they could be minimized or eliminated if effective needle-free alternatives become available. The non-steroidal anti-inflammatory drug ketorolac (Sprix®) and the influenza vaccine (FluMist®) were successfully developed in the medical field to reduce the potential adverse effects of needles (12-14). These medications are administered via the nostril as is Kovanaze®, the drug investigated in the current study.

Double-blind, randomized clinical trials have found that a 3% tetracaine plus 0.05% oxymetazoline (Kovanaze®) nasal spray effectively prevented pain during restorative procedures in maxillary anterior and premolar teeth in 83% to 88% of patients (15, 16). In 2012, Giannakopoulos et al. (17) investigated the cardiovascular and pharmacokinetic effects of this nasal spray and found that volunteers tolerated the maximum recommended doses well. Two other studies (16, 18) also reported no serious adverse events or systemic effects. The most frequent adverse events were rhinorrhea (57%) and nasal congestion (26%) that resolved within two hours after administration.

The studies described above (15, 16, 18) evaluated Kovanaze® in patients with carious lesions where there is potential variability in pain based on the depth of the cavity preparation and the length of the restorative procedure. A more objective way to determine local anesthetic success is with an electric pulp tester, which can be applied

over time with no harmful effects to the teeth (19, 20). No study has investigated the efficacy of a 3% tetracaine plus 0.05% oxymetazoline (Kovanaze®) nasal spray for maxillary pulpal anesthesia. Moreover, no investigation has determined patient preference for inducing maxillary dental local anesthesia with a nasal spray versus a traditional infiltration injection. Therefore, the purpose of this study was to determine the patient preference for and anesthetic efficacy of a 3% tetracaine plus 0.05% oxymetazoline (Kovanaze®) nasal spray in maxillary teeth.

Chapter 2: Materials and Methods

Subjects 18 years and older in good health (ASA classification I or II) as determined by a health history and oral questioning were included in the study. Subjects were excluded from the study if they were under 18 years of age, had an allergy to local anesthetics or oxymetazoline, a history of significant medical problems (ASA classification III or greater), recently taken CNS depressants (including alcohol or any analgesic medications), used a nasal spray or decongestant on the day of the appointment, nasopharyngeal obstructions, respiratory infections, sinusitis, or if they were pregnant, lactating, or unable to provide informed consent. Written informed consent, Health Insurance Portability and Accountability Act (HIPAA) authorization, and medical history were obtained from each subject. Approval for this study was obtained from the University Human Subjects Review Committee.

A total of 50 subjects, including 27 in the lateral incisor group and 23 in the first premolar group, received two different sets of anesthetic administration in two appointments spaced at least one week apart, in a single-blind crossover design. A random number table (random.org) determined the anesthetic to administer at each appointment and assigned the test tooth and anatomical side for each subject. The same

tooth and side randomly chosen for the first appointment was used again for the second appointment.

The test teeth were the maxillary lateral incisor and maxillary first premolar. The contra-lateral mandibular canine was used as the unanesthetized control to ensure that the electric pulp tester (EPT) (Analytic Technology Corp., Redmond, WA) was operating properly and that the subjects were responding appropriately during the experiment. At the beginning of the appointment and before any anesthetic administration, clinical examinations indicated that all test teeth were free of caries, large restorations, and periodontal disease, and that none had a history of trauma or sensitivity. The test teeth and control canine were then tested three times each with the EPT to record average baseline vitality. After isolating the tooth with cotton rolls and drying with gauze, toothpaste (Colgate Total®, Colgate-Palmolive Company, New York, NY) was applied to the EPT probe tip, which was placed midway between the gingival margin and the occlusal edge of the tooth being tested. The current rate on the EPT was set at 25 seconds to increase from no output (0) to the maximum output (80). The numeric read-out at initial sensation was recorded. All test teeth in the experiment were confirmed to be vital. Trained personnel who were blind to the sets of anesthetic administered performed all pre-injection and post-injection tests. Subjects were blindfolded during all real and mock anesthetic administrations.

At one visit, subjects received an initial administration of the Kovanaze® nasal spray (one spray delivered 0.2 mL of solution containing 6 mg tetracaine and 0.1 mg oxymetazoline; St. Renatus, Fort Collins, CO) inside the nostril on the ipsilateral side of

the test tooth. For all nasal sprays the contents of the atomizer syringe were expressed in 0.5 seconds or less and directed posteriorly in the sagittal plane, which created a plume of solution. The target deposition site for the first spray was the inferior meatus of the nose, which was achieved by aligning the spray syringe approximately perpendicular to an imaginary vertical line connecting the subject's nasion and subnasale. The first spray initiated the anesthetic administration protocol. Three minutes after the first spray, topical anesthetic (20% benzocaine, Patterson Brand Dental Supply, Inc., Mendota Heights, MN) was applied with a cotton tipped applicator to the mucosa in the facial vestibule at the apex of the test tooth.

Four minutes after the first spray, a second nasal spray (0.2 mL) of Kovanaze[®] was administered in the same nostril followed immediately by a mock infiltration injection. The target deposition site for the second Kovanaze[®] nasal spray was the middle meatus of the nose, which was achieved by aiming the spray syringe at a positive 45 degree angle. For the mock infiltration injection, a loaded anesthetic syringe with the needle cap remaining over the needle was placed at the apex of the test tooth with some pressure for 1 minute. Fourteen minutes after the first spray, a third nasal spray (0.2 mL) of Kovanaze[®] was administered in the same manner as the second spray if pulpal anesthesia (80 reading with the EPT) had not been achieved. The delivery of the second or third spray (if needed) concluded the anesthetic administration protocol. Pulp testing began ten minutes after the conclusion of the anesthetic administration protocol and continued every two minutes for one hour.

At the second appointment, the same subjects received two administrations of a placebo nasal spray (0.2 mL each of sterile 0.9% sodium chloride solution, Hospira; Central Ohio Compounding Pharmacy, Columbus, OH) via a syringe fitted with a Luer Lock intranasal spray nozzle tip (MAD Nasal™ Intranasal Mucosal Atomization Device, Teleflex, Morrisville, NC) and a traditional infiltration of 1.8 mL of 2% lidocaine with 1:100,000 epinephrine (Xylocaine®, Dentsply Pharmaceutical, York, PA) after the same topical anesthetic application, at the same target deposition sites, and following the same anesthetic administration protocol. To maintain blinding, a third administration of placebo spray was still given if pulpal anesthesia (80 reading with the EPT) had not been achieved fourteen minutes after the first nasal spray.

Ten minutes after the anesthetic administration protocol was concluded the depth of anesthesia of the test teeth was monitored with the EPT in 2-minute cycles for a period of 60 minutes. No response from the subject to the maximum output (no response at the 80 reading) of the pulp tester was used as the criterion for pulpal anesthesia. Anesthesia was considered successful when an 80 reading was obtained at time period zero, which was recorded ten minutes after the conclusion of the anesthetic administration protocol. The ten minute waiting period was based on the Kovanaze® manufacturer's instructions (37) and the reported ten minute onset time of tetracaine (21) rather than the 2-5 minute onset time of lidocaine (4-7) to maintain subject blinding. Onset and duration of local anesthesia were not quantified because this study followed the Kovanaze® manufacturer's instructions for use for both groups to maintain blinding (37).

Side effects from the nasal spray were documented. Prior to any anesthetic administration the subject was asked if, in general, they would prefer a nasal spray or a traditional shot to get their tooth numb and their answer was recorded. After each nasal spray administration the subject was asked to record any comments about the experience (Appendix F). Subjects were asked to document any persistent side effects from the nasal spray occurring that evening, at 24 hours, and at one week after each appointment. Side effects included drainage, nasal congestion, burning, pressure, sinus congestion, and pain. One week after the second appointment the subject was additionally asked which appointment they preferred and the reasons why.

Between-anesthetic administration differences in anesthetic success for each of the two test teeth were evaluated using logistic regression. With an alpha risk of 0.05 and assuming a null probability of anesthetic success of 0.62 (6), a sample size of 22 subjects would yield a power of 0.80 to demonstrate an odds ratio of 15.0 anesthetic success to failure. Comparisons were considered significant at $p < 0.05$.

Chapter 3: Results

Fifty subjects served as their own control and completed two anesthetic administration appointments: one for a nasal spray (3% tetracaine with 0.05% oxymetazoline) and a mock injection, and another for a mock nasal spray (saline) and an infiltration injection (2% lidocaine with 1:100,000 epinephrine), and responded to report any side-effects that occurred the evening of, 24 hours after, and 1 week after each appointment. Table 1 shows that 54% of the experimental teeth were maxillary lateral incisors and 46% were maxillary first premolars. Overall, 54% of the experimental teeth were on the left side and 46% were on the right side. The mean subject age was 26 years (± 3). The subject composition was 58% female and 42% male (Table 1).

Anesthetic success is presented in Table 2a and Table 2b. Local anesthesia was considered successful if the experimental tooth (maxillary lateral incisor or first premolar) achieved an 80/80 reading with the electric pulp tester at time period 0, which was recorded 10 minutes after the completion of the study anesthetic administration protocol, as dictated by the Kovanaze[®] administration protocol. Anesthetic success in the maxillary lateral incisor group was 37% for the Kovanaze[®] nasal spray and mock injection and 89% for the mock nasal spray and lidocaine injection ($p = 0.0001$). Anesthetic success in the maxillary first premolar group was 22% for the Kovanaze[®]

nasal spray and mock injection and 91% for the mock nasal spray and lidocaine injection ($p < 0.0001$). The mock nasal spray and lidocaine injection was calculated to be 15.7 times more likely to achieve successful pulpal anesthesia than the Kovanaze[®] nasal spray and mock injection for maxillary lateral incisors ($p = 0.0001$) with 95% confidence limits of 3.72 – 66.73. The mock nasal spray and lidocaine injection was calculated to be 37.8 times more likely to achieve successful pulpal anesthesia than the Kovanaze[®] nasal spray and mock injection for maxillary first premolars ($p < 0.0001$) with 95% confidence limits of 5.96 – 239.92.

Table 3 and Figure 1 demonstrate how, prior to participating in the study, more subjects (56% vs. 44%) preferred the nasal spray route of maxillary dental local anesthesia over the traditional infiltration injection. After experiencing both routes of administration, however, 100% of subjects preferred the infiltration injection route of maxillary dental local anesthesia.

As shown in Table 4, subjects reported more side effects and pain after the Kovanaze[®] nasal spray and mock injection appointment than after the mock nasal spray and lidocaine injection appointment. The most commonly reported side effects of the Kovanaze[®] nasal spray and mock injection the evening of the appointment were nasal drainage (86%), nasal congestion (80%), and nasal burning (64%), with a mean pain of 4/10 that evening. Few subjects (2-8%) reported side effects the evening of the mock nasal spray and lidocaine injection appointment, most commonly nasal drainage (8%) and nasal congestion (8%), but no pain was reported that evening. The most commonly reported side effects of the Kovanaze[®] nasal spray and mock injection 24 hours after the

appointment were nasal drainage (72%) and nasal congestion (66%), with a mean pain of 1/10 at 24 hours. Few subjects (0-4%) reported side effects 24 hours after the mock nasal spray and lidocaine injection appointment, most commonly nasal drainage (4%) and nasal congestion (4%), but no pain was reported at 24 hours. The most commonly reported side effects of the Kovanaze[®] nasal spray and mock injection 1 week after the appointment were nasal drainage (16%) and nasal congestion (16%), with no pain reported at one week. No subjects (0%) reported side effects or pain 1 week after the mock nasal spray and lidocaine injection appointment.

Table 5, Figure 2, and Figure 3 illustrate anesthetic efficacy via the percentage of 80/80 readings on the EPT. Anesthetic success was around 90% with the mock nasal spray and lidocaine injection for both the lateral incisor and first premolar groups at time period 0. However, the percentages of 80/80 readings with the Kovanaze[®] nasal spray and mock injection were 37% for the lateral incisor group and 22% for the first premolar group at time period 0, both of which declined more rapidly than the mock nasal spray and lidocaine injection.

The information presented in Table 6 and Figure 4 shows the percentage of 80/80 readings over time after administration of the Kovanaze[®] nasal spray and mock injection for the maxillary central incisor and canine. Overall percentages were initially between 50-70%, but rapidly declined. Subjects in the Kovanaze[®] nasal spray and mock injection group were noticing a more profound sensation of anesthesia toward the midline and, therefore, the central incisor and canine were pulp tested and their results were reported without a mock nasal spray and lidocaine injection comparison.

Chapter 4: Discussion

Subjects in the current study served as their own control and the anatomical side was randomized in the maxillary lateral incisor and first premolar groups. The subject population was generally composed of young adults (mean age 26 ± 3 years) (Table 1), so our results may not apply to all populations.

Most subjects (56%) reported an initial preference for the nasal spray route of maxillary dental local anesthesia (Table 3, Figure 1). This aversion to dental injections coincides with several other previous studies which have shown that between 10% and 59% of dental patients avoid their appointments because of needle-related anxiety or fear (1-3, 8). Even though the current study included responses from a population consisting mostly of dental students who are familiar with and exposed to needles almost daily, the initial preferences were still in favor of a needle-free administration. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (22) describes a specific phobia during which affected individuals often experience a syncopal episode triggered by blood, injections, and bodily injury. These needle-phobic patients are not receiving the level of dental care needed to maintain a healthy dentition (8, 22). Since these fears usually develop during childhood, needle-free products like Kovanaze® could presumably

resolve or even prevent a meaningful portion of dental anxiety and fear in the pediatric and adult populations.

The prevention of needlestick injuries is another benefit of developing a needle-free method for local anesthetic administration. Government organizations have implemented several pieces of legislation to prevent the occurrence of needlestick injuries and enhance the safety of dental offices for dentists, staff, and patients (9, 10). In one study (10), approximately 25% of reported injuries in dental offices were from anesthetic syringe needles and more than half could have been prevented with safer handling practices or re-capping systems. Another article (11) reviewed safe injection practices for dental local anesthesia in an effort to prevent iatrogenic injuries due to a poor understanding of normal head and neck anatomy. These articles are a reminder that local anesthetic needles have the potential to cause harm to the dentist, the staff, and the patient, and although these complications are rare, they could be minimized or eliminated if an effective needle-free alternative becomes available.

One potentially useful needle-free route of administering medications is with an intranasal spray. Two examples are Sprix[®] and FluMist[®], which are an NSAID (ketorolac) for moderate to severe postoperative pain and a trivalent cold-adapted influenza vaccine for the seasonal flu virus, respectively (12-14). Sprix[®] is an intranasal ketorolac tromethamine spray developed to address the side effects of opioids and decrease the length of hospital stays, thereby decreasing the overall impact of those burdens on the healthcare system. Pergolizzi et al. (12) found that patients are generally comfortable with intranasal sprays, as some have reported needle phobia or an aversion to

swallowing pills. Sprix[®] is effective because it is absorbed by the nasal mucosa and avoids the first pass metabolism of oral tablets. In a 4-year review of FluMist[®] (13) in children, the vaccine was considered safe with only occasional mild systemic side effects usually after the first dose. The goals when initially creating FluMist[®] were to find an ideal flu vaccine; one which improves patient compliance and is safe, efficacious, inexpensive, easy to use, and well-tolerated by patients (13, 14). FluMist[®] is not available at this time due to low clinical efficacy rather than unpleasant side effects, but current research and development will hopefully provide a new and improved nasally administered flu vaccine soon (23, 24). These same benefits and drawbacks may theoretically be applied to other intranasal drugs like Kovanaze[®], the subject of our current investigation.

Unfortunately, the apparent benefits of a needle-free route of administration may still be outweighed by the realistic drawbacks of that method, as discovered in the current study with the Kovanaze[®] nasal spray. We found that 100% of subjects preferred the infiltration injection for maxillary dental local anesthesia after experiencing both routes of administration (Table 3, Figure 1). One likely reason that all subjects preferred the injection after participating in the study was the high rate of side effects that were reported with the Kovanaze[®] nasal spray and mock injection (Table 4).

Previous studies (15-18, 21, 25-29) have evaluated the local and systemic side effects of an intranasal administration of tetracaine and oxymetazoline, the active ingredients in Kovanaze[®]. The most commonly reported local side effects were rhinorrhea, nasal congestion, and nasal discomfort and the less commonly reported local

side effects were oropharyngeal pain or irritation, headache, and lacrimation (15-18, 29). All local side effects resolved within a couple of hours, but in contrast to the current study, only one (17) followed up for an extended period of time (with a 24-hour phone call to record any adverse events). The otolaryngology study by Gaviola et al. (29) contrasts other investigations in that field because the authors administered an oxymetazoline nasal spray followed by nasal sprays of either 2% tetracaine or 4% lidocaine. Both anesthetic groups in that study experienced similar side effects, most commonly unpleasant taste (mean 2.4/10), globus sensation (mean 2/10), and pain/discomfort (mean 1.9/10). Similar side effects were reported in the current study, even though most otolaryngology studies applied a cotton pellet soaked in the local anesthetic formulation to the target tissues rather than a nasal spray. In addition to the side effects recorded in Table 3, subjects frequently recorded an unpleasant taste, stinging of the nasal passages, throat numbness, and lacrimation immediately following the administration. Three subjects (6%) reported nose bleeds 24-48 hours after administration of the Kovanaze[®] nasal spray and mock injection.

There are two drugs administered that could have caused these reported side effects: tetracaine and oxymetazoline. Tetracaine is an amino-ester local anesthetic (30, 31). As for systemic toxicity, tetracaine has received some negative attention likely because the maximum recommended dose varies with the route of administration. Most otolaryngologists (21, 25-29) prefer tetracaine for local anesthesia during endoscopic and surgical procedures because it anesthetizes the deeper submucosal tissues better and for longer than other local anesthetics. The ability to penetrate into the deeper tissues could

be one reason tetracaine was used in Kovanaze[®] to anesthetize the maxillary dentition. However, tetracaine is potent and when applied to mucosal membranes, the drug can reach blood levels similar to those seen with an intravenous injection, even when a vasoconstrictor is added (25). According to Adriani and Campbell (25), most adverse events occurred with inexperienced clinicians administering more than 160 mg of tetracaine. These authors (25) still argued that tetracaine can be a safe and useful drug for infiltrations as long as the recommended maximum dose of 100 mg is not exceeded. A more recent article (28) defined the safe dosages for tetracaine to be 20 mg if applied to mucosal membranes and 200 mg if administered as an infiltration injection. According to the manufacturer of Kovanaze[®], each of the 0.2 mL sprays contained 6 mg of tetracaine and 0.1 mg of oxymetazoline (32). In the current study the maximum dosage of tetracaine administered was therefore 18 mg, which follows the recommendation of Davis and Channick (28). The only significant systemic finding from the phase 2 trial of the Kovanaze[®] nasal spray for dentistry (15) was an increase in diastolic blood pressure. In another dental study (17) of the cardiovascular effects and pharmacokinetics of Kovanaze[®], slight increases in diastolic blood pressure, slight decreases in heart rate, and no clinically relevant blood changes occurred over the two-hour period. It is worth noting that these dental studies were funded, at least partially, by St. Renatus. Dr. Ciancio is a member of the St. Renatus Scientific Advisory Council and Drs. Hutcheson and Moore are consultants employed by St. Renatus, while the current study was independently funded.

Oxymetazoline is an alpha-receptor agonist (31, 33, 34) for nasal decongestion and peripheral vasoconstriction. Oxymetazoline is combined with tetracaine in Kovanaze[®] for dental procedures and other local anesthetics for otolaryngology procedures to compensate for the vasodilatory effects of the local anesthetic (36). Previous publications have reported the side effects of tetracaine and oxymetazoline combined and as individual components (18, 31, 32, 35). According to Ciancio et al. (18), the combination 3% tetracaine plus 0.05% oxymetazoline caused more nasal discomfort (25% vs. 11%) than tetracaine alone, while tetracaine alone had more procedural pain, toothache, and congestion in the clinical study. These findings support the idea that adding oxymetazoline to tetracaine improves the local anesthetic effect, but also illustrate how oxymetazoline can make the administration much more unpleasant than administering tetracaine alone. One example of a plain 0.05% oxymetazoline intranasal spray is the over-the counter nasal decongestant Afrin[®]. Side effects of Afrin[®] can include temporary discomfort such as burning, stinging, sneezing, or increased nasal discharge (35). Another author (31) described the side effects of an intranasal oxymetazoline spray to include dryness or stinging of the nasal passages, headaches, heart palpitations, and insomnia. One editorial (36) explains that oxymetazoline can have even more serious side effects such as hypertensive crisis. These reports demonstrate how it is very possible that the adverse local side effects experienced with Kovanaze[®] were due to the oxymetazoline in the solution rather than the tetracaine.

Onset of local anesthesia was not measured in the current study because we followed the Kovanaze[®] Instructions for Use for both groups to maintain subject blinding

(37). St. Renatus recommends waiting 10 minutes after the second and third nasal sprays (37) before performing a “test drill,” presumably because the reported onset time for a tetracaine nasal spray is 10 minutes (21) while the reported onset time for an oxymetazoline nasal spray is only a few seconds (34). When using tetracaine and oxymetazoline for local anesthesia, otolaryngologists also typically wait 10 minutes prior to beginning their endoscopic procedures (26, 27, 38). The higher pKa of tetracaine compared to lidocaine (8.4 vs. 7.8) also indicates waiting a longer time to allow for local anesthetic onset (30, 31). With these considerations in mind, time period 0 was recorded 10 minutes after the completion of the anesthetic administration protocol in the current study. Since the administration protocol required potentially delivering a third spray if the experimental tooth was not numb 10 minutes after the second spray, time period 0 occurred at either 14 minutes or 24 minutes after the initial spray depending on whether 2 sprays or 3 sprays, respectively, were necessary. During the Kovanaze[®] nasal spray and mock injection appointment, 82% of subjects in the lateral incisor group and 83% of subjects in the first premolar group required 3 sprays. During the mock nasal spray and lidocaine injection appointment, 11% of subjects in the lateral incisor group and 13% of subjects in the first premolar group received 3 sprays of saline. From a clinical standpoint, choosing to deliver local anesthesia for maxillary teeth with the Kovanaze[®] nasal spray will require a longer appointment more often than choosing a traditional infiltration injection as onset time for a maxillary infiltration is typically around 2-5 minutes (4-7). Some needle-phobic patients may accept the longer appointment time,

however, and the dentist will need to weigh the costs and benefits of providing Kovanaze® in his or her practice.

Duration of local anesthesia can be defined as ending when the last of two consecutive 80 readings is recorded with an electric pulp tester (19, 20). However, in the current study we could not determine the true duration of local anesthesia because time period 0 varied as dictated by the anesthetic administration protocol previously described. As a general observation, pulpal anesthesia was around 90% with the mock nasal spray and lidocaine injection for both the lateral incisor and first premolar groups at time period 0 (Table 5, Figure 2, Figure 3). In contrast, pulpal anesthesia with the Kovanaze® nasal spray and mock injection was 37% for the lateral incisor group and 22% for the first premolar group at time period 0, both of which declined more rapidly than the mock nasal spray and lidocaine injection (Figure 2, Figure 3). Several authors have published articles that may explain the difference in the observed local anesthetic duration between the local anesthetic groups (4, 39, 40). Nusstein et al. (5) have explained that after an infiltration injection there is a bolus of anesthetic solution retained within the submucosal tissue near the apex of the tooth which replenishes the site and prolongs the local anesthesia. After an intranasal spray the solution is free to diffuse throughout the nasal passages and maxillary sinus, potentially migrating away from the targeted site (39). Fowler et al. (40) examined the collateral local anesthesia of adjacent teeth after an infiltration injection of the maxillary lateral incisors and first molars and found that those adjacent teeth usually achieved lower anesthetic success, except for the second molar which achieved higher anesthetic success than the intended first molar tooth. Even

though adjacent teeth become anesthetized, dental infiltration injections of 1.8 mL of solution are typically meant to anesthetize a single tooth. In contrast, the maximum dose (3 sprays) of the Kovanaze[®] nasal spray is only 0.6 mL of solution and is intended to anesthetize 4 teeth (maxillary central incisor through first premolar). Moreover, the targeted space for the administration of the Kovanaze[®] nasal spray (the maxillary sinus) is much larger than the submucosal tissues targeted during an infiltration injection. The combination of using a small volume of local anesthetic and administering into a large space is a possible explanation for the poor duration and success of local anesthesia observed in the Kovanaze[®] nasal spray and mock injection group.

As determined by electric pulp tester readings, anesthetic success between the treatment and control groups was significantly different for both tooth groups (Table 2a, Table 2b). In the maxillary lateral incisor group, the Kovanaze[®] nasal spray and mock injection was less successful than the mock nasal spray and lidocaine injection (37% vs. 89%); the mock nasal spray and lidocaine injection was 15.7 times more likely to achieve successful pulpal anesthesia than the Kovanaze[®] nasal spray and mock injection. In the maxillary first premolar group, the Kovanaze[®] nasal spray and mock injection was also less successful than the mock nasal spray and lidocaine injection (22% vs. 91%); the mock nasal spray and lidocaine injection was 37.8 times more likely to achieve successful pulpal anesthesia than the Kovanaze[®] nasal spray and mock injection. To be thorough, electric pulp testing was also performed and reported for the central incisor and canine (Table 6, Figure 4) in the Kovanaze[®] nasal spray and mock injection group because subjects were describing a more profound sensation of anesthesia toward the

midline. Pulpal anesthesia after administration of the Kovanaze® nasal spray and mock injection for the maxillary central incisor and canine (Table 6, Figure 4) was initially between 50-70%, but rapidly declined. Even though the central incisor and canine achieved a higher anesthetic success than the study teeth with the Kovanaze® nasal spray and mock injection, the success was still not high enough to ensure reliable pulpal anesthesia.

Overall, pulpal anesthesia for any given tooth with the Kovanaze® nasal spray is not as predictable as a lidocaine injection. Three sprays of Kovanaze® costs approximately \$60, takes about 24 minutes to administer, has persistent side effects, and works less than 50% of the time. In contrast, an infiltration of lidocaine costs approximately \$1, takes about 5 minutes to administer, has minimal side effects, and works more than 90% of the time. The major advantage of the nasal spray is that there is no needle and the major disadvantage of the injection is that there is a needle. In addition to these costs and benefits, the clinician will also need to consider his or her patient's level of fear, anxiety, and other contraindications to needle-based anesthesia before offering Kovanaze® in his or her dental practice.

One reason for the low anesthetic success of Kovanaze® in the current study (22%-71%) compared to previous studies (74%-100%) could be the variety of definitions used for anesthetic success (15, 16, 18). The other clinical studies (15, 16, 18) considered local anesthesia successful if the subject tolerated a restorative dental procedure without requesting a rescue anesthetic injection, but these restorations involved carious lesions where there is variability in pain based on the depth of the cavity preparation and the

length of the procedure. A more objective way to determine pulpal anesthesia is with an electric pulp tester (19, 20). Recent reviews of Kovanaze® (39, 41) have concluded that more studies will be needed to determine anesthetic success during “more invasive” dental procedures such as endodontic therapy. With the current study’s use of an electric pulp tester, we have answered their call for an investigation of the efficacy of Kovanaze® for maxillary pulpal anesthesia. In the phase 2 clinical trial (15) involving a restorative dental procedure, success with the 3% tetracaine plus 0.05% oxymetazoline nasal spray was 83% and success with the lidocaine injection was 93%, defined as none or mild pain during the procedure. The success rate increased to 90% if the molars were excluded from the study, but the sample size was small. In a follow-up restorative clinical trial (18), procedural success with a 3% tetracaine plus 0.05% oxymetazoline nasal spray was 100% in the anterior teeth and 74% in the premolars. Another restorative dentistry clinical trial (16) achieved procedural success 88% of the time with a 3% tetracaine plus 0.05% oxymetazoline nasal spray. Similar to previous studies (4-7, 15), the current study showed that anesthetic success with the mock nasal spray and lidocaine injection was 89% and 91% for the lateral incisor and first premolar groups, respectively. However, anesthetic success for the Kovanaze® nasal spray and mock injection in both tooth groups in the current study are greatly different from the previous studies.

The target deposition sites for the first and second nasal sprays were the inferior and middle meati of the nose, respectively. It is important to note that the technique for properly aiming the Kovanaze® nasal spray syringe to reach the target sites is sensitive. As previously explained, the manufacturer describes very specific three-dimensional

directions for administering the atomized solution (37). Even if all of those instructions are followed, each subject's nasal cavity has a slightly different morphology and the atomized plume of local anesthetic solution may still condense along the nasal wall rather than reach the maxillary sinus in mist form as intended. Upon reaching the inferior and middle meati of the nose, Kovanaze[®] bathes the anterior wall and floor of the maxillary sinus, penetrates the Schneiderian membrane and/or bony cortex there, and anesthetizes the anterior and middle superior alveolar (ASA and MSA) nerves before they reach the anterior and premolar tooth apices. Several authors have documented the variable course and presence of the superior alveolar nerves in the maxillary sinus (41-45). The superior alveolar nerves branch from the infraorbital nerve and usually travel within bony canals along the roof, anterior, posterior, and lateral walls of the maxillary sinus, but occasionally travel just below the Schneiderian membrane, before forming the superior dental plexus housed within the maxillary bone (43, 45). The posterior superior alveolar (PSA) and ASA nerves are always present, but the MSA nerve is only present 37-82% of the time (42-44). When the MSA nerve is absent, pulpal innervation to the maxillary premolars is provided by a plexus of nerve branches from both the PSA and ASA nerves.

Hersh et al. (41) cited the absence of the MSA nerve to explain the 60-66% success rate of the 3% tetracaine plus 0.05% oxymetazoline nasal spray during restorative procedures on second premolars. In the current study, one might explain that the poor anesthetic success rate of the Kovanaze[®] nasal spray and mock injection in first premolars (22%) is because the MSA nerve is frequently absent and also not traveling along the anterior wall of the maxillary sinus 75% of the time (42). However, anesthetic

success was also fairly low in the anterior teeth (37-71%), which are supplied by a nerve most authors have agreed is present in the anterior portion of the maxillary sinus 100% of the time (42-44). Since pulpal anesthesia was 89-91% successful with the mock nasal spray and lidocaine injection in the current study, there must be another reason to explain the difference in success between the two routes of local anesthetic administration. The answer may be related to whether the superior alveolar nerve (ASA or MSA) or the superior dental plexus of nerves is anesthetized. An ASA or MSA nerve block with the Kovanaze[®] nasal spray may be ineffective because the solution has to be administered correctly, enter the maxillary sinus, remain at the site, and penetrate the bony cortex (in most cases) housing the ASA or MSA nerves. Alternatively, an infiltration injection is more successful because it deposits a solution near the apices of the teeth near the superior dental plexus to create a bolus of solution which is retained at the site. The buccal cortical plate is only 0.7-1.8 mm thick (46), so during an infiltration injection the local anesthetic is deposited very close to the apices of the teeth. In contrast, the first premolar apices are 8-9 mm from the sinus floor (46) and the anterior tooth apices are 19 mm from the nasal floor (47). The local anesthetic in an infiltration injection therefore would have to travel a much shorter distance to reach the apices of the teeth than a Kovanaze[®] nasal spray which is administered into the maxillary sinus.

One issue we encountered was that Kovanaze[®] became unavailable at the end of the study; it is still unavailable at the time of this manuscript. If the product becomes available again as the St. Renatus representative states, future studies could include a pediatric population, as children generally do not tolerate needles as well as adults. In

addition, the local anesthetic effects of Kovanaze[®] on palatal soft tissues could be evaluated for use prior to palatal injections and surgical procedures. In conclusion, the 3% tetracaine plus 0.05% oxymetazoline (Kovanaze[®]) nasal spray and mock injection was less preferable, caused more side effects, and had significantly less anesthetic success than the mock nasal spray and 2% lidocaine with 1:100,000 epinephrine injection in maxillary lateral incisors and first premolars.

Chapter 5: Summary and Conclusions

Unfortunately, the 3% tetracaine plus 0.05% oxymetazoline nasal spray (Kovanaze[®]) did not work as well as we had anticipated when compared to a traditional 2% lidocaine with 1:100,000 epinephrine infiltration injection for maxillary local anesthesia. A major drawback to the study drug was the persistent side effects reported by subjects, sometimes lasting for a week or more. It would have been beneficial to the dental patient population to be able to confirm and support the efficacy of a needle-free alternative to our traditional local anesthetic administration techniques.

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Appendix A: Tables

Table 1: Subject Demographics

a.

	Lateral Incisor	First Premolar	Total
Number (n)	27/50 (54%)	23/50 (46%)	50
Side (Right/Left)	R: 14/27 (52%) L: 13/27 (48%)	R: 9/23 (39%) L: 14/23 (61%)	R: 23/50 (46%) L: 27/50 (54%)
Age (Years)	26 ± 4	26 ± 2	26 ± 3
Sex (Male/Female)	M: 11/27 (41%) F: 16/27 (59%)	M: 10/23 (43%) F: 13/23 (57%)	M: 21/50 (42%) F: 29/50 (58%)

b.

Subject Demographics	
Side (Right/Left)	R: 23/50 (46%) L: 27/50 (54%)
Tooth (Lat/Pre)	Lat: 27/50 (54%) Pre: 23/50 (46%)
Age (Years)	26 ± 3
Sex (Male/Female)	M: 21/50 (42%) F: 29/50 (58%)

Table 2: Anesthetic Success

a.

Lateral Incisor						
	Group			Outcome	n	%
	Kovanaze® Spray/Mock Injection			Success	10/27	37
	Kovanaze® Spray/Mock Injection			Failure	17/27	63
	Mock Spray/Lidocaine Injection			Success	24/27	89
	Mock Spray/Lidocaine Injection			Failure	3/27	11
Comparison				Odds Ratio	95% Confidence Limits	
Mock Spray/Lidocaine Injection vs. Kovanaze® Spray/Mock Injection				15.7	3.72 – 66.73	
	Type III Tests of Fixed Effects					
	Effect	Num DF	Den DF	Chi-Square	Pr > ChiSq	
	Group	1	51	14.68	0.0001	

b.

First Premolar						
	Group			Outcome	n	%
	Kovanaze® Spray/Mock Injection			Success	5/23	22
	Kovanaze® Spray/Mock Injection			Failure	18/23	78
	Mock Spray/Lidocaine Injection			Success	21/23	91
	Mock Spray/Lidocaine Injection			Failure	2/23	9
Comparison				Odds Ratio	95% Confidence Limits	
Mock Spray/Lidocaine Injection vs. Kovanaze® Spray/Mock Injection				37.8	5.96 – 239.92	
	Type III Tests of Fixed Effects					
	Effect	Num DF	Den DF	Chi-Square	Pr > ChiSq	
	Group	1	43	15.71	<.0001	

Table 3: Subject Anesthesia Preference

	Before Study	After Study
Spray	28/50 (56%)	0
Injection	22/50 (44%)	50/50 (100%)

Table 4: Nasal Spray Follow-up Side Effects

	Evening	24 hours	1 week
Drainage			
Kovanaze® Spray/Mock Injection	43/50 (86%)	36/50 (72%)	8/50 (16%)
Mock Spray/Lidocaine Injection	4/50 (8%)	2/50 (4%)	0
Nasal Congestion			
Kovanaze® Spray/Mock Injection	40/50 (80%)	33/50 (66%)	8/50 (16%)
Mock Spray/Lidocaine Injection	4/50 (8%)	2/50 (4%)	0
Burning			
Kovanaze® Spray/Mock Injection	32/50 (64%)	7/50 (14%)	0
Mock Spray/Lidocaine Injection	1/50 (2%)	1/50 (2%)	0
Pressure			
Kovanaze® Spray/Mock Injection	24/50 (48%)	12/50 (24%)	1/50 (2%)
Mock Spray/Lidocaine Injection	3/50 (6%)	0	0
Sinus Congestion			
Kovanaze® Spray/Mock Injection	17/50 (34%)	11/50 (22%)	3/50 (6%)
Mock Spray/Lidocaine Injection	1/50 (2%)	0	0
Pain 1-10 (Mean, n=50)			
Kovanaze® Spray/Mock Injection	4	1	0
Mock Spray/Lidocaine Injection	0	0	0

Table 5: Percent 80/80 with Kovanaze® vs. Lidocaine

Time Period	Lateral Incisor		First Premolar	
	Kovanaze®	Lidocaine	Kovanaze®	Lidocaine
0	10/27 (37%)	24/27 (89%)	5/23 (22%)	21/23 (91%)
1	8/27 (30%)	22/27 (81%)	5/23 (22%)	21/23 (91%)
2	8/27 (30%)	24/27 (89%)	5/23 (22%)	21/23 (91%)
3	7/27 (26%)	23/27 (85%)	3/23 (13%)	21/23 (91%)
4	8/27 (30%)	23/27 (85%)	3/23 (13%)	20/23 (87%)
5	8/27 (30%)	23/27 (85%)	1/23 (4%)	21/23 (91%)
6	6/27 (22%)	23/27 (85%)	1/23 (4%)	21/23 (91%)
7	7/27 (26%)	23/27 (85%)	0	21/23 (91%)
8	4/27 (15%)	22/27 (81%)	0	19/23 (83%)
9	4/27 (15%)	21/27 (78%)	0	20/23 (87%)
10	3/27 (11%)	20/27 (74%)	0	18/23 (78%)
11	3/27 (11%)	17/27 (63%)	0	17/23 (74%)
12	1/27 (4%)	15/27 (56%)	0	16/23 (70%)
13	1/27 (4%)	16/27 (59%)	0	15/23 (65%)
14	1/27 (4%)	14/27 (52%)	0	13/23 (57%)
15	1/27 (4%)	14/27 (52%)	0	12/23 (52%)
16	1/27 (4%)	10/27 (37%)	0	13/23 (57%)
17	1/27 (4%)	10/27 (37%)	0	12/23 (52%)
18	1/27 (4%)	8/27 (30%)	0	9/23 (39%)
19	1/27 (4%)	8/27 (30%)	0	9/23 (39%)
20	1/27 (4%)	7/27 (26%)	0	8/23 (35%)
21	1/27 (4%)	7/27 (26%)	0	8/23 (35%)
22	0	4/27 (15%)	0	5/23 (22%)
23	0	5/27 (19%)	0	5/23 (22%)
24	0	5/27 (19%)	0	6/23 (26%)
25	0	4/27 (15%)	0	5/23 (22%)
26	0	3/27 (11%)	0	3/23 (13%)
27	0	4/27 (15%)	0	3/23 (13%)
28	0	3/27 (11%)	0	3/23 (13%)
29	0	3/27 (11%)	0	2/23 (9%)
30	0	3/27 (11%)	0	1/23 (4%)

Table 6: Percent 80/80 with Kovanaze®

Time period	Central Incisor	Canine
0	25/45 (56%)	32/45 (71%)
1	24/45 (53%)	29/45 (64%)
2	22/45 (49%)	30/45 (67%)
3	25/45 (56%)	28/45 (62%)
4	24/45 (53%)	27/45 (60%)
5	23/45 (51%)	28/45 (62%)
6	21/45 (47%)	25/45 (56%)
7	21/46 (46%)	22/45 (49%)
8	21/46 (46%)	20/45 (44%)
9	20/46 (43%)	20/45 (44%)
10	19/46 (41%)	18/45 (40%)
11	17/46 (37%)	15/45 (33%)
12	15/46 (33%)	16/46 (35%)
13	13/46 (28%)	14/46 (30%)
14	13/46 (28%)	15/46 (33%)
15	12/46 (26%)	12/46 (26%)
16	12/46 (26%)	12/46 (26%)
17	11/46 (24%)	12/46 (26%)
18	10/46 (22%)	11/46 (24%)
19	8/46 (17%)	10/46 (22%)
20	7/46 (15%)	8/46 (17%)
21	7/46 (15%)	7/46 (15%)
22	6/46 (13%)	6/46 (13%)
23	5/46 (11%)	5/46 (11%)
24	5/46 (11%)	5/46 (11%)
25	6/46 (13%)	5/46 (11%)
26	4/46 (9%)	3/46 (7%)
27	3/46 (7%)	2/46 (4%)
28	2/46 (4%)	1/46 (2%)
29	2/46 (4%)	2/46 (4%)
30	2/46 (4%)	1/46 (2%)

Appendix B: Figures

Figure 1: Subject Anesthesia Preference

Figure 2: Percent 80/80 over Time for Lateral Incisors

Figure 3: Percent 80/80 over Time for First Premolars

Figure 4: Percent 80/80 with Kovanaze® for Adjacent Teeth

Appendix C: Medical History Form

The Ohio State University
College of Dentistry

FORM 1/87

Patient Name _____
Date _____
Date of Birth _____

Medical Information

Biographical Data _____

Chief Complaint (Why is the patient seeking dental care?) _____

Present Illness (History of Chief Complaint) _____

MEDICAL HISTORY

1. Do you have or have you had any of the following?

a. rheumatic fever or rheumatic heart disease.....	NO	YES
b. heart murmur or mitral valve prolapse.....	NO	YES
c. heart disease/heart attack.....	NO	YES
d. artificial heart valve.....	NO	YES
e. irregular heart beat.....	NO	YES
f. pacemaker.....	NO	YES
g. high blood pressure.....	NO	YES
h. chest pains or angina.....	NO	YES
i. stroke.....	NO	YES
j. artificial joint.....	NO	YES
k. hepatitis/liver disease.....	NO	YES
l. tuberculosis (TB).....	NO	YES
m. thyroid trouble.....	NO	YES
n. kidney disease.....	NO	YES
o. diabetes (sugar).....	NO	YES
p. asthma.....	NO	YES
q. HIV or other immunosuppressive disease.....	NO	YES
r. radiation or cancer therapy.....	NO	YES

2. Do you have or have you had any disease, condition, or problem not listed here? NO YES

3. Have you ever been hospitalized? NO YES

4. Have you had excessive or prolonged bleeding requiring special treatment? NO YES

5. Have you had an allergic reaction to any drugs or medications?
(Circle all that apply: penicillin; codeine; aspirin; anesthetics; other) NO YES

6. Are you currently under the care of a physician (M.D., D.O.)? NO YES

When were you last seen by a physician? _____
Name of Physician _____
Street address _____
City, State, and Zip Code _____
Phone _____

7. Are you pregnant or nursing? Estimated Date of Delivery _____ NO YES

8. Have you had any trouble associated with previous dental treatment? NO YES

9. Do you have any lumps or sores in your mouth now? NO YES

10. Do you smoke or use smokeless tobacco? NO YES

11. How often do you have dental check ups? _____ Date of last Exam _____

12. Are you currently taking any drugs or medications
(such as antibiotics, heart medicine, birth control pills?)..... NO YES

CURRENT MEDICATIONS

Trade Name	Generic Name	Dose/Frequency	Reason

I have reviewed the information I have provided, and to the best of my knowledge it is correct and complete.

Patient/Guardian Signature _____ Date: _____

SUMMARY OF PATIENT'S MEDICAL STATUS: _____

MEDICAL RISK ASSESSMENT (check one)

- ☐ ASA I (healthy individual) ☐ ASA III (severe disease but not incapacitating)
☐ ASA II (mild systemic disease) ☐ ASA IV (incapacitating systemic disease, constant threat to life)

MEDICAL CONSULTATION REQUIRED

- ☐ No (healthy and/or stabilized disease)
☐ Yes (ASA III or IV; cardiac murmur; vague hx; recent major disease; recent diagnosis/operation; uncontrolled disease; blood pressure; etc.)

Does the chief complaint require emergency treatment?..... NO YES

_____ Student / I.D.# _____ Instructor / I.D.# / / Date

Appendix D: Consent Form

The Ohio State University Consent to Participate in Research

Study Title: Anesthetic efficacy of intranasal 3% tetracaine plus 0.05% oxymetazoline (Kovanaze) in maxillary teeth

Principal Investigator: Dr. Melissa Drum

Sponsor: Division of Endodontics

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

The purpose of this study is to see if a nose spray that numbs upper teeth works the same, better, or worse than a normal numbing shot.

2. How many people will take part in this study?

Up to one hundred and fifty (150) people will take part in this study.

3. What will happen if I take part in this study?

In this study you will get a tooth-numbing shot and a tooth-numbing nose spray. The tooth will be either an upper (maxillary) right or left front tooth (lateral incisor) OR an upper right or left back tooth (first premolar), decided at random. You will also be given the option of participating for both teeth, in which case we will randomly determine which tooth is tested first. For each tested tooth you will have two appointments spaced at least one week apart. In the first appointment you will complete this consent form, a HIPAA authorization, and a medical history form followed by tooth testing with an electric pulp tester. This battery-operated device sends a small current through the tooth to excite the nerve. You will experience a warming, tingling, or painful feeling in the tooth that can last up to one second. Then you will receive either a numbing nose spray (Kovanaze; 3% tetracaine plus 0.05% oxymetazoline) with a fake shot (mock injection) OR a non-numbing nose spray (saline placebo) with a real shot (infiltration with 2% lidocaine with 1:100,000 epinephrine). Kovanaze is a mix of a numbing medicine (local anesthetic) commonly used by medical doctors (otolaryngologists) and an over-the-counter nose spray (Afrin). Before the shot, numbing gel (20% benzocaine) will be put on the gums. You will be blindfolded only while you receive the nose spray and shot so you do not know which one you are getting. The assistant testing the tooth will not know which medicine you get. However, your doctor will know what medicine you get. The tooth plus a lower (mandibular) control tooth on the opposite side will be tested with the electric pulp tester every 2 minutes for a total of 60 minutes. In the second appointment you will get a shot and nose spray on the same tooth, but with the opposite medicine.

4. How long will I be in the study?

You will have two appointments spaced at least one week apart, which will last approximately 75 minutes each (15 minutes for paperwork and numbing, and 60 minutes of pulp testing) per test tooth. If you decide to participate for both test teeth then you will have four appointments lasting 75 minutes each spaced at least one week apart.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

You may have pain associated with the numbing solution (local anesthetic) or soreness at the site of the shots (injections) for approximately two days. Where you receive the injection, you may have some swelling, or a bruise (hematoma) may develop. You may experience a feeling of anxiety, lightheadedness or fainting, and/or a temporary increase in your heart rate. The tingling sensation and/or slight pain (discomfort) produced by the pulp tester may be uncomfortable to you. You may have some itching or hives (allergic reaction, very rare) to the local anesthetic, or have an unexpected infection (rare) which could result in permanent nerve damage. You may have soreness of your gum tissue for a few days after the injection. More common reactions with Kovanaze include runny nose, stuffy nose, sore nose, throat pain, and watery eyes. If you are a woman able to have children, you will be questioned regarding pregnancy or suspected pregnancy and will not be allowed to participate if you are pregnant, suspect a pregnancy, trying to become pregnant, or nursing. Additionally, you will be required to take a urine pregnancy test before you can start this study. The reason for excluding pregnant or potentially pregnant women is an attempt to minimize this population in the study because the potential risks to the fetus and nursing baby are unknown. There are no adequate and well-controlled studies of lidocaine or Kovanaze in pregnant women. This test will be paid for by the investigator.

7. What benefits can I expect from being in the study?

You will not directly benefit from this study. Society may ultimately benefit from this nose spray by having a different option than a shot.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled. No dental treatment will be done, so no other choices are available.

9. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

You may also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form if the study involves the use of your protected health information.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

10. What are the costs of taking part in this study?

The study will pay for the cost of the study drug (lidocaine and Kovanaze) and urine pregnancy test. You may need to pay for parking while participating in the study.

11. Will I be paid for taking part in this study?

After completing the first appointment you will receive \$20 in cash. You will be paid \$30 in cash at the end of the second appointment, which equals a total of \$50 for completing all aspects of the study. If you choose to participate in the

study for the second tooth, you will be paid \$20 in cash for the first appointment and \$30 in cash for the second appointment for that tooth. This equals a grand total of \$100 in cash for participating in the study for both teeth. By law, payments to subjects are considered taxable income.

12. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

13. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact Dr. Melissa Drum or Dr. Jeremy Capetillo at 614 292-3596

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the

research team, you may contact Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact Dr. Melissa Drum or Dr. Jeremy Capetillo at 614 292-3596

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form.

_____ Printed name of subject	_____ Signature of subject
	_____ Date and time
	AM/PM
_____ Printed name of person authorized to consent for subject (when applicable)	_____ Signature of person authorized to consent for subject (when applicable)
_____ Relationship to the subject	_____ Date and time
	AM/PM

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

_____ Printed name of person obtaining consent	_____ Signature of person obtaining consent
	_____ Date and time
	AM/PM

Witness(es) - *May be left blank if not required by the IRB*

_____ Printed name of witness	_____ Signature of witness
	_____ Date and time
	AM/PM

_____ Printed name of witness	_____ Signature of witness
	_____ Date and time
	AM/PM

Appendix E: HIPAA Privacy Form

**THE OHIO STATE UNIVERSITY
AUTHORIZATION TO USE
PERSONAL HEALTH INFORMATION IN RESEARCH**

**Title of the Study: Anesthetic efficacy of intranasal 3% tetracaine plus 0.05%
oxymetazoline (Kovanaze) in maxillary teeth**

OSU Protocol Number: 2016H0424

Principal Investigator: Dr. Melissa Drum

Subject Name _____

Before researchers use or share any health information about you as part of this study, The Ohio State University is required to obtain your authorization. This helps explain to you how this information will be used or shared with others involved in the study.

- The Ohio State University and its hospitals, clinics, health-care providers and researchers are required to protect the privacy of your health information.
- You should have received a Notice of Privacy Practices when you received health care services here. If not, let us know and a copy will be given to you. Please carefully review this information. Ask if you have any questions or do not understand any parts of this notice.
- If you agree to take part in this study your health information will be used and shared with others involved in this study. Also, any new health information about you that comes from tests or other parts of this study will be shared with those involved in this study.
- Health information about you that will be used or shared with others involved in this study may include your research record and any health care records at the Ohio State University. For example, this may include your medical records, x-ray or laboratory results. Psychotherapy notes in your health records (if any) will not, however, be shared or used. Use of these notes requires a separate, signed authorization.
- Please read the information carefully before signing this form. Please ask if you have any questions about this authorization, the University's Notice of Privacy Practices or the study before signing this form.

Initials/Date: _____

Those Who May Use, Share And Receive Your Information As Part Of This Study

- Researchers and staff at The Ohio State University will use, share and receive your personal health information for this research study. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information. If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician's office records.
- Those who oversee the study will have access to your information, including:
 - Members and staff of the Ohio State University's Institutional Review Boards, including the Western Institutional Review Board
 - The Office for Responsible Research Practices
 - University data safety monitoring committees
 - The Ohio State University Research Foundation
- Your health information may also be shared with federal and state agencies that have oversight of the study or to whom access is required under the law. These may include:
 - The Food and Drug Administration
 - The Office for Human Research Protections
 - The National Institutes of Health
 - The Ohio Department of Job and Family Services

These researchers, companies and/or organization(s) outside of The Ohio State University may also use, share and receive your health information in connection with this study:

- None

The information that is shared with those listed above may no longer be protected by federal privacy rules.

Initials/Date_____

Authorization Period

This authorization will not expire unless you change your mind and revoke it in writing. There is no set date at which your information will be destroyed or no longer used. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

Signing the Authorization

- You have the right to refuse to sign this authorization. Your health care outside of the study, payment for your health care, and your health care benefits will not be affected if you choose not to sign this form.
- You will not be able to take part in this study and will not receive any study treatments if you do not sign this form.
- If you sign this authorization, you may change your mind at any time. Researchers may continue to use information collected up until the time that you formally changed your mind. If you change your mind, your authorization must be revoked in writing. To revoke your authorization, please write to:

Dr. Melissa Drum at the College of Dentistry, 305 W. 12th Avenue, The Ohio State University, Columbus, Ohio 43210 or Dr. Henry Fischbach at the College of Dentistry, 305 W. 12th Avenue, The Ohio State University, Columbus, Ohio 43210

- Signing this authorization also means that you will not be able to see or copy your study-related information until the study is completed. This includes any portion of your medical records that describes study treatment.

Contacts for Questions

- If you have any questions relating to your privacy rights, please contact Dr. Henry Fischbach at the College of Dentistry, 305 W. 12th Avenue, The Ohio State University, Columbus, Ohio 43210.
- If you have any questions relating to the research, please contact Dr. Melissa Drum at the College of Dentistry, 305 W. 12th Avenue, The Ohio State University, Columbus, Ohio 43210.

Signature

I have read (or someone has read to me) this form and have been able to ask questions. All of my questions about this form have been answered to my satisfaction. By signing below, I permit Dr. John Nusstein and the others listed on this form to use and share my personal health information for this study. I will be given a copy of this signed form.

Signature _____

(Subject or Legally Authorized Representative)

Name _____

(Print name above)

(If legal representative, also print relationship to subject.)

Date _____ Time _____ AM / PM

Appendix F: Follow-Up Side Effects Form

Kovanaze Administration Times and Effects

Patient #:	Date:
Appointment #:	Pulp Tester:
Age:	Sex:
Tooth Type	Side:

Nasal Spray Administration:	Time of Day:	Comments:
1 st Spray		
2 nd Spray		
3 rd Spray (if necessary)		
End of Appointment		

Appendix G: Electric Pulp Testing Forms

EPT Values – Maxillary Lateral Incisor

Patient #:	Date:
Appointment #:	Pulp Tester:
Age:	Side:
Sex:	

	Lateral Incisor	Contralateral Canine
1 st Baseline		
2 nd Baseline		
3 rd Baseline		
Average Baseline		

	Lateral Incisor	Contralateral Canine
0		
1		
2		
3		
4		
5		
6		
7		
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EPT Values – Maxillary First Premolar

Patient #:	Date:
Appointment #:	Pulp Tester:
Age:	Sex:
	Side:

	1 st Premolar	Contralateral Canine
1 st Baseline		
2 nd Baseline		
3 rd Baseline		
Average Baseline		

	1 st Premolar	Contralateral Canine
0		
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