Comparison of 3 intranasal mists for anesthetizing maxillary teeth in adults

A randomized, double-masked, multicenter phase 3 clinical trial

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The most common method of anesthetizing a maxillary tooth is intraoral supraperiosteal injection of local anesthetic, commonly referred to as maxillary infiltration. Although this procedure is effective, the need for injection carries several drawbacks that can complicate treatment.

Fear of painful injections and subsequent avoidance behavior are significant barriers to regular dental care.[1] An estimated 30 to 40 million Americans avoid visiting the dentist because of fear of pain and anesthetic injections.[2-4] Injection of dental anesthetic also carries the occupational hazard of possible exposure to blood-borne pathogens via needlestick. To reduce this risk, Congress passed the Needlestick Safety and Prevention Act,[5] which requires the use of needle-free technology whenever possible. This law provides incentives to develop anesthetics that can be delivered via such technologies.

Supplemental material is available online.

Even with perfect administration technique, the onset, effectiveness, and duration of maxillary infiltration anesthesia can vary widely among patients. Success rates can range from 65% to 100%; time between injection and onset of anesthesia can range from 2 to 5 minutes in the maxillary arch; and duration of pulpal anesthesia can range from 10 to 100 minutes.[6-17] In a survey of 93 general practitioners, 42% of respondents reported at least 1

ABSTRACT

Background. This double-masked, parallel-design, clinical trial assessed whether a combination nasal spray (K305; 3% tetracaine hydrochloride and 0.05% oxymetazoline hydrochloride) compared with a tetracaine-only spray and a placebo spray would be safer and superior in producing local anesthesia sufficient to complete a direct restorative procedure in maxillary nonmolar teeth.

Methods. The authors randomized eligible patients to receive K305 spray (n = 44), tetracaine hydrochloride spray (n = 44), or a placebo solution (n = 22). The authors compared the incidence of the primary efficacy end point—completion of the procedure without rescue local anesthetic—by means of a 1-tailed Fisher exact test.

Results. The end point incidence was 84.1% (95% confidence interval [CI], 69.9-93.4) with K305, 27.3% (95% CI, 15.0-42.8) with tetracaine only, and 27.3% (95% CI, 10.7-50.2) with placebo ($P < .001$ for K305 versus tetracaine only and versus placebo). Combination spray was associated with statistically significant but transient increases in blood pressure. The most frequent adverse events were rhinorrhea and nasal congestion, which resolved within 2 hours after treatment and occurred more often in the K305 group and tetracaine-only group.

Conclusions. In this study population, the K305 combination nasal spray was safe and more effective in attaining pulpal anesthesia of maxillary teeth from premolar to premolar compared with tetracaine-only and placebo sprays.

Practical Implications. The combination nasal spray might represent a valuable alternative to injected local anesthetic for patients undergoing invasive maxillary dental procedures.

Key Words. Anesthesia; clinical trial; nasal spray; tetracaine hydrochloride; oxymetazoline hydrochloride.

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anesthetic failure in maxillary posterior teeth, and 26% reported at least 1 failure in maxillary anterior teeth.[18] Infiltration injection may fail because of individual variations in response to the drug administered, cortical plate bone density, tissue vascularity, and neuroanatomy.

An anesthetic procedure that obviates the need for injection could benefit both patients and practitioners. For many years, practitioners have used nasally applied compounds to anesthetize tissues before diagnostic and surgical otolaryngological procedures.[19-24] For procedures involving the nasal cavity, practitioners often add a vasoconstrictor such as oxymetazoline hydrochloride to reduce swelling and the risk of experiencing bleeding.[19] In a phase 2 study of combination tetracaine–oxymetazoline spray, 83% of patients receiving the spray required no rescue anesthesia via lidocaine injection.[25] Among procedures involving maxillary nonmolar teeth, the success rate was even higher (90%), and the spray was safe and well tolerated.[25] Initial phase 3 testing showed similar success rates—88% for the combination spray versus 28% for placebo spray.[26]

The objective of this phase 3 study was to determine the efficacy and safety of combination tetracaine–oxymetazoline nasal spray (K305) compared with an active control (tetracaine-only spray) and a placebo spray for anesthetizing maxillary teeth in adults.

METHODS

This was a multicenter, randomized, double-masked, parallel-group clinical trial comparing a combination nasal anesthetic spray (K305 [also called Kovanaze], St. Renatus) with a tetracaine-only spray and with a placebo spray among adults undergoing a dental procedure in a maxillary nonmolar tooth. We recruited patients seeking treatment at the University at Buffalo, The State University of New York, Buffalo, NY (n = 50) (center 1), and at Family and Cosmetic Dentistry, Salt Lake City, Utah (n = 60) (center 2). We conducted this study in compliance with the approval of the institutional review board at each center.

Inclusion criteria. We included patients 18 years or older who required local anesthesia for a restorative dental procedure in 1 vital maxillary nonmolar tooth. Patients could have no evidence of pulpal pathology. They were required to be able to give informed consent and understand and comply with the protocol's requirements; have a patent naris ipsilateral to the target tooth; have a resting heart rate of 55 to 100 beats per minute; and have a systolic blood pressure of 95 to 140 millimeters of mercury and a seated diastolic blood pressure of 60 to 90 mm Hg.

Exclusion criteria. We excluded patients who had inadequately controlled thyroid disease; 5 or more nosebleeds each month; allergy or intolerance to any study drug or preparation ingredient; or congenital or idiopathic methemoglobinemia. We also excluded patients who had received a monoamine oxidase inhibitor within the previous 3 weeks or who had used a nasal spray or decongestant on the day of the study procedure.

Study procedures. An independent statistician prepared a computer-generated randomization schedule in blocks, within which we assigned annotations for treatment groups. We numbered each drug kit in randomization order and assigned it to a study center on shipment. We assigned a sequential number to each patient who met the eligibility criteria, and these numbers determined the kit assignments. Therefore, the patients, investigators (S.C., A.M., D.G., S.B., F.A., S.A., S.M.), and the investigation team members who administered the spray (A.M., C.P., E.P.) all were masked as to the treatment administered. At the Buffalo site, 2 members of the investigation team (C.P., E.P.) administered the spray, and at the Utah site, the investigator (A.M.) administered the spray.

We randomly assigned patients in a 2:2:1 ratio to receive a total of 3 intranasal sprays (BD Accuspray nasal spray system, Becton, Dickinson and Company) of 200 microliters each of K305, tetracaine-only, or placebo spray ipsilateral to the treatment tooth, each given at 4 (± 1) minute intervals. The K305 spray contained 3% tetracaine hydrochloride and 0.05% oxymetazoline hydrochloride. The 3-spray dose (600 μL) therefore contained 18 milligrams tetracaine hydrochloride and 0.3 mg oxymetazoline hydrochloride. The tetracaine-only spray was a 3% tetracaine hydrochloride solution, and the 3-spray dose contained 18 mg of the drug. The placebo spray was identical to the active treatments in volume and administration technique. All 3 sprays were clear, colorless, odorless, and tasteless aqueous solutions.

At mean (standard deviation [SD]) 15 (3) minutes after administering the first spray dose, the investigators measured pulpal anesthesia by means of a subjective numbness assessment (SNA) (Appendix 1, available online at the end of this article) and performed a soft-tissue anesthesia assessment (STAA) (Appendix 2, available online at the end of this article) with a periodontal probe (PDT Sensor Probe, DenMat) on the incisive papilla and greater palatine foramen. If the investigator deemed the patient's dental anesthesia to be sufficient, the investigator began the procedure with a test drill. If the investigator deemed the patient's dental anesthesia to be insufficient, the investigator delayed the procedure another 5 minutes, at which time, the investigator repeated the SNA and STAA. If the anesthesia remained insufficient, the investigator immediately administered rescue anesthetic, consisting of up to 3.4 milliliters of articaine hydrochloride 4% with epinephrine 1:200,000.

ABBREVIATION KEY. **BPM:** Beats per minute. **ND:** Not done. **SNA:** Subjective numbness assessment. **STAA:** Soft-tissue anesthesia assessment.

The investigators measured vital signs, noted the results of the SNA and STAA, and documented the incidence of adverse events every 15 (± 3) minutes for an hour after the first dose of study drug, then at mean (standard deviation) 90 (± 3) minutes. The investigators also performed a participant-reported safety assessment (Appendix 3, available online at the end of this article), naris examination, and alcohol sniff test at 120 (± 3) minutes after the first dose of the study drug and at the next-day follow-up visit.

Statistical analysis. The primary end point was the success rate, which we defined as completion of the dental procedure without the use of a rescue injection of local anesthetic. We expected the success rate to be approximately 83% with K305 spray.[25] Because each pairwise comparison was a 1-tailed test, we set the type I error (α) for each test at 0.025 (that is, 0.05/2). We determined that the study results were to be declared positive only if we could show that K305 was superior to both tetracaine-only and placebo sprays. We set the type II error (β) at 0.10. We determined that the power of the study results to detect a 50% relative difference in success rate for K305 spray versus tetracaine only and versus placebo was to be at least 90%. We determined that the intended sample sizes—44 patients in the K305 group, 44 patients in the tetracaine-only group, and 22 patients in the placebo group—were sufficient to detect such differences at the desired power and α levels. We computed power using StatXact 8 (Cytel) for Fisher exact test comparing 2 binomial proportions. We included all randomized patients in the analyses.

The secondary efficacy end points were the incidence, time of onset, and duration of soft-tissue anesthesia as assessed by the results of the STAA. We defined onset as the time from completion of dosing to the time that the patient reported no pain on pressure probing at the incisive papilla and greater palatine foramen. We defined duration as the time from anesthesia onset to the time the patient reported pain on soft-tissue pressure probing.

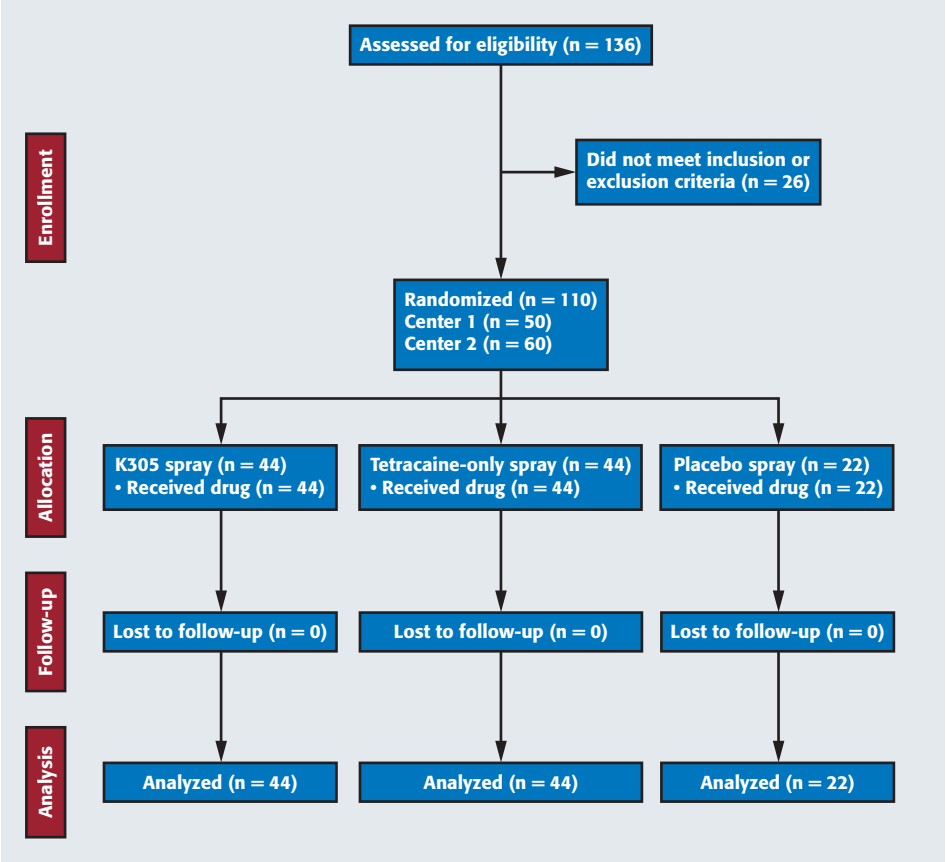

Figure 1. Flowchart indicating disposition of patients.

During a preliminary post hoc analysis, we noticed that a disproportionate number of patients at study center 1 had reported no pain on pressure probing, even before treatment. Additional investigation revealed confusion over the question's wording—the expected baseline answer was "yes," in contrast with expected baseline answer to the other study questions. As far as we could determine, the STAA was the only assessment that generated such confusion. Because of the questionable baseline data for the STAA at this study center, we could not define the onset and duration for a large number of patients. We therefore conducted a post hoc analysis of STAA results, stratified by study center.

We also conducted exploratory analyses of homogeneity of treatment effect across subgroups. We used the Breslow-Day test to assess homogeneity in treatment effect with regard to study center, tooth type (anterior versus premolar), age, sex, ethnicity, and weight.

We assessed predefined changes in heart rate and blood pressures through the next-day follow-up visit. We also compared the mean maximum change from baseline

TABLE 1

Demographic and baseline characteristics of patients.

CHARACTERISTIC	K305 SPRAY (N = 44)	TETRACAINE-ONLY SPRAY (N = 44)	PLACEBO SPRAY (N = 22)	*P* VALUE
Sex, No. (%)				.011
Male	14 (31.8)	28 (63.6)	10 (45.5)	
Female	30 (68.2)	16 (36.4)	12 (54.5)	
Race, No. (%)				.267
White	35 (79.5)	36 (81.8)	13 (59.1)	
Black	2 (4.5)	3 (6.8)	2 (9.1)	
Asian	1 (2.3)	2 (4.5)	4 (18.2)	
Native Hawaiian/Pacific Islander	2 (4.5)	0 (0)	1 (4.5)	
Other	4 (9.1)	3 (6.8)	2 (9.1)	
Ethnicity, No. (%)				.876
Hispanic or Latino	3 (6.8)	2 (4.5)	1 (4.5)	
Not Hispanic or Latino	41 (93.2)	42 (95.5)	21 (95.5)	
Medical History, No. (%)				ND*
Hypertension	4 (9.1)	2 (4.5)	4 (18.2)	
Seasonal allergy	9 (20.5)	11 (25.0)	5 (22.7)	
Exercise-induced asthma	2 (4.5)	2 (4.5)	2 (9.1)	
Current smoking	11 (25.0)	10 (22.7)	5 (22.7)	
Dental Pathology, No. (%)				ND
Caries	32 (72.7)	34 (77.3)	18 (81.8)	
Recurrent decay	12 (27.3)	7 (15.9)	4 (18.2)	
Fracture	4 (9.1)	4 (9.1)	2 (9.1)	
Target Tooth Number, No. (%)				ND
4 (second premolar)	6 (13.6)	7 (15.9)	2 (9.1)	
5 (first premolar)	7 (15.9)	8 (18.2)	5 (22.7)	
6 (canine)	3 (6.8)	2 (4.5)	2 (9.1)	
7 (lateral incisor)	3 (6.8)	2 (4.5)	2 (9.1)	
8 (central incisor)	2 (4.5)	5 (11.4)	2 (9.1)	
9 (central incisor)	3 (6.8)	5 (11.4)	4 (18.2)	
10 (lateral incisor)	5 (11.4)	3 (6.8)	0 (0)	
11 (canine)	1 (2.3)	3 (6.8)	0 (0)	
12 (first premolar)	4 (9.1)	2 (4.5)	3 (13.6)	
13 (second premolar)	10 (22.7)	7 (15.9)	2 (9.1)	
Age, y, Mean (SD†)	37.1 (14.73)	31.3 (12.01)	35.7 (14.64)	.128
Height, Centimeters, Mean (SD)	167.3 (8.38)	175.5 (8.88)	169.4 (9.19)	< .001
Weight, Kilograms, Mean (SD)	85.2 (23.3)	82.6 (21.1)	80.8 (19.2)	.718

* ND: Not done.
† SD: Standard deviation.

TABLE 2

Primary end point results: completion of dental procedure without need for rescue local anesthetic.

RESULT	K305 SPRAY (N = 44)		TETRACAINE-ONLY SPRAY (N = 44)		PLACEBO SPRAY (N = 22)	
	No. (%) of Patients	95% CI*	No. (%) of Patients	95% CI	No. (%) of Patients	95% CI
Success	37 (84.1)	69.9-93.4	12 (27.3)	15.0-42.8	6 (27.3)	10.7-50.2
Failure	7 (15.9)	ND†	32 (72.7)	ND	16 (72.7)	ND
***P* Value**	—‡		< .001§		< .001§	

* CI: Confidence interval.
† ND: Not done.
‡ Not applicable.
§ Versus K305 spray; 1-sided Fisher exact test.

in heart rate and blood pressures by means of analysis of variance, with treatment group and study center as factors. We used the same method to analyze findings from the alcohol sniff test from the next-day follow-up visit.

We compared profiles over time for heart rate and blood pressures by means of repeated-measures analysis of covariance (implemented by using SAS/STAT PROC MIXED, SAS Institute) with treatment, time, study center, and prestudy vital sign measurements as fixed effects and patient as a random effect.

We assessed the incidence and relationship to the study drug through the next-day follow-up visit for adverse events and through 30 days for serious adverse events.

RESULTS

Patients. Between October 2012 and February 2013, we screened 136 patients, of whom we randomized 110 as previously described, and all patients completed their dental procedure and study assessments (Figure 1). One patient in the tetracaine-only group had a change in the target tooth (from tooth no. 11 to tooth no. 6), but no other major protocol violations occurred. Four dentists (A.M., B.S., D.G., F.A.) placed the restorations.

The patients' mean age was 34.5 years, and 76.4% were white (Table 1). The tetracaine-only group included significantly more men, and the mean height was significantly greater in this group as well. The most frequent pathology in the target tooth was caries, with recurrent decay and tooth fractures accounting for the remainder. Target teeth (each patient had only 1 target tooth) were distributed similarly

between the left and right sides, with premolars predominating. Intraoral examinations were normal for all patients except for 1 patient in the placebo group who showed localized gingival enlargement.

Primary end point. In all, 84.1% of the patients who received K305 completed their class IV restoration without the need for rescue anesthesia, compared with 27.3% of patients in both the tetracaine-only and placebo groups (Table 2; $P < .001$ for K305 versus each of the other treatments). For patients requiring rescue anesthesia, the injection was given at similar mean times: 16.0 minutes, 15.2 minutes, and 16.3 minutes after the first dose of K305, tetracaine-only, and placebo spray, respectively.

Secondary end points. At the prestudy visit, most patients reported pain on pressure probing at the incisive papilla and greater palatine foramen. Beginning at 15 minutes after the first dose of the study drug, and continuing through the 90-minute assessment, the proportion of patients reporting no pain at the incisive papilla was highest in the K305 group (77.3% at 15 minutes versus 47.7% for tetracaine only and 36.4% for placebo). At the 120-minute and next-day follow-up visits, the proportions of patients reporting no pain at this site were similar across treatment groups. For the greater palatine foramen, the proportions of patients reporting no pain were smaller (compared with the incisive papilla) and similar among groups at all time points.

