Title: Kovanaze Vs. Articaine in Achieving Pulpal Anesthesia of Maxillary Teeth

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Kovanaze vs. Articaine in Achieving Pulpal Anesthesia of Maxillary Teeth: A Randomized, Open-label, Non-Inferiority Trial

Background:

The words a common man would associate with a dentist are 'pain', 'drill' and 'needle'. This association is unfortunate for dentists because a majority of dental procedures require local anesthesia to ensure patient safety and comfort. In clinical dentistry, local anesthetics are directly injected in various sites of the mouth.

Studies have shown that it is the psychological aspect of seeing the needle or expecting a needle to enter the mouth that scares most patients. From a patient's perspective, the needle has been identified as the most fear provoking part of the dentists' armamentarium. The sight of a sharp, metallic needle entering a protected part of the body greatly increases the anxiety and triggers the 'fight or flight' response. The resulting release of adrenaline might be as much as 40 times the normal levels. This adrenaline burst can result in syncopal episodes that accounts for more than half of medical emergencies in dental practice. Heart attacks and strokes can occur in patients suffering from cardiovascular diseases (hypertension, myocardial infarction, angina, arrhythmia). [1] It is recommended that more medically compromised the patient is, more efforts should be made to reduce anxiety. [2]

The aspirating syringe and needle used today was introduced around 150 years ago. [3] It is estimated that up to 40 million Americans avoid visiting the dentist because of fear of pain and anesthetic injections. [4-6] One study found most patients view the injection as the only painful part of the dental procedure. [7]

In June 2016, an intranasal delivery system of local anesthesia called Kovanaze, gained FDA approval. [8] Kovanaze is available as a 0.2 ml metered spray and is intended to achieve pulpal anesthesia of 5 maxillary teeth on either side of the face. Even though success rates between 83 and 90 % have been reported for adults and children >40kg, FDA label (Section 14.2) provides data for children (>10 kg) indicating that the drug is safe for use in children as long as the dose is adjusted to bodyweight of the child. [9]

- One 0.1 mL spray for patients weighing 10 kg to less than 20 kg;
- Two 0.1 mL sprays for 20 kg to less than 40 kg; or
- Two 0.2 mL sprays for patients weighing 40 kg or more.

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Specific Aims:

With the ability to avoid the traditional painful injection Kovanaze offers promise in the field of maxillary anesthesia and this study intends to:

1. Compare Kovanaze to conventional needle anesthetic in different settings (procedures other than fillings and/or involving multiple teeth) in adults and children (at least 6 years of age and weighing > 20 kg)

2. Evaluate patient anxiety, tolerance and acceptability of Kovanaze in patients undergoing dental procedures

Location:

The study will be conducted in three departments in VCU School of Dentistry; General Practice, Endodontics and Pediatric Dentistry and will explore the effectiveness of Kovanaze in different populations and circumstances.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

- Pathology in the maxillary permanent (incisors, canines and premolars) or deciduous (incisors, canines and molars) teeth that require treatment under local anesthesia
- American Society of Anesthesiologists Class I or II
- Maximum blood pressure reading of 166/100 mmHg
- Vital pulp (Cold and EPT positive)

Exclusion Criteria:

- History of inadequately controlled hypertension or active thyroid disease
- Five or more nosebleeds in the past month
- Known allergy to oxymetazoline, tetracaine, benzylalcohol or para-aminobenzoic acid
- History of congenital or idiopathic methemoglobinemia
- Taking monoamine oxidase inhibitors, tricyclic antidepressants (e.g. amitriptyline), or non-selective beta adrenergic antagonists (e.g. propranolol)
- Taking oxymetazoline-containing products (i.e., Afrin) in the last 24 hours

- Pregnant and lactating women
- Non vital pulp (Cold and EPT negative)

Study Characteristics:

Design:
Randomized, open label clinical trial

Non-inferiority threshold and Sample size calculation:
The anesthetic efficiency of articaine has been reported in the literature to be around 78 – 88% (Evans et al.). The non-inferiority threshold is the maximum allowable excess of outcome events arising from the novel treatment compared with the standard treatment. The threshold for this study has been selected based on draft guidance set by the FDA (Temple et al.) and was set at 25%. Using nQuery Advisor v7.0, we verified that a sample size of 38 subjects per group would be needed to show a non-inferiority of <25% (one sided alpha of 0.05 and a power of 83%).
Accordingly, each of our study arms will have 90 subjects: 45 in Kovanaze and 45 in Articaine groups. Accounting for screen failures and dropouts, we will recruit 100 participants in each population totaling 300 for the entire study.

