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.

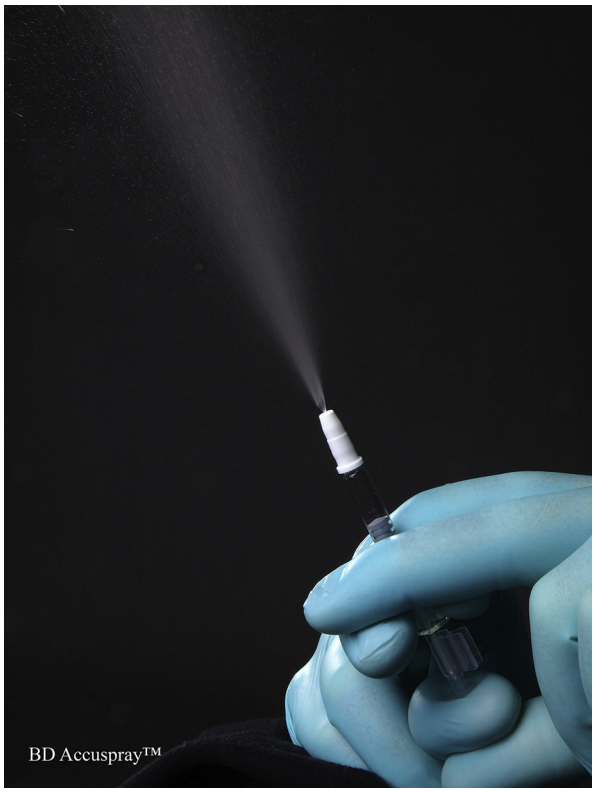

Figure 1. Image of intranasal 3% tetracaine plus 0.05% oxymetazoline delivered as a plume of mist. *Courtesy of and © Becton, Dickinson and Company. Reprinted with permission.*

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.

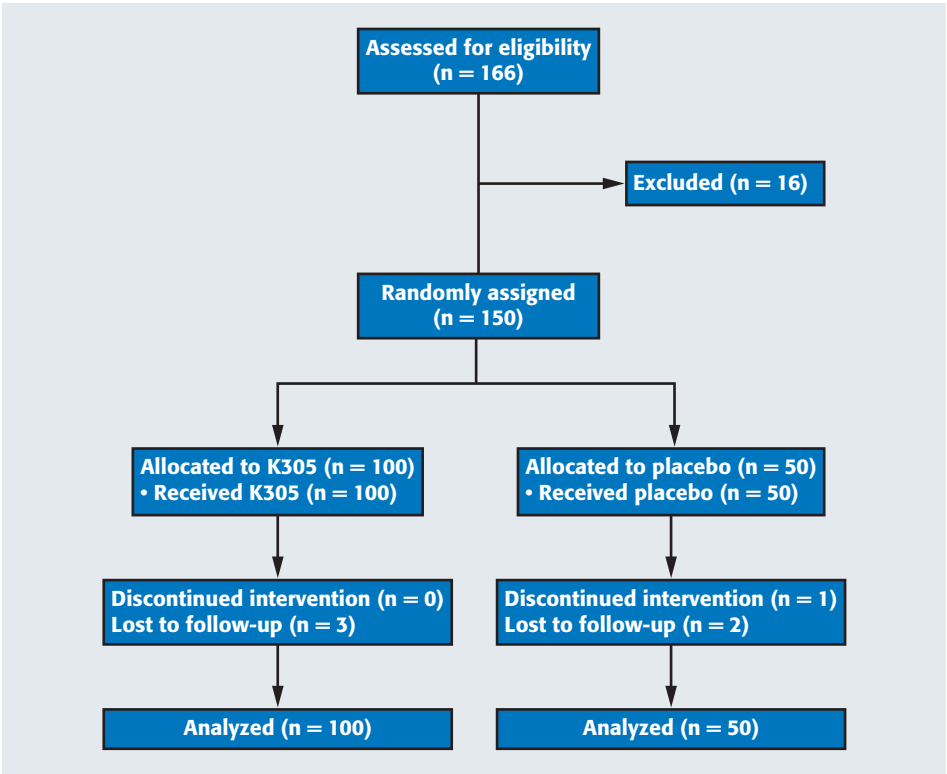

Figure 2. Flow diagram of participant study inclusion and exclusion.

TABLE 1

Demographic and baseline characteristics of the study cohort.

CHARACTERISTIC	K305 (n = 100)	PLACEBO (n = 50)
Age at Dose Administration, y, Mean (SD*)	42 (14.0)	40 (15.2)
Sex, No. (%)		
Male	43 (43.0)	25 (50.0)
Female	57 (57.0)	25 (50.0)
Race, No. (%)		
White	64 (64.0)	30 (60.0)
Black	16 (16.0)	4 (8.0)
Native Hawaiian or other Pacific Islander	16 (16.0)	14 (28.0)
Other	4 (4.0)	2 (4.0)
Hispanic or Latino Ethnicity, No. (%)		
Yes	12 (12.0)	7 (14.0)
No	88 (88.0)	43 (86.0)
Height, Centimeters, Mean (SD)	169.9 (10.4)	172.1 (10.2)
Weight, Kilograms, Mean (SD)	81.1 (20.2)	85.4 (24.7)

* SD: Standard deviation.

coordinators then measured each participant's height, weight, heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP), the latter 3 by using an automated blood pressure and pulse oximetry unit (Dash 3000 Vital Signs Monitor, Atlas Model 621 NP, Welch Allyn). We did not measure oxygen saturation.

Key exclusion criteria included blood pressure higher than 150/100 mm Hg; a resting pulse lower than 55 beats per minute (BPM) or higher than 100 BPM; inadequately controlled active thyroid disease (a relative contraindication to oxymetazoline); a history of allergy or intolerance to tetracaine or other ester local anesthetics, benzyl alcohol (the study drug vehicle), para-aminobenzoic acid (an ester local anesthetic metabolite), oxymetazoline, articaine, epinephrine, or sulfite preservatives; for women, being pregnant or breast-feeding; the intake of monoamine oxidase inhibitors within 3 weeks of study drug administration (a relative contraindication to oxymetazoline); having 5 or more nosebleeds per month; receiving any local anesthetic within 24 hours of study drug administration; having a history of idiopathic or congenital methemoglobinemia; and participation in any clinical trial within 30 days of screening. Inclusion criteria included resting HR between 55 and 100 BPM; seated SBP between 95 and 150 mm Hg; seated DBP between 60 and 100 mm Hg; and participants' report of normal lip, nose, cheek, and eyelid sensation.

All women of childbearing potential received a urine pregnancy test, the results of which had to be negative for participation in the study. One of the investigators then performed a nares examination in which they examined the inside of the nostril ipsilateral to the tooth to be treated by using a nasal otoscope (Model 26538, Welch Allen). The investigator recorded the patency (yes, no), color (pink, slightly red, red), presence or absence of inflammation (no inflammation, slight inflammation, inflammation), and presence or absence of bleeding

(none, slight or minor, significant or major). An investigator had to judge the nasal passage as patent for continued participation in the study.

Dose administration visit. In most instances, the study drug dose administration visit occurred on the same day as the screening visit. The research coordinators recorded readings of HR, SBP, and DBP by using the automated blood pressure and pulse oximetry unit and measured body temperature before administering the study drug. In the few cases in which the study drug dose administration visit occurred on a day subsequent to the screening visit, all the screening-related procedures were repeated.

The research coordinators also administered an alcohol sniff test before the administration of the study drug to measure baseline olfactory sensitivity. This test involved placing a 70% isopropyl alcohol preparation pad beneath the participant's nostrils while he or she inhaled twice to become familiar with the alcohol odor. Then the research coordinator instructed the participant to close his or her mouth and eyes and breathe normally through the nostril ipsilateral to the treatment tooth while closing the other nostril. The research coordinator then placed the alcohol pad 30 centimeters below the nose and with each expiration moved it 2 cm closer to the naris until the participant detected the odor. The research coordinator used a standard metric ruler to record the distance in centimeters from the anterior naris to the alcohol pad at the point at which the participant first detected the odor. In a previous study, patients with normal olfactory function reported a mean olfactory threshold distance of approximately 14 cm, and those with diminished or lack of olfactory function reported a threshold of approximately 8 cm.[13]

The study drug was packaged in 200-μL volumes in 3 spray devices (Accuspray, Becton, Dickinson and Company). The spray devices were identical and contained either K305 or placebo, and both the K305 and placebo solutions (benzyl alcohol) looked identical. The investigators administered the first spray with the participant sitting upright in the dental chair and the tip of the device positioned inside the nostril up to the edge of the nasal valve at slightly greater than a horizontal angle to the floor of the nose. The whole dose was then expelled as a plume in one-half of a second or less (Figure 1). The second spray occurred approximately 4 minutes after the first spray. In this instance, the tip was positioned inside the nostril at a 45° angle to horizontal and, as before, the investigators delivered

TABLE 2

Success and failure rates of K305 versus placebo spray.

OUTCOME	K305 (n = 100)		PLACEBO (n = 50)		*P* VALUE
	No. (%)	95% Confidence Interval	No. (%)	95% Confidence Interval	
Overall					
Success*	88 (88.0)	80.0-93.6	14 (28.0)	16.2-42.5	< .0001‡
Failure†	12 (12.0)	6.4-20.0	36 (72.0)	57.5-83.8	
50 Years or Younger					
Success	60 (87.0)	76.7-93.4	7 (20.6)	8.7-37.9	
Failure	9 (13.0)	6.6-23.3	27 (79.4)	62.1-91.3	< .0001§
Older Than 50 Years					
Success	28 (90.3)	74.3-98.0	7 (43.8)	19.7-70.1	
Failure	3 (9.7)	2.0-25.7	9 (56.2)	29.9-80.3	

* Success is defined as completed without rescue injection.
† Failure is defined as requiring a rescue injection.
‡ One-sided Fisher exact test.
§ One-sided stratified Cochran-Mantel-Haenszel test. Breslow-Day test for homogeneity in treatment effect between age strata was not significant ($P = .43$).

TABLE 3

Success rates of K305 and placebo stratified according to tooth location and tooth number.

STRATIFICATION STRATUM	ANESTHETIC SUCCESS RATE				*P* VALUE*
	K305 (n = 100)		Placebo (n = 50)		
	No.	Count (%)	No.	Count (%)	
Tooth Location					
Anterior (6-11)	53	51 (96.2)	26	8 (30.8)	< .0001
Premolar (4, 5, 12, and 13)	47	37 (78.7)	24	6 (25.0)	
Tooth Number					
4 (second premolar)	15	10 (66.7)	5	0 (0)	
5 (first premolar)	12	11 (91.7)	8	2 (25.0)	
6 (canine)	5	5 (100.0)	1	0 (0)	
7 (lateral incisor)	13	13 (100.0)	7	3 (42.9)	
8 (central incisor)	16	16 (100.0)	5	2 (40.0)	NP†
9 (central incisor)	8	7 (87.5)	3	1 (33.3)	
10 (lateral incisor)	5	4 (80.0)	7	1 (14.3)	
11 (canine)	6	6 (100.0)	3	1 (33.3)	
12 (first premolar)	10	10 (100.0)	6	2 (33.3)	
13 (second premolar)	10	6 (60.0)	5	2 (40.0)	

* Comparison of K305 with placebo success rates adjusting for anterior teeth versus premolars (stratified Cochran-Mantel-Haenszel test). The Breslow-Day test of treatment effect homogeneity between anterior teeth and premolar strata had a *P* value of .10.
† NP: Not performed.

TABLE 4

TEAEs* for K305 and placebo spray that occurred in 3% or more of participants.

MedDRA† SYSTEM ORGAN CLASS‡ AND PREFERRED TERM	K305 (n = 100) No. (%)	PLACEBO (n = 50) No. (%)
Participants With at Least 1 TEAE	88 (88.0)	44 (88.0)
Respiratory, Thoracic and Mediastinal Disorders§	83 (83.0)	13 (26.0)
Rhinorrhoea§	57 (57.0)	3 (6.0)
Nasal congestion§	26 (26.0)	3 (6.0)
Nasal discomfort§	24 (24.0)	2 (4.0)
Oropharyngeal pain§	15 (15.0)	0 (0)
Intranasal hypoaesthesia§	9 (9.0)	1 (2.0)
Throat irritation§	8 (8.0)	0 (0)
Rhinalgia§	5 (5.0)	1 (2.0)
Nasal dryness	4 (4.0)	1 (2.0)
Pharyngeal hypoaesthesia	4 (4.0)	0 (0)
Sneezing	4 (4.0)	0 (0)
Epistaxis	3 (3.0)	0 (0)
Injury, Poisoning and Procedural Complications	26 (26.0)	33 (66.0)
Procedural pain	26 (26.0)	33 (66.0)
Gastrointestinal Disorders§	22 (22.0)	5 (10.0)
Hypoaesthesia oral§	11 (11.0)	0 (0)
Hypoaesthesia teeth	3 (3.0)	0 (0)
Nervous System Disorders§	22 (22.0)	3 (6.0)
Headache§	9 (9.0)	1 (2.0)
Dysgeusia§	7 (7.0)	1 (2.0)
Paraesthesia§	5 (5.0)	1 (2.0)
Dizziness	3 (3.0)	0 (0)
Eye Disorders§	12 (12.0)	2 (4.0)
Lacrimation increased§	8 (8.0)	2 (4.0)
Investigations§	11 (11.0)	4 (8.0)
Blood pressure systolic increased§	8 (8.0)	2 (4.0)
Blood pressure diastolic increased§	6 (6.0)	1 (2.0)

* TEAE: Treatment-emergent adverse event.
† MedDRA: Medical Dictionary for Regulatory Activities (http://www.meddra.org/).
‡ Each participant counts only once for each system organ class.
§ Incidence in the K305 group is both 5% or greater and greater than the incidence in the placebo group.

the total volume of study drug in one-half of a second or less.

At 15 minutes after the first spray, the investigators used a high-speed handpiece to penetrate the participant's dentin. Participants had been instructed to raise their hands if they felt any pain during this initial penetration into dentin. Participants who experienced any pain on initial penetration into dentin had their procedure halted, and they received a third spray administered in an identical fashion to the second spray. In these participants, investigators waited an additional 10 minutes before attempting to penetrate dentin again. Participants who experienced any pain during penetration into the dentin after the third spray or experienced any pain regardless of painless dentin penetration during the cavity preparation procedure after 2 or 3 sprays had their procedure halted. The investigators then administered a rescue infiltration injection of 4% articaine plus 1:200,000 epinephrine to complete the cavity preparation and restoration. Use of a rescue infiltration injection was considered a study drug failure. Participants with continued pulpal anesthesia after the second or third spray had their cavity preparation and restoration completed without the use of injectable local anesthetic, and this was considered a study drug success.

Research coordinators recorded SBP, DBP, and HR at 10 minutes after the first spray and then at 30, 45, 60, 90, and 120 minutes after the first spray as long as the restorative procedure had been completed. Research coordinators recorded treatment-emergent adverse events (TEAEs) when and if they occurred. Before participant discharge, the research coordinators performed a second alcohol sniff test and scheduled the participant for his or her 1-day follow-up visit.

Follow-up visit. At the 1-day follow-up visit, we recorded SBP, DBP, and HR and repeated the nares examination and alcohol sniff test. We questioned participants concerning the resolution of any adverse effects reported during the dose administration visit or the appearance of any new adverse effects.

Statistical analyses. The study was to enroll 150 patients, nearly balanced with 40 to 60 patients per study site, so that approximately 150 patients completed the study dental procedure. Results from a previous study indicate that the proportion of patients treated with K305 who did not require rescue medication (success proportion) was approximately 83.3%, from consideration of the bilateral study results as well as those from a smaller unilateral study.[12] The proportion of success anticipated in the placebo arm was expected to be 20%. A study with 100 patients in the K305 group and 50 in the placebo group has a 99% power to detect a difference this large by using a 1-sided Fisher exact test at $\alpha = 2.5\%$.

The protocol-specified efficacy and safety analysis included all participants who received at least 1 dose of study medication. In the efficacy analysis, we grouped participants on the basis of the treatments they were randomly assigned to (modified intention-to-treat population). In the safety analysis, we grouped participants on the basis of the treatments that they actually received (safety population). We defined the primary efficacy end point as successful completion of the restorative procedure without the need for a local anesthetic rescue injection. We compared the difference in the success rates between the K305 and placebo groups by using a 1-sided Fisher exact test at $\alpha = 2.5\%$. The secondary end point was defined as completion of the study dental procedure without need for rescue by injection of local anesthetic according to age groups (age 50 years or younger versus

older than 50 years). We used a 1-tailed stratified Cochran-Mantel-Haenszel (CMH) test at $\alpha = 2.5\%$ to compare the success proportions while adjusting for a third factor, such as age groups, study site, or tooth location. We used a Breslow-Day test to assess treatment effect homogeneity across the strata.

We calculated descriptive statistics for all safety and tolerability parameters, including adverse events, vital signs, and alcohol sniff test results. We used repeated measures analysis of covariance to assess vital sign (SBP, DBP, and HR) results over time. The model features vital sign data between 10 and 120 minutes after initial dose administration as outcomes; treatment, visit, study site, age group, and prestudy vital sign measurement of interest as fixed effects; and patients as a random effect, as well as an unstructured covariance structure. Because we did not record vital signs while the participants were undergoing the restorative procedures, values may have been missing at 30, 45, and 60 minutes after the first 200-µL dose of study medication.

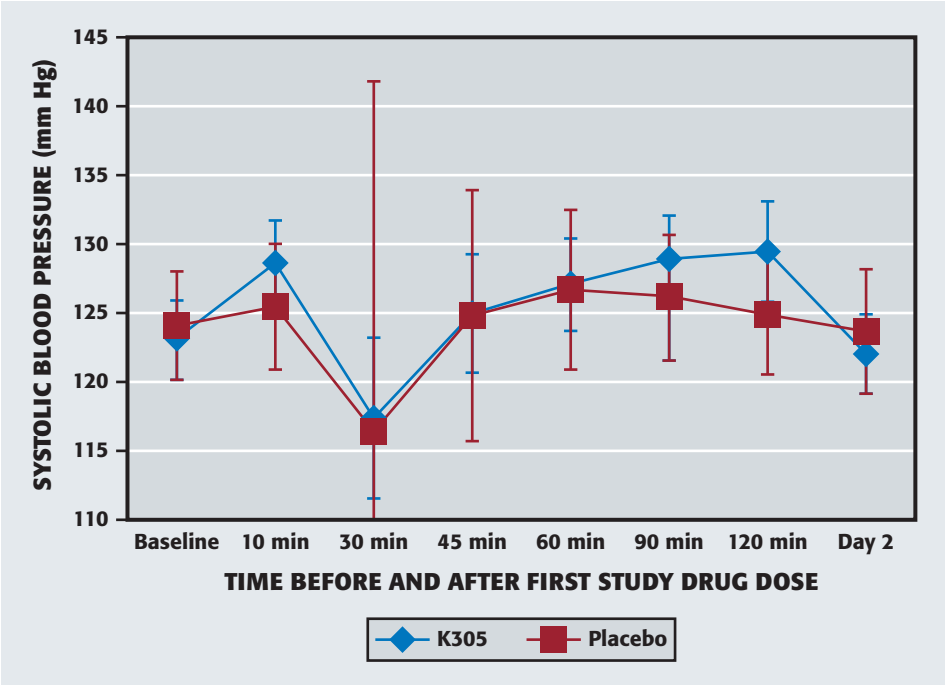

Figure 3. Mean and 95% confidence intervals of the mean time-effect curves for systolic blood pressure from baseline through 120 minutes and then at the 1-day follow-up appointment. At 10, 90, and 120 minutes, mean values represent 100 participants in the K305 group and 50 participants in the placebo group. At 30 minutes, mean values represent 23 participants in the K305 group and 3 participants in the placebo group. At 45 minutes, mean values represent 71 participants in the K305 group and 18 participants in the placebo group. At 60 minutes, mean values represent 97 participants in the K305 group and 44 participants in the placebo group. The clinician administered the study drug after recording baseline measurements. Notches indicate 95% confidence interval ranges. min: Minutes. mm Hg: Millimeters of mercury.

RESULTS

We screened 166 adults and randomly assigned 150 participants to 1 of the 2 study drug groups: 100 to K305 and 50 to placebo (Figure 2). Patients and study personnel were masked to the study drug actually received by the patient. Participants were enrolled at University of Pennsylvania (n = 32 to K305, n = 16 to placebo), University of Maryland (n = 24 to K305, n = 12 to placebo), and Loma Linda University (n = 44 to K305, n = 22 to placebo). One participant assigned to the K305 treatment did not return for the 1-day follow-up visit and could not be contacted by telephone for adverse effect evaluations. Five other participants also did not return for their alcohol sniff tests but were contacted by phone for reports of any residual or new adverse effects. One participant in the K305 group experienced insufficient pulpal anesthesia to complete the restorative procedure even after the rescue 4% articaine with 1:200,000 epinephrine injection. We placed a temporary restoration, and this participant returned for the follow-up safety examination.

Table 1 summarizes key demographic and baseline characteristics. Treatment groups were reasonably well-balanced in terms of age, ethnicity, height, and weight. There was a slightly higher percentage of women (57%) in the K305 group than in the placebo group (50%). In addition, black participants made up 16% of the K305 group and only 8% of the placebo group, and Native Hawaiian or other Pacific Islander participants made up 28% of the placebo group and only 16% of the K305 group. These differences were not statistically significant.

The overall success rates were 88.0% (88 of 100; 95% confidence interval, 80.0-93.6%) for K305 and 28.0% (14 of 50; 95% confidence interval, 16.2-42.5%) for placebo (1-sided Fisher exact test, $P < .0001$), supporting the hypothesis that K305 was superior to placebo (Table 2). The impact of study site on this primary outcome variable was not significant (Breslow-Day test of treatment effect homogeneity across the study sites, $P = .068$). The success rates for participants 50 years or younger (n = 103) was 87.0% for K305 and 20.6% for placebo. The

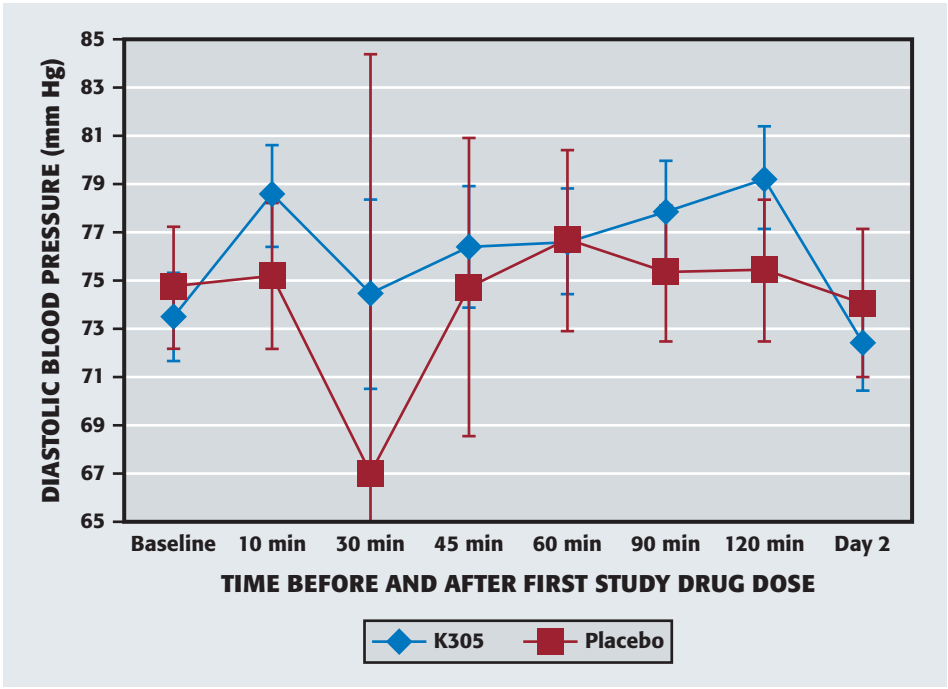

Figure 4. Mean and 95% confidence intervals of the mean time-effect curves for diastolic blood pressure from baseline through 120 minutes and at the 1-day follow-up appointment. At 10, 90, and 120 minutes, mean values represent 100 participants in the K305 group and 50 participants in the placebo group. At 30 minutes, mean values represent 23 participants in the K305 group and 3 participants in the placebo group. At 45 minutes, mean values represent 71 participants in the K305 group and 18 participants in the placebo group. At 60 minutes, mean values represent 97 participants in the K305 group and 44 participants in the placebo group. The clinician administered the study drug after recording baseline measurements. Notches indicate 95% confidence interval ranges. min: Minutes. mm Hg: Millimeters of mercury.

success rates for participants older than 50 years (n = 47) was 90.3% for K305 and 43.8% for placebo. With adjustment for the age stratum, the success rate after K305 treatment was statistically significantly higher than that after placebo treatment (stratified CMH test, $P < .0001$). The Breslow-Day test of homogeneity in treatment effect between the age strata was not significant ($P = .43$). Table 3 displays the success rates according to tooth location and tooth number. With adjustment for the tooth location, the success rate after K305 treatment was statistically significantly higher than that after placebo treatment (stratified CMH test, $P < .0001$). The Breslow-Day test of homogeneity in treatment effect between the tooth location strata was not significant ($P = .10$).

Table 4 displays the most common (≥ 3%) TEAEs for K305 and the placebo. The overall percentage of participants experiencing at least 1 adverse event after dose administration was 88.0% in both treatment groups. Compared with those treated with placebo, participants treated with K305 displayed a greater incidence of rhinorrhea, nasal congestion, nasal discomfort, oropharyngeal pain, throat irritation, headache, and lacrimation of the eye with respect to the most frequently reported TEAEs. The high incidence (66.0%) of procedural pain in the placebo group was because of its inability to provide local anesthesia during the restorative procedure.

Using the previously described repeated measures analysis of covariance models, we found a statistically significant difference between the 2 treatment groups in all 3 vital sign outcomes, indicating treatment effect on these variables. The treatment-by-time interaction effect was not significant. Thus, the final models featured main effects only. For HR, the treatment effect P value was .015 (K305 effect size, −1.98). For SBP, the treatment effect P value was .0028 (K305 effect size, 4.20). For DBP, the treatment effect P value was less than .0001 (K305 effect size, 4.01). Figures 3 through 5 present graphic displays of these longitudinal vital sign data according to treatment group. The incidence of SBP recordings greater than 160 mm Hg was 10% in the K305 group and 4% in the placebo group. The incidence of SBP increase of at least 25 mm was 11% in the K305 group versus 6% in the placebo group. The incidence of DBP increase from baseline of at least 15 mm Hg was 27% in the K305 group and 8% in the placebo group. At the 1-day follow-up visit, vital signs were similar between the K305 and placebo groups (K305 mean [standard deviation] versus placebo mean [standard deviation]): SBP (122 [13.8] versus 123.6 [15.3] mm Hg), DBP (72.4 [9.5] versus 74.0 [10.5] mm Hg) and HR (74.2 [12.1] versus 75.8 [14.5] BPM).

Table 5 displays the results for the alcohol sniff test. In both groups, there were minimal changes from baseline, with the placebo group score improving slightly from baseline and the K305 group decreasing slightly from baseline at the 1-day follow-up appointment.

DISCUSSION

K305 is an intranasal delivery system of 3% tetracaine and 0.05% oxymetazoline. St. Renatus is developing it to provide maxillary pulpal anesthesia for restorative procedures of premolars, canines, and incisors without the

use of standard infiltration injection techniques. The results from our study indicate an 88.0% success rate with the K305 nasal spray compared with a success rate of only 28.0% for an identical-appearing placebo spray. The success rate of 88.0% approaches the 93% success rate previously reported with infiltration injections of 2% lidocaine plus 1:100,000 epinephrine.[12] The reduction in success rate for K305 for the maxillary second premolars (only 60-66%) was somewhat surprising. A possible reason for this finding is that the middle superior alveolar nerve is present in only 72% of people; when it is absent, innervation to the second premolar usually is provided by the posterior superior alveolar nerve, and the anterior superior alveolar nerve may provide the bulk of the innervation for the first premolars.[14,15] The present delivery system for K305 does not anesthetize the posterior superior alveolar branch of the maxillary nerve predictably.[12] Ciancio and colleagues[12] did not report reduced success rates in the second premolar region relative to those in more anterior teeth, in all likelihood because only 4 participants requiring restorations of the second premolars received K305. Theirs was a phase 2 study with a total sample size of 40 participants, and they simply did not observe this phenomenon because of the small sample size.

The use of placebos in analgesic trials, including postsurgical dental pain trials, has been standard for more than 40 years.[16-18] Even after impacted third-molar extraction, placebo treatments typically occupy 15% to 20% of the theoretical maximum area under a 6-hour analgesic time-effect curve.[17] Meta-analyses of postsurgical dental pain trials in which the investigators evaluate the numbers needed to treat to obtain 50% maximum pain relief always compare the active analgesic with placebo.[19,20] In our study, we compared the active K305 spray with a placebo spray made up of the drug vehicle benzyl alcohol. This design is similar to the one we used in another topical anesthetic study that was

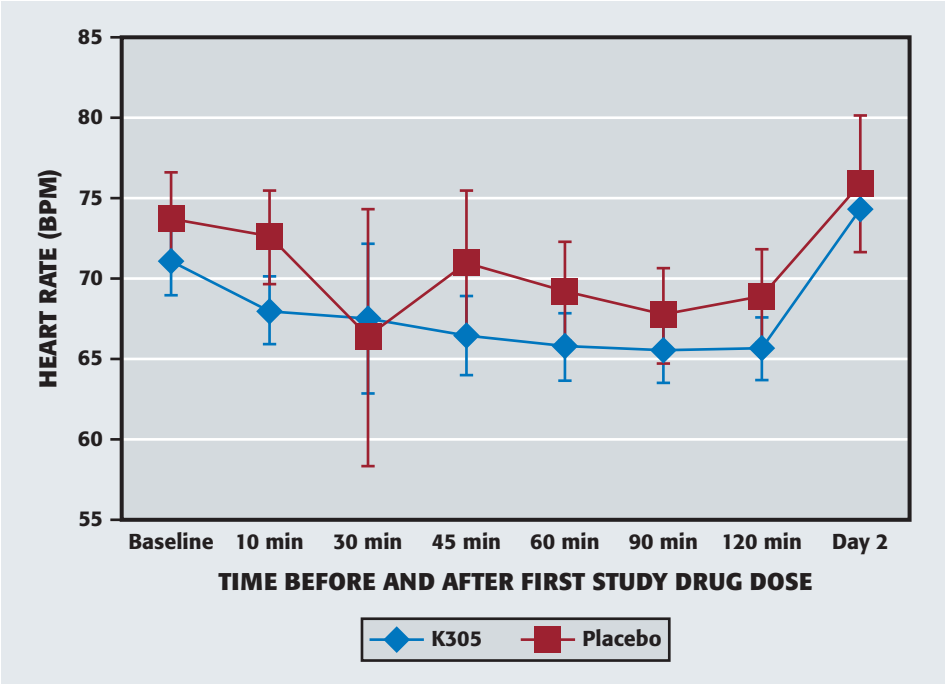

Figure 5. Mean and 95% confidence intervals of the mean time-effect curves for heart rate from baseline through 120 minutes and at the 1-day follow-up visit. At 10, 90, and 120 minutes, mean values represent 100 participants in the K305 group and 50 participants in the placebo group. At 30 minutes, mean values represent 23 participants in the K305 group and 3 participants in the placebo group. At 45 minutes, mean values represent 71 participants in the K305 group and 18 participants in the placebo group. At 60 minutes, mean values represent 97 participants in the K305 group and 44 participants in the placebo group. The clinician administered the study drug after recording baseline heart rate measurements. Notches indicate 95% confidence interval ranges. BPM: Beats per minute. min: Minutes.

TABLE 5

Alcohol sniff test results for the K305 and placebo groups.

TIME POINT STATISTIC	K305 (n = 100)	PLACEBO (n = 50)
Prestudy*		
No.	99	50
Mean (SD†), cm‡	18.0 (7.58)	17.3 (8.00)
Median, cm	19.0	18.3
120 Minutes After First Dose*		
No.	99	50
Mean (SD), cm	17.2 (8.62)	17.6 (8.46)
Median, cm	19.0	18.3
Day 2§		
No.	95	47
Mean (SD), cm	17.2 (7.71)	18.1 (7.15)
Median, cm	17.0	20.0

* One participant in the K305 group did not undergo the alcohol sniff test.
† SD: Standard deviation.
‡ cm: Centimeters.
§ Three participants in the K305 group and 3 in the placebo group did not return for their 1-day follow-up visits. An additional 2 participants in the K305 group did not undergo the alcohol sniff test.

published in The Journal of the American Dental Association in 2013 in which we compared 2 concentrations of benzocaine with a placebo vehicle in relieving spontaneous toothache pain due to acute pulpitis.[21] Investigators in a previously published study of 45 participants compared the success rates of 3 sprays of K305 with that of a single cartridge of 2% lidocaine plus 1:100,000 epinephrine from the second premolar forward; there was a 90% success rate for K305 and a 93% success rate for lidocaine plus epinephrine.[12] To try to maintain the masking, the investigators administered a sham injection of lidocaine with epinephrine to all participants who received K305, which means the cap remained on the needle while being pushed against the injection site. Participants who received the injection of active lidocaine with epinephrine also received 3 placebo nasal sprays.[12] The limitations of this methodology are that some participants can discern when they receive the real injection versus when they receive the sham injection. In addition, it is the opinion of the US Food and Drug Administration (FDA) that historical controls (rather than placebo controls) should be reserved for special circumstances, notably cases in which the disease to be treated in the clinical trial has high and predictable mortality (as in the case of studying new human immunodeficiency virus drugs).[22] However, investigators in numerous studies use both a placebo control and a historical control when evaluating novel analgesic drugs.

The common adverse effects reported in this study of rhinorrhea and nasal discomfort appear on the package insert for the oxymetazoline-containing product Afrin (Bayer Consumer Care Products),[9] which commonly is used as an OTC nasal decongestant at dosages used in this study. Rebound nasal congestion, another common adverse event seen in this study, also has been reported after oxymetazoline administration.[23] K305 produced modest and generally clinically nonsignificant changes in cardiovascular parameters. The modest increases in SBP and DBP, which also were reported in a previous safety and pharmacokinetic study published in The Journal of the American Dental Association,[11] are also likely the result of the oxymetazoline component of the formulation. Being a postsynaptic α-2 receptor agonist, oxymetazoline affects the cardiovascular system primarily by means of vasoconstriction.

K305 produced clinically nonsignificant decreases in olfactory function when compared with the placebo spray. Alcohol sniff test results remained greater than 17 cm for both the K305 and placebo groups. In a previous study, participants with normal olfactory function displayed a mean olfactory threshold distance of approximately 14 cm.[13]

CONCLUSIONS

Our study results show that the intranasal administration of K305 provides adequate maxillary pulpal anesthesia to perform single restorative procedures on premolars, canines, and incisors in 88.0% of participants. Adverse effects included rhinorrhea, nasal discomfort, nasal congestion, and modest increases in SBP and DBP, and these appear to be related to the 0.05% oxymetazoline, which is FDA approved as an OTC nasal decongestant. A new drug application for approval of K305 was filed with the FDA in May 2015. ■

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