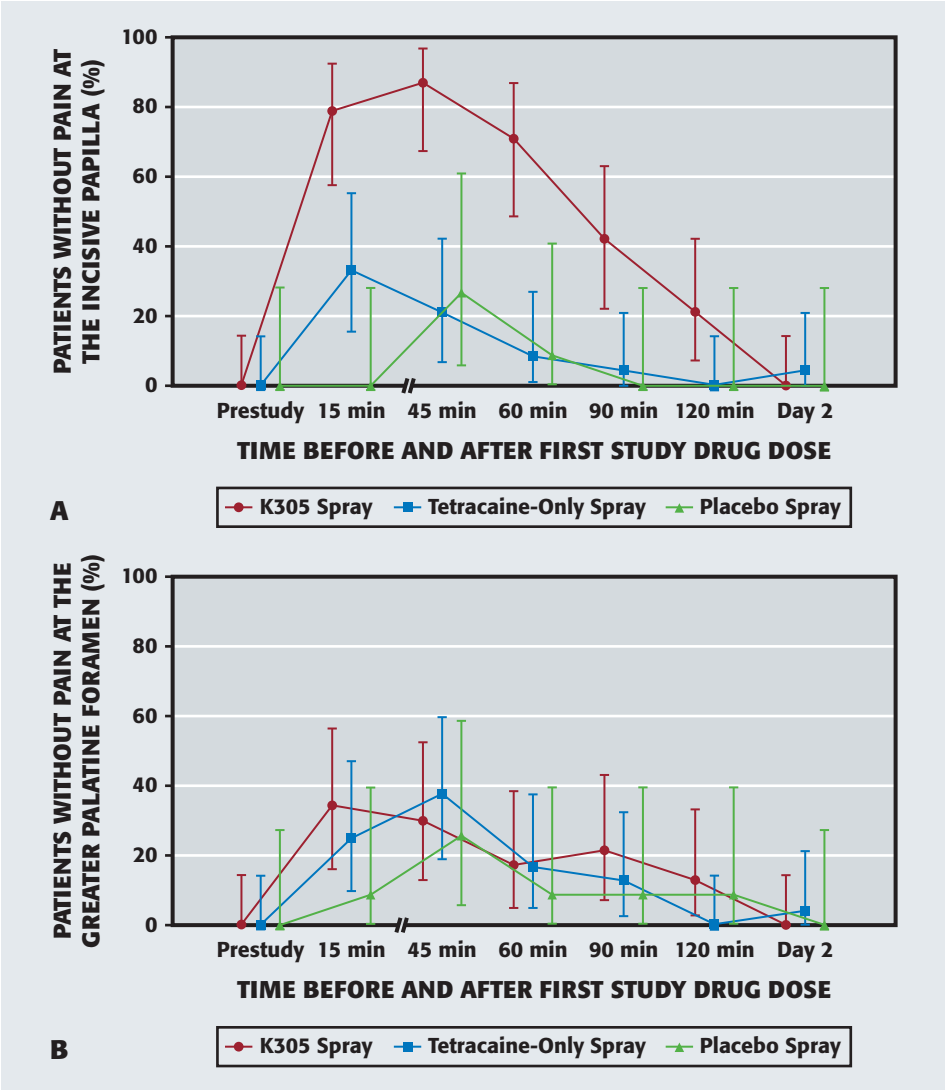

Figure 2. Proportions of patients at center 2 reporting no pain from probing pressure at the incisive papilla (**A**) and greater palatine foramen (**B**) over time with K305 spray, tetracaine-only spray, or placebo spray, in post hoc analysis. Data at 30 minutes are not shown because of the large number of missing data points (patients were still undergoing the dental procedure). Vertical lines denote 95% confidence intervals. min: Minutes.

In post hoc analysis of data from center 2 (see Methods; Figure 2), all patients reported pain from probing pressure in both oral locations before drug administration. Onset of anesthesia in the incisive papilla occurred at mean (SD) 9.7 (7.5) minutes in the K305 group (n = 22), 19.5 (17.6) minutes in the tetracaine-only group (n = 13), and 37.0 (0.0) minutes in the placebo group (n = 3; no *P* value calculated). Anesthesia persisted for mean (SD) 79.2 (27.0) minutes, 32.1 (15.2) minutes, and 26.0 (17.3) minutes, respectively (no *P* value calculated). At 15 minutes, anesthesia of the incisive papilla was present in 79.2%, 33.3%, and 0% of patients in the K305, tetracaine-only, and placebo groups, respectively ($P < .001$). At 60, 90, and 120 minutes, these proportions had decreased somewhat but remained significantly different by treatment. Anesthesia at the greater palatine foramen occurred at

TABLE 3

Adverse events and vital sign–related end points, by treatment.

EVENT	K305 SPRAY (N = 44)	TETRACAINE-ONLY SPRAY (N = 44)	PLACEBO SPRAY (N = 22)
	No. (%) of Patients	No. (%) of Patients	No. (%) of Patients
Rhinorrhea	17 (38.6)	17 (38.6)	0 (0)
Nasal Congestion	15 (34.1)	27 (61.4)	3 (13.6)
Nasal Discomfort	11 (25.0)	5 (11.4)	1 (4.5)
Lacrimation Increased	7 (15.9)	4 (9.1)	0 (0)
Oropharyngeal Pain	6 (13.6)	4 (9.1)	0 (0)
Headache	6 (13.6)	1 (2.3)	1 (4.5)
Procedural Pain	6 (13.6)	22 (50.0)	13 (59.1)
Hypoesthesia	5 (11.4)	17 (38.6)	5 (22.7)
Throat Irritation	4 (9.1)	1 (2.3)	0 (0)
Paresthesia	4 (9.1)	0 (0)	0 (0)
Bradycardia	4 (9.1)	2 (4.5)	1 (4.5)
Hypertension	4 (9.1)	1 (2.3)	1 (4.5)
Rhinalgia	3 (6.8)	2 (4.5)	0 (0)
Upper-airway Cough Syndrome	3 (6.8)	2 (4.5)	0 (0)
Tachycardia	3 (6.8)	2 (4.5)	0 (0)
Toothache	2 (4.5)	10 (22.7)	5 (22.7)
Dysgeusia	2 (4.5)	1 (2.3)	0 (0)
Sinus Headache	2 (4.5)	0 (0)	0 (0)
Vital Sign–Related End Points			
Heart rate < 50 bpm*	1 (2.3)	2 (4.5)	0 (0)
Heart rate > 125 bpm	1 (2.3)	0 (0)	0 (0)
Decrease in systolic blood pressure of ≥ 15 mm Hg† and to < 90 mm Hg	0 (0)	0 (0)	0 (0)
Increase in systolic blood pressure of ≥ 25 mm Hg and to > 160 mm Hg	2 (4.5)	1 (2.3)	0 (0)
Decrease in diastolic blood pressure of ≥ 10 mm Hg and to < 50 mm Hg	1 (2.3)	0 (0)	0 (0)
Increase in diastolic blood pressure of ≥ 15 mm Hg and to > 105 mm Hg	1 (2.3)	0 (0)	0 (0)

* bpm: Beats per minute.
† mm Hg: Millimeters of mercury.

Safety end points. All but 2 patients (1 each in the K305 and placebo groups) had at least 1 adverse event, neither of which led to discontinuing the patients' participation in the study or death. The most common adverse events were rhinorrhea, nasal congestion, and nasal discomfort, of which most were considered mild (Table 3). Four patients in the K305 group had 5 severe events: 1 each of nasal discomfort, oropharyngeal pain, rhinalgia, sneezing, and throat irritation. Three patients in the tetracaine-only group also had severe events: 1 had toothache, and 1 had procedural pain. Another patient was the only study participant to have multiple serious adverse events—orbital cellulitis requiring hospitalization, headache, and sinusitis—that occurred 10 days after the patient's dental procedure. The investigator (S.C.) judged these latter events to be remotely related to treatment.

The incidence of vital sign–related end points was low across treatment groups (Table 3). For heart rate, the mean values over time and mean maximum changes did not differ significantly among groups ($P = .30$ and .49, respectively; Figure 3). For systolic blood pressure, the mean over time did differ significantly among groups ($P < .002$; Figure 4), as did the mean (SD) maximum change in the K305 group (13.7 [10.74] mm Hg) versus the placebo group (5.1 [9.32] mm Hg; $P = .004$). For diastolic blood pressure, the mean over time did not differ by treatment ($P = .133$), but the mean (SD) maximum change was again significantly higher in the K305 group (10.5 [7.12] mm Hg) than in the tetracaine-only (7.3 [4.96] mm Hg) or placebo group (6.7 [4.91] mm Hg; $P = .013$). The increases in blood pressure observed in the K305 group were transient in all but 1 patient, asymptomatic, and required no medical intervention.

Posttreatment olfactory sensitivity, assessed by results of the alcohol sniff test, decreased slightly in all patients after drug administration. By the next-day follow-up visit, sensitivity had continued to decrease in

mean (SD) 15.5 (11.4) minutes in the K305 group (n = 14), 24.6 (17.6) minutes in the tetracaine-only group (n = 13), and 29.5 (15.0) minutes in the placebo group (n = 4), and persisted for 45.9 (36.3) minutes, 35.4 (22.6) minutes, and 31.8 (29.5) minutes, respectively (no *P* values calculated).

Results of Breslow-Day tests for homogeneity revealed no significant differences in treatment effect according to study center, age, sex, or ethnicity. The benefit of K305 over placebo was significantly greater in anterior teeth—a success rate of 17 of 17 (100%; 95% confidence interval [CI], 80.5-100) versus 1 of 10 (10%; 95% CI, 0.3-44.5), respectively—than in premolars (20 of 27 [74.1%; 95% CI, 53.7-88.9] versus 5 of 12 [41.7%; 95% CI, 15.2-72.3]; $P = .006$). The incremental benefit of using K305 versus tetracaine alone did not vary significantly by type.

the tetracaine-only and placebo groups, whereas it had returned slightly toward baseline in the K305 group. Nasal examinations revealed no major clinical findings by the next-day follow-up visit.

DISCUSSION

In this study, the use of a combination tetracaine–oxymetazoline nasal anesthetic spray permitted completion of a restorative dental procedure on a maxillary nonmolar tooth without the need for rescue local anesthetic injection in 84.1% of cases, compared with rates of 27.3% for tetracaine-only and placebo sprays. Study participants tolerated all 3 treatments well.

The success rate with the K305 combination spray that we observed in this study is nearly identical to the success rate revealed in a corresponding multicenter phase 3 trial, which compared K305 with placebo spray alone.[26]

In this study, the benefit of using K305 spray instead of the placebo was significantly greater in anterior teeth than in premolars. This phenomenon might reflect genetic differences among the study participants. For example, although 3 branches of the superior alveolar nerve—anterior, middle, and posterior—can supply the maxillary teeth, the middle branch (which is associated with premolars) is absent in 30% to 54% of people.[27] How the body compensates for this absence is unknown and might vary, but this nerve's function might be replaced by another nerve for which the combination spray is less effective. Experience with the spray device in the future might allow more of the compound to reach the rear of the nasal cavity, increasing the degree of anesthesia to the premolars and possibly the molars.

K305 showed a large effect relative to placebo and to tetracaine alone, thus allowing sufficient statistical power to detect differences despite small sample sizes. In addition, K305 is not being developed as a general substitute for dental anesthesia; to date, it

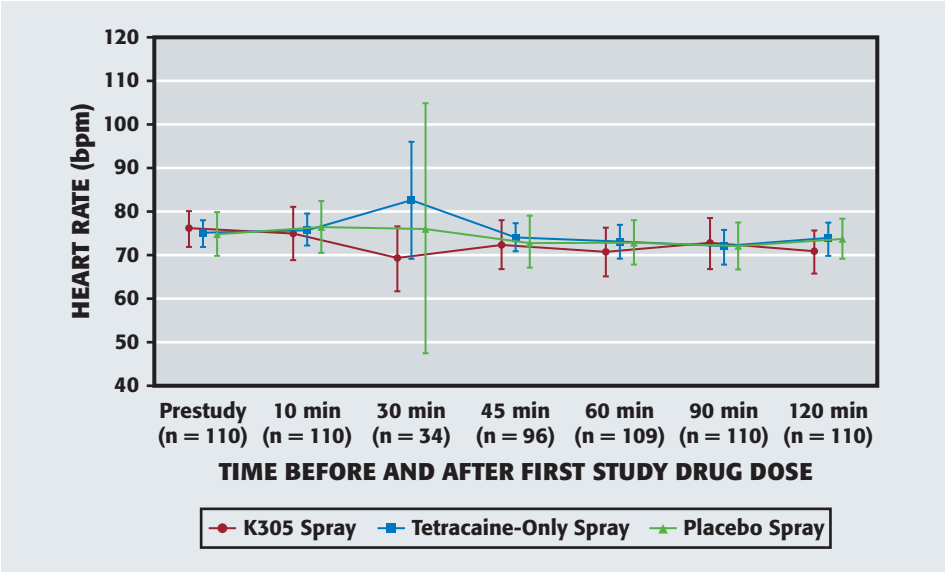

Figure 3. Mean heart rate over time in the K305, tetracaine-only, and placebo groups. Vertical lines denote 95% confidence intervals. bpm: Beats per minute.

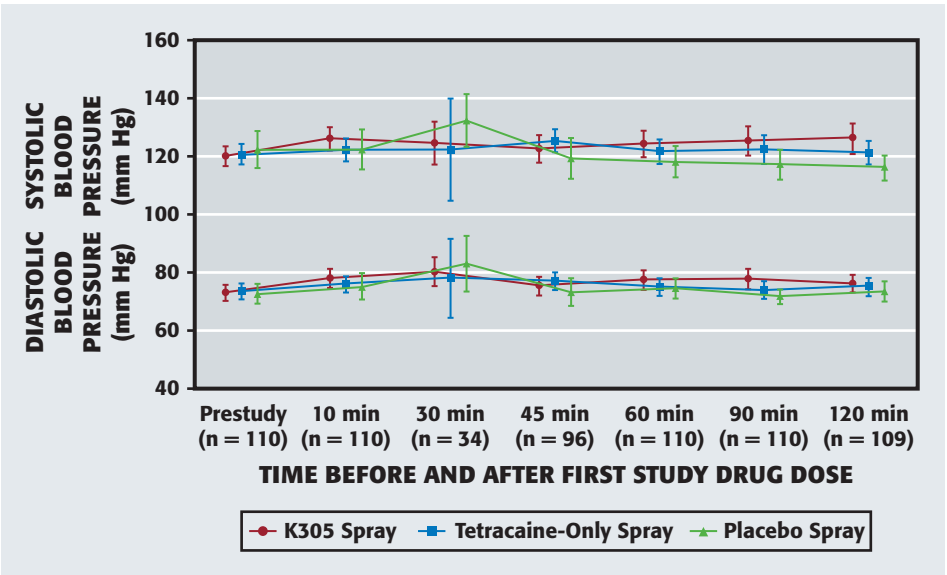

Figure 4. Mean systolic and diastolic blood pressures over time in the K305, tetracaine-only, and placebo groups. Vertical lines denote 95% confidence intervals. mm Hg: millimeter of mercury.

has shown effects only in maxillary nonmolar teeth in adults.

As might be expected with an intervention involving nasal sprays, the most frequent adverse events were rhinorrhea, nasal congestion, and nasal discomfort, most of which were considered mild. By the day after treatment, most patients had returned to baseline status with no clinically significant problems manifest.

Mean maximum changes in blood pressure were significantly greater in the K305 group versus the placebo group, counter to phase 2 findings.[25] These differences could be attributed to the mechanism of action of oxymetazoline, a sympathomimetic drug that selectively agonizes α1- and (partly) α2-adrenergic receptors, causing vasoconstriction.[28] At the same time, the placebo group showed marked decreases in blood pressure, possibly related to the more frequent use of rescue (articaine or epinephrine) injections in this group.[29] Such decreases would have magnified any potential hypertensive effects of oxymetazoline. In any event, these changes in blood pressure were generally transient, as in a previous pharmacokinetic study,[30] and required no intervention.

Although we attempted to minimize the possibility of bias through randomization and double-masking, we noticed that a discrepancy emerged between study centers regarding how investigators conducted the STAA. We therefore performed both the intention-to-treat analysis and a post hoc analysis from the study center that had more complete data. We also did not control for possible interobserver variability in some assessments (for example, nasal examination for inflammation or ulceration). Such variables were secondary end points, however, and should not have influenced the main analyses.

Nasally administered anesthetic can preclude many of the risks and drawbacks of injected anesthetics, for both patients and practitioners, including needlesticks. In addition, if the patient requires a more complicated procedure, providers can administer additional palatal anesthetic with a reduced possibility of pain in some cases.

CONCLUSIONS

In this study, combination tetracaine–oxymetazoline nasal spray was superior to tetracaine-only and placebo sprays in producing anesthesia sufficient to allow completion of a direct dental restorative procedure on a maxillary nonmolar tooth in adults. This novel compound could offer a valuable alternative to injected local anesthesia for patients and practitioners alike. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at http://dx.doi.org/10.1016/j.adaj.2015.11.009.

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APPENDIX 1: INSTRUCTIONS FOR SUBJECTIVE NUMBNESS ASSESSMENT

To assess conditions that could be associated with investigative drug, ask the study participant the following questions:

- Do you notice any abnormal sensation when you tap your front teeth together?
- Do you notice any abnormal sensation in the roof of your mouth?

Record the response (yes or no) in the source documents.

APPENDIX 2: INSTRUCTIONS FOR SOFT-TISSUE ANESTHESIA ASSESSMENT

To assess soft-tissue anesthesia, use a mechanical periodontal probe to exert pressure on the following:

- incisive papilla
- greater palatine foramen ipsilateral to the study dental procedure.

For each site tested, ask the study participant, "Do you feel any pain?" and record the response (yes or no) in the source documents.

Testing at each of the 2 soft-tissue sites will take place at baseline; at 15, 30, 45, 60, 90, and 120 minutes after the procedure (unless pain is detected); and at the next-day follow-up visit.

APPENDIX 3: INSTRUCTIONS FOR PARTICIPANT-REPORTED SAFETY EVALUATION

To assess conditions that could be associated with the investigative drug, ask the study participant (and record the responses in the source documents) the following questions:

- Do you feel any different now than when you came in for treatment today?
- Are you currently feeling or exhibiting any of the following conditions?

Restlessness	Yes	No
Dizziness	Yes	No
Confusion	Yes	No
Body Numbness	Yes	No
Tinnitus	Yes	No
Blurred Vision	Yes	No
Tremors	Yes	No
Nausea	Yes	No
Itching	Yes	No
Breathing Problems	Yes	No
Light-headedness	Yes	No
Metallic Taste	Yes	No
Numbness Around Mouth	Yes	No
Agitation	Yes	No