Intervention:

Metered Kovanaze sprays (0.2 ml each spray, St. Renatus) in the nostril on the same side as the tooth of interest. The dose involves:
2 sprays in adult and kids weighing 40 kg or more
1 spray in kids > 6 years but weighing between > 20 kg and < 40 kg

Control:

- Children: 1.0 ml of 4% articaine (containing 1:100000 epinephrine) delivered in the periapex of the tooth of interest by labial/buccal infiltration
- Adults: 1.8ml of 4% articaine (containing 1:100000 epinephrine) delivered in the periapex of the tooth of interest by labial/buccal infiltration

Population:
Our study will evaluate the effectiveness of Kovanaze in three different populations.

Population 1: *Children (aged 6-17 years and weighing >20 kg) requiring specific procedures for treatment of oral disease*

Location: Department of Pediatric Dentistry, 3rd floor, Wood Building

Eligible procedures: Procedures that would require local anesthesia include direct restorations (fillings), pulpotomy or pulpectomy (partial or complete removal of pulp) and placement of stainless steel crowns.

The standard of care in Department of Pediatric Dentistry is to administer nitrous before start of the treatment to alleviate patient anxiety. We will follow routine clinical protocol to titer the dose of nitrous oxide to individual patient needs.

Additionally, we hypothesize that the degree and depth of anesthesia would vary based on the initial disease state as well as the intended procedure. Accordingly, impact of the anesthesia will be analyzed at the completion of study using subgroup analysis.

Population 2*: Symptomatic adults (>18 years) with symptomatic irreversible pulpitis*

Location: Department of Endodontics, 2nd floor, Lyons Building

Eligible procedures:
Root canal treatment in teeth with significant decay but presenting with signs and symptoms of irreversible pulpitis (symptomatic)

Additional Inclusion Criteria:

- Tooth with a diagnosis of symptomatic irreversible pulpitis with or without periapical periodontitis
- Diagnosis is confirmed by history of spontaneous pain or prolonged (lingering) pain on application of cold or electronic pulp testing
- Tooth should have moderate to severe pain at the study onset (>54 on Heft Parker VAS scale)

Additional Exclusion criteria:

- Tooth with no response to cold / electronic pulp testing
- Tooth with periapical pathosis as seen in the radiograph
- Tooth with no vital coronal pulp tissue upon access

Population 3: *Asymptomatic adults (>18 years) requiring restorations or crowns*

Location: Department of General Practice, 2nd floor, Lyons/ Wood Building

Eligible procedures:
Direct and indirect restorations in teeth with significant decay but presenting with signs and symptoms of healthy pulp or reversible pulpitis

Additional Inclusion Criteria:

- Asymptomatic maxillary tooth with a diagnosis of primary or secondary dental caries extending more than 70% the thickness of dentin as seen in the radiograph

Additional Exclusion criteria:

- Tooth with no response to cold / electronic pulp testing
- Tooth with periapical pathosis as seen in the radiograph
- Endodontically treated tooth

Randomization

a. Sequence Generation:

The biostatistician on the study team (Dr. Carrico) will generate random sequence using a computer. The randomization will be in block of varying size (4 or 6) and the list will be provided to the following lead faculty who will serve as co-investigators as listed below:

Population 1: Pediatric Dentistry, Dr. William Dahlke
Population 2: Endodontics, Dr. Sameer Jain
Population 3: General Practice, Dr. Mark Barry

b. Allocation Concealment:

All random assignments will be placed in sequentially numbered opaque envelopes and will be handled by a staff in the respective department (not a part of the study team). If the participant is found to be eligible for the study, the resident/ student will inform the patient about the study. The team will answer all questions regarding the study and will request consent to participate in the study. After obtaining written patient consent, the department staff (not a member of the study team) will reveal the allocation.

Outcomes:

Patient important outcomes are considered including the primary outcome of completion of intended procedure without rescue anesthetic. This dichotomous outcome (success or failure of anesthesia) is linked to patients' rating of pain on a validated Heft-Parker visual analog scale. The emoji scale will be used for children. Group comparison between the articaine and Kovanaze formulations for anesthetic success will be analyzed by using Fisher's exact test.

Secondary outcomes include objective assessment of hard tissue and soft tissue anesthesia, anxiety scale (STAI-Y6 short form for children and MDAS scale for adults).

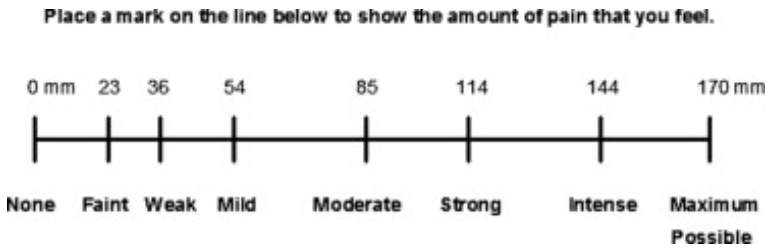
Adult participants who receive Kovanaze will also be asked to complete a survey to assess the impact of Kovanaze on patient confidence in seeking dental care.

Primary Outcome Measure in Adults:

Proportion of study participants in whom intended dental procedure could be successfully completed without the need for rescue anesthetic.

Heft Parker Scale: Each patient will rate his or her initial pain on a Heft Parker visual analogue scale, a 170-mm line with various descriptive terms. The subjects will be asked to place a mark on the scale where it best described their pain level both at the start and any time during the procedure. To interpret the data, the VAS is divided into the following four categories:

a. No pain corresponded to 0 mm on the scale.
b. Mild pain was defined as greater than 0 mm and less than or equal to 54 mm. Mild pain included the descriptors of faint, weak, and mild pain.
c. Moderate pain was defined as greater than 54 mm and less than 114 mm.
d. Severe pain was defined as equal to or greater than 114 mm. Severe pain included the descriptors of strong, intense, and maximum possible.



If study participants experience pain/ sensitivity/ discomfort at any time during the procedure (VAS >54), the local anesthesia would be considered a failure and rescue anesthetic (0.7 ml of articaine deposited at the periapex of the tooth of interest) administered to complete the intended procedure.

Secondary Outcome Measures in Adults:

1. **Onset of meaningful anesthesia:** Patient will be given a stopwatch and will be instructed to press the watch at two different time points:
   a. Onset of anesthesia (T-1 in min): Press the watch when they first perceive pain relief after the administration of local anesthetic
   b. Significant pain relief (T-2 in min): Press the watch the second time when the patient report significant pain relief (<54 in VAS scale)

At each time of the stopwatch/ timer, the patient will record their pain in VAS scale. Treatment will proceed as long as the VAS rating is below 54mm. i.e. no to mild pain. If the pain is moderate to high at any point of the procedure (score of 54 or higher), the event would be considered anesthetic failure and a rescue anesthetic administered.

2. Spread of anesthesia:

The teeth and the soft tissues on the side of the mouth ipsilateral to the tooth of interest will be evaluated for spread of anesthesia. The number of teeth that are anesthetized will be counted after cold and electronic pulp tests and recorded (maximum possible score is 5). Similarly, the buccal and lingual gingiva will be tested for anesthesia 1 cm below the gingival margin for each of the 5 teeth ipsilateral to the tooth of interest (maximum score of 5). The hard tissue and soft tissue scores will be compared between two groups.

3. Duration and depth of anesthesia:

In addition to the initial onset, we would gather information about the depth of anesthesia (as tested by EPT and cold tests) at 15 min, 30 min and 1 hour after administration of anesthesia. This would help us identify the duration for which reliable pulpal anesthesia is maintained.

4. Anxiety in Adults:

Modified Dental Anxiety Scale (MDAS):

The Modified Dental Anxiety Scale (MDAS) consists of 5 questions each with a 5-category rating scale, ranging from 'not anxious' to 'extremely anxious'. This answering scheme is a simplified rating system in comparison with Corah's Dental Scale that was an early 4-question measure of dental anxiety. The MDAS has an extra item about the respondent's anxiety to a local anesthetic injection that is particularly relevant for this study. (Humphris et al). Cut off is 19 or above (out of 25) for questions 1-5, which indicates a highly dentally anxious patient, possibly dentally phobic. Questions 6-8 are specific to this study to assess the effect of Kovanaze on dental anxiety.

CAN YOU TELL US HOW ANXIOUS YOU GET, IF AT ALL, WITH YOUR DENTAL VISIT BY INSERTING 'X' IN THE APPROPRIATE BOX?

1. If you went to your Dentist for TREATMENT TOMORROW, how would you feel?

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

2. **If you were sitting in the WAITING ROOM (waiting for treatment), how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

3. **If you were about to have a TOOTH DRILLED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

4. **If you were about to have your TEETH SCALED AND POLISHED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

5. **If you were about to have a LOCAL ANAESTHETIC INJECTION in your gum, above an upper back tooth, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

4. Satisfaction Questionnaire (for KOVANAZE Participants only)

These questions are to be administered at the end of the study visit to participants in Kovanaze arm only:

1. Have you ever experienced a LOCAL ANESTHETIC INJECTION in your gum, for dental treatment?

Yes ☐ *No* ☐

2. When was the last time you received a LOCAL ANESTHETIC INJECTION in your gum?

> 1 year ☐ *6 months ago* ☐ *Less than a month ago* ☐

3. Compared to INJECTION, how effective do you think was NASAL SPRAY ANESTHETIC in reducing your anxiety and comfort during dental procedure?

Not Effective ☐ *Slightly Effective* ☐ *No Difference* ☐ *Very Effective* ☐ *Extremely Effective* ☐

4. How likely is it that you would ask your dentist for a NASAL SPRAY ANESTHETIC, for your future treatment needs (compared to needle anesthetic)?

Never ☐ *No preference* ☐ *Every time* ☐

5. What is the most important deciding factor for you to choose NASAL SPRAY ANESTHETIC for your dental needs?

Cost ☐ *Fear and Anxiety* ☐

6. How much extra money would you be willing pay for the NASAL SPRAY ANESTHETIC?

$20 ☐ *$50* ☐ *Up to $100* ☐ *It is not worth paying extra* ☐

7. Did your experience with the NASAL SPRAY ANESTHETIC change your outlook towards receiving future dental care?

Nothing changed; Still scared of dental visits ☐ *This appointment was better but am still concerned about my future visits* ☐ *This appointment definitely eased my apprehension of future dental visits* ☐

8. If you had known that there was an option of NASAL SPRAY ANESTHETIC, would you have sought dental care early?

Definitely No ☐ *Maybe* ☐ *Definitely Yes* ☐

5. Survey after 24 hours:

A short one question about the side effects of local anesthetic will be asked to the patient in person or over phone at 24 hours.

Did you suffer any of the following side-effects after your dental visit?

- nasal drainage,
- nasal congestion,
- burning,
- pressure,
- sinus congestion,
- pain and soreness at the site of the anesthesia (scored from 1–10)
- Numbing or tingling in throat
- other (Specify)_____

Flow of research study visit in adults (>18 years):

Screening of EHR will be done to identify potential study participants on a routine clinical visit. During the study visit the study related procedures would be preformed in the following order:

1. Go over the study details, answer participant questions and obtain informed consent
2. Administer MDAS anxiety survey
3. Ask patient to rate pain (if present) in the Heft Parker Scale
4. Reveal allocation (Kovanaze or Articaine)
5. Take baseline BP and heart rate
6. Administer local anesthetic
7. Wait for patient to signal achievement of meaningful anesthesia (using stop watch)
8. Map the extent of soft tissue and hard tissue anesthesia in data collection form
9. Proceed with the intended procedure
10. Assign anesthetic **failure** if subject perceives pain after start of procedure. Record the failure in data collection form and proceed with rescue anesthetic to complete the procedure
11. Assign anesthetic **success** if local anesthesia was adequate to complete the intended procedure without need for rescue anesthetic. Record in data collection form
12. Administer MDAS survey for all participants
13. Administer satisfaction questionnaire to subjects in Kovanaze group only
14. Take end of appointment BP and heart rate

Primary Outcome Measure in Children:

Proportion of study participants in whom intended dental procedure could be successfully completed without the need for rescue anesthetic. We will use a 7 point pictorial emoji scale for children. [6] Each patient will rate his or her initial pain on this pictorial scale and will be asked to place a mark on the scale where it best described their pain level both at the start and any time during the procedure. A cut off point of 4 will be chosen to consider anesthetic failure (anything less than 4 will be interpreted as painful).

Secondary Outcome Measures in Children:

1. Onset of meaningful anesthesia:

Patient will be given a stopwatch and will be instructed to press the watch at two different time points:

a. Onset of anesthesia (T-1 in min): Press the watch when they first perceive pain relief after the administration of local anesthetic
b. Significant pain relief (T-2 in min): Press the watch the second time when the patient report significant pain relief (>4 in Emoji scale)

At each time of the stopwatch/ timer, the patient will record their pain in VAS scale. Treatment will proceed as long as the Emoji rating is below 4. i.e. no to mild pain. If the pain is moderate to high at any point of the procedure (score >4), the event would be considered anesthetic failure and a rescue anesthetic administered.

2. Spread of anesthesia:

The teeth and the soft tissues on the side of the mouth ipsilateral to the tooth of interest will be evaluated for spread of anesthesia. The number of teeth that are anesthetized will be counted after cold and electronic pulp tests and recorded (maximum possible score is 5). Similarly, the buccal and lingual gingiva will be tested for anesthesia 1 cm below the gingival margin for each of the 5 teeth ipsilateral to the tooth of interest (maximum score of 5). The hard tissue and soft tissue scores will be compared between two groups.

3. Anxiety and Behavior Score in Children:

Two validated questionnaires will be used in children to assess their anxiety and behavior.

a. STAI-Y6 short form Questionnaire:

Participants will be requested to fill in the short form of the State-Trait Anxiety Inventory questionnaire (STAI: Y6 item) before and after the dental appointment. (Marteau et al.)

Spielberger State-Trait Anxiety Inventory (STAI: Y-6 item): Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

Measure	Not at all	Somewhat	Moderately	Very much
1. I feel calm	1	2	3	4
2. I am tense	1	2	3	4
3. I feel upset	1	2	3	4
4. I am relaxed	1	2	3	4
5. I feel content	1	2	3	4
6. I am worried	1	2	3	4

b. Venham Anxiety and behavior scale: The resident dentist will rate the dental anxiety and behavior in children at the end of the appointment based on a validated scale. (Venham et al.)

Rating scales for anxiety and uncooperative behavior

Anxiety rating scale

1. Relaxed, smiling, willing and able to converse.
2. Uneasy, concerned. During stressful procedure may protest briefly and quietly to indicate discom-fort. Hands remain down or partially raised to signal discomfort. Child willing and able to inter-pret experience as requested. Tense facial expression, may have tears in eyes.
3. Child appears scared. Tone of voice, questions and answers reflect anxiety. During stressful proce-dure, verbal protest, (quiet) crying, hands tense and raised, (not interfering much — may touch dentist's hand or instrument, but not pull at it). Child interprets situation with reasonable accuracy and continues to work to cope with his/her anxiety.
4. Shows reluctance to enter situation, difficulty in correctly assessing situational threat. Pronounced verbal protest, crying. Using hands to try to stop procedure. Protest out of proportion to threat. Copes with situation with great reluctance.
5. Anxiety interferes with ability to assess situation. General crying not related to treatment. More prominent body movement. Child can be reached through verbal communication, and eventually with reluctance and great effort he or she begins the work of coping with the threat.
6. Child out of contact with the reality of the threat. General loud crying, unable to listen to verbal communication, makes no effort to cope with threat. Actively involved in escape behavior. Physical restraint required.

Behavior rating scale

1. Total cooperation, best possible working conditions, no crying or physical protest.
2. Mild, soft verbal protest or (quiet) crying as a signal of discomfort, but does not obstruct progress. Appropriate behavior for procedure, i.e., slight start ot injection, "ow" during drilling if hurting, etc.
3. Protest more prominent. Both crying and hand signals. May move head around making it hard to administer treatment. Protest more distracting and troublesome. However, child still complies with request to cooperate.
4. Protest presents real problem to dentist. Complies with demands reluctantly, requiring extra effort by dentist. Body movement.
5. Protest disrupts procedure, requires that all of the dentist's attention be directed toward the child's behavior. Compliance eventually achieved after considerable effort by dentist, but without much actual physical restraint. (May require holding child's hands or the like to start). More prominent body movement.
6. General protest, no compliance or cooperation. Physical restaint is required.

Flow of research related procedures on study visit in children:

Screening of EHR will be done to identify potential study participants on a routine clinical visit. During the study visit the study related procedures would be performed in the following order:

1. Go over the study details, answer participant questions and obtain informed consent
2. Administer STAI-Y6 questionnaire
3. Ask patient to rate pain (if present) in the Emoji Scale
4. Reveal allocation (Kovanaze or Articaine)
5. Take baseline BP and heart rate
6. Administer local anesthetic
7. Wait for patient to signal achievement of meaningful anesthesia (using stop watch)
8. Map the extent of soft tissue and hard tissue anesthesia in data collection form
9. Proceed with the intended procedure
10. Assign anesthetic **failure** if subject perceives pain after start of procedure. Record the failure in data collection form and proceed with rescue anesthetic to complete the procedure
11. Assign anesthetic **success** if local anesthesia was adequate to complete the intended procedure without need for rescue anesthetic. Record in data collection form
12. Record patient anxiety and behavior using Venham scale
13. Take end of appointment BP and heart rate

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