Potassium oxalate mouthrinse reduces dentinal hypersensitivity

A randomized controlled clinical study

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ABSTRACT

Background. Dentinal hypersensitivity is a prevalent oral condition that can be treated with in-office application of potassium oxalate (KO), which has US Food and Drug Administration 510(k) clearance. In this study, the authors assessed a KO mouthrinse for home use. The authors evaluated clinically meaningful improvement by analyzing the proportions of participants who responded to treatment.

Methods. In this multicenter, double-blind, parallel-group controlled study, the authors randomly assigned 375 participants with dentinal hypersensitivity to 1 of 2 mouthrinse groups: KO (189 participants) and placebo (186 participants). Participants used their assigned mouthrinses for 4 weeks. Each participant's success (defined as a $\geq$ 30% reduction from baseline in mean cold air stimulus response) was the primary efficacy measurement. The authors further defined success, on the basis of 2012 criteria from the American Dental Association, as a statistically significant difference of 20% or more between experimental and placebo groups for 1 sensitivity index.

Results. KO mouthrinse had statistically significantly higher success rates (the primary efficacy measurement) than did placebo (69.3% versus 44.6%; estimated odds ratio [OR], 2.817; 95% confidence interval [CI], 1.843 to 4.307; $P < .001$). At week 4, KO had statistically significant improvements compared with placebo in cold air stimulus score (estimated difference, −14.27 millimeters; 95% CI, −18.68 to −9.87; 35.6% improvement; $P < .001$) and tactile sensitivity (estimated difference, 13.45 grams; 95% CI, 9.83 to 17.08; 88.0% improvement; $P < .001$). The authors also observed statistically significant improvements for KO at week 2. Cold air stimulus and tactile sensitivity scores at weeks 2 and 4 were secondary efficacy measurements.

Conclusions. This study's results demonstrated that KO mouthrinse used as an adjunct to tooth-brushing statistically and clinically significantly controlled and reduced dentinal hypersensitivity.

Practical Implications. Clinicians can use these results when determining appropriate at-home care regimens for patients with hypersensitivity.

Key Words. Potassium oxalate; sensitivity; cold air stimulus; Yeaple probe; visual analog scale; mouthrinse; dentin

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Cervical dentinal hypersensitivity is a condition characterized by sharp pain associated with thermal, evaporative, tactile, osmotic, or chemical stimuli.[1] Investigators have described this condition clinically as an exaggerated response to nonnoxious stimuli that is dependent on dentin exposure and the lack of obstruction of the dentinal tubules. More than 90% of hypersensitive tooth surfaces are at the cervical margin on the facial aspects of the teeth.[2] The cause of dentinal hypersensitivity can be the result of dentinal tubules exposure because of loss of enamel or gingival recession.[3] The prevalence of dentinal hypersensitivity varies from 4% through 57% in the general population studied.[4] In our study, we evaluated the potential of a potassium oxalate

(KO) mouthrinse formulation to reduce and control dentinal hypersensitivity compared with a placebo control mouthrinse.

Results from previous in vitro permeability and scanning electron microscope studies and in vivo studies have shown that pastes or aqueous solutions containing KO occlude dentinal tubules by creating acid-resistant calcium oxalate crystals on the dentinal surface and inside the dentinal tubules.[5] This precipitation blocks fluid movement and so reduces dentinal hypersensitivity discomfort or pain. Various desensitizing devices containing KO (Remesense [K082594],[6] Seal Block [K123653],[7] and Super Seal [K983477][8]) have US Food and Drug Administration (FDA) 510(k) clearance. In particular, Super Seal (Bisco) was designed specifically as an in-office, topical, single-use product for exposed dentinal surfaces. The KO mouthrinse in this study is intended as an over-the-counter product used as a twice-daily mouthrinse to reduce and control dentinal hypersensitivity. The FDA clearance, coupled with prior clinical experience with KO mouthrinse and risk assessment, shows that KO can be used in humans without causing harm and that twice-daily use (up to 20 milliliters per day, maximum dose) does not pose significant risk, although we did not include people prone to developing kidney stones in this study.[9]

The FDA, in response to previous KO device study results submitted for review, requested an additional study to demonstrate the clinically significant effectiveness of the mouthrinse device that included sensitivity to cold as a primary measure because this is a common symptom among those who experience dentinal hypersensitivity, as well as detailed documentation of adverse events (AEs). In our study, we incorporated feedback from the FDA on demonstrating safety and effectiveness in reducing and controlling dentinal hypersensitivity.

METHODS

Study design

We conducted this multicenter, double-blind, randomized, parallel-group, controlled clinical study in the United States. After a 2-week screening period, participant random assignment began April 11, 2014, and the study ended by May 30, 2014, at Salus Research in Fort Wayne, Indiana (site 1001) and Silverstone Research Group in Las Vegas, Nevada (site 1002).

We conducted the study in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (E6),[10] in agreement with the Declaration of Helsinki[11] and applicable local regulations. The institutional ethics committee on research involving humans approved the study protocol (14.03.0049 for site 1001; 14.03.0050 for site 1002). We obtained written informed consent from all participants after each received a thorough explanation of the study and had the opportunity to ask questions in private.

Participants

Participants at site 1001 were from the Fort Wayne, IN, area, and those at site 1002 were from the Las Vegas, NV, area. Investigators at both sites selected participants from their databases or recruited through advertising. Participants were men and women 18 years or older, in good general and oral health, with a minimum of 2 natural premolars, canines, or incisors with caries-free facial or buccal surfaces with cervical abrasion, erosion, or gingival recession. We selected up to 2 eligible teeth per quadrant, each separated by 2 other teeth, as study teeth, and the teeth exhibited these criteria: cold air stimulus visual analog scale (VAS) scores of 40 to 80 millimeters on a 100-mm VAS,[12] tactile sensitivity scores of 10 to 30 grams of pressure after Yeaple probe application, and VAS scores after Yeaple probe application of 40 to 80 mm at screening (−2 weeks) and baseline. In addition, participants had no significant oral soft-tissue disease, adequate oral hygiene, no severe marginal gingivitis or moderate or advanced periodontitis, and no extensive supragingival calculus, on the basis of results from a clinical examination at each visit and the discretion of the investigator.

Exclusion criteria included kidney disease, celiac or inflammatory bowel disease, chronic pancreatitis, weight-loss surgery or stomach or intestinal problems, eating disorders, uncontrolled gastroesophageal reflux disease, excessive dietary or environmental exposure to acids or other systemic conditions that would predispose the participant to sensitivity, chronic medical disease associated with episodes of daily pain, and long-term use of analgesics (more than 7 days). Exclusion criteria also included use of certain products or procedures before screening: desensitizing agents (8 weeks previously), whitening or tooth bleaching products (4 weeks), participation in another

ABBREVIATION KEY

ADA: American Dental Association.
AE: Adverse event.
FDA: US Food and Drug Administration.
KO: Potassium oxalate.
NA: Not applicable.
VAS: Visual analog scale.

oral care study (30 days), periodontal surgery or orthodontic treatment (3 months), dental prophylaxis (2 weeks), and no regular dental treatment planned during the study. Exclusion criteria also included allergy to study products or the need to premedicate with antibiotics before dental procedures, self-reported pregnancy or lactation, teeth or periodontium with disease likely to cause pain, or teeth with clinical mobility greater than grade 1 on a scale of 0 to 3.

Interventions

Qualified participants entered the 2-week prestudy run-in phase during which we instructed them to brush their teeth twice daily with the provided sodium fluoride toothpaste (Cavity Protection Regular, Crest) and a soft-bristled toothbