Double-masked, randomized, placebo-controlled study to evaluate the efficacy and tolerability of intranasal K305 (3% tetracaine plus 0.05% oxymetazoline) in anesthetizing maxillary teeth

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ABSTRACT

Background. The authors compared the local anesthetic efficacy and safety of an intranasally administered formulation of tetracaine and oxymetazoline (K305) with placebo in adult participants undergoing single dental restorative procedures in teeth nos. 4 through 13.

Methods. The authors screened and allocated 150 participants in a double-masked, randomized fashion to either K305 or placebo nasal spray. The authors delivered the study drug as two 0.2-milliliter sprays separated by 4 minutes inside the nostril on the side ipsilateral to the tooth being treated. The authors administered a third 0.2-mL spray, if necessary, and administered 4% articaine with 1:200,000 epinephrine by means of injection if anesthesia was inadequate. Safety evaluations included participant reports of adverse events, vital signs, and alcohol sniff tests during the 2-hour study period and at a 1-day follow-up visit. The primary efficacy end point was anesthetic success defined as the completion of the dental procedure without the need for rescue injectable local anesthetic. The authors evaluated differences in success rates observed between K305 and placebo by using a 1-sided Fisher exact test.

Results. The overall success rates were 88.0% (95% confidence interval, 80.0-93.6) and 28% (95% confidence interval, 16.2-42.5) for K305 and placebo, respectively ($P < .0001$). The most frequent adverse effects in the K305 group were rhinorrhea (57.0%) and nasal congestion (26.0%). No serious adverse events occurred during this study.

Conclusions. K305 was effective and well tolerated during restorative procedures in adult participants.

Practical Implications. K305 provides a needleless alternative for obtaining maxillary pulpal anesthesia on premolars, canines, and incisors.

Key Words. Dental local anesthesia; tetracaine; oxymetazoline; intranasal delivery; clinical trial.

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The development of safe and effective local anesthetic agents is possibly the most important advance in providing pain control in dental practice.[1] The standard of care for providing anesthesia to maxillary anterior teeth and premolars is the delivery of injected local anesthetic agents through the buccal mucosa to branches of the anterior superior and middle superior alveolar nerves.[2] Often the pain produced by these injections is considered the most painful part of the dental procedure.[3] Fear of dental injections is still a major barrier to patients' seeking routine care.[4-6]

K305 (Kovanaze, St. Renatus) is a combination of the local anesthetic 3% tetracaine, used widely in otolaryngology practice to block regional nasal sensation,[7,8] and the commercial over-the-counter (OTC) decongestant 0.05% oxymetazoline.[9] Oxymetazoline is included in this intranasal local anesthetic formulation to slow the systemic absorption of the tetracaine and prolong the maintenance of adequate tissue concentrations of the anesthetic because of its vasoconstrictive properties via direct α-2 receptor stimulation.[10]

This phase 3 trial was preceded by several dose-finding, safety, and pharmacokinetics studies. Investigators performed a dose-escalation safety and pharmacokinetic study in 12 participants to evaluate an intranasal tetracaine plus oxymetazoline dose equal to

the highest that we used in this study (18 milligrams tetracaine plus 0.3 mg oxymetazoline) followed 1 to 3 weeks later by double that dose (36 mg tetracaine plus 0.6 mg oxymetazoline).[11] In this study, blood pressure, pulse, and oxygen saturation remained relatively stable, with the most common adverse effects of the 18 mg tetracaine plus 0.3 mg oxymetazoline dose being rhinorrhea in 6 of the 12 participants, nasal stuffiness in 5, headache in 3, and a mild nosebleed in 2. One participant experienced a moderate pressor response with this dose; his blood pressure increased from 114/69 to 140/99 millimeters of mercury, which resolved spontaneously. All participants fasted for at least 6 hours in this study, and the investigators obtained 16 blood samples through an indwelling catheter during the 2-hour observation period.

Results from a second proof-of-concept study in 45 participants revealed that a total dose of 18 mg tetracaine plus 0.3 mg oxymetazoline administered bilaterally provided an anesthetic success rate of 90% from the maxillary second premolar forward, with success defined as the ability to complete a dental restorative procedure, including the removal of caries and placement of the dental restoration, without the need for a rescue local anesthetic injection. In this same study, the criterion standard 2% lidocaine plus 1:100,000 epinephrine injection produced a success rate of 93%.[12]

With regard to the dose amount and technique used in our study, results from 2 trials helped confirm the efficacy of unilateral 200-microliter sprays ipsilateral to the tooth being treated in total volumes of 400 or 600 μL (12 mg tetracaine plus 0.2 mg oxymetazoline or 18 mg tetracaine plus 0.3 mg oxymetazoline, respectively) for anesthesia of premolars and anterior maxillary teeth (data on file with St Renatus). The investigators defined anesthetic success as a lack of response to an electric pulp tester. The purpose of our study was to compare the efficacy and tolerability of 3% tetracaine plus 0.05% oxymetazoline with placebo spray when administered unilaterally in 400- or 600-μL dose volumes in participants undergoing restorative dentistry procedures of the maxillary anterior teeth and premolars.

METHODS

The institutional review boards at the University of Pennsylvania, Philadelphia, PA; University of Maryland, Baltimore, MD; and Loma Linda University, Loma Linda, CA, approved the protocol and informed consent forms. We listed the trial in ClinicalTrials.gov under the identifier NCT01745380. Men and women 18 years or older from all ethnic backgrounds were eligible to participate in this study. Study participants were required to have a vital maxillary premolar, canine, or incisor requiring restorative dentistry treatment. Dental procedures performed in this study included Class 1, 2, 3, or 5 preparations followed by the placement of amalgam, composite, or temporary sedative restorations. The clinical trial consisted of 3 study-related visits: a screening visit to assess participant eligibility, the dose administration visit at which either K305 or placebo spray was administered and the restoration was completed, and a 1-day follow-up visit to evaluate safety.

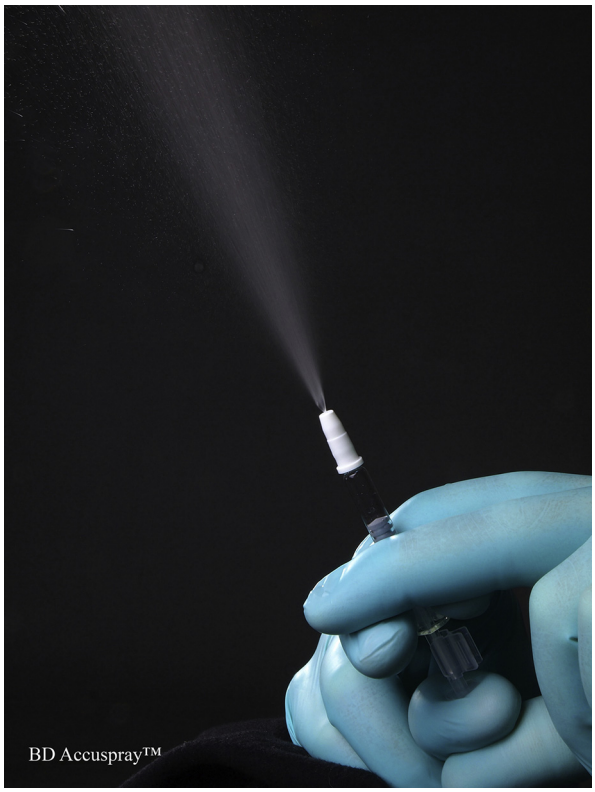

Figure 1. Image of intranasal 3% tetracaine plus 0.05% oxymetazoline delivered as a plume of mist. *Courtesy of and © Becton, Dickinson and Company. Reprinted with permission.*

Screening visit. The screening and dose administration visits could be (and usually were) performed on the same day. During the screening visit, the potential participants read and signed the informed consent forms and had all study-related questions answered by 1 of the investigators (P.A.M., D.Y.H.) or the research coordinators. The investigators confirmed the need for a restorative procedure between teeth nos. 4 through 13, and if a recent radiograph of the target tooth was not available, it was obtained at this time. The research

ABBREVIATION KEY. **BPM:** Beats per minute. **DBP:** Diastolic blood pressure. **FDA:** Food and Drug Administration. **HR:** Heart rate. **MedDRA:** Medical Dictionary for Regulatory Activities. **NP:** Not performed. **OTC:** Over the counter. **SBP:** Systolic blood pressure. **TEAE:** Treatment-emergent adverse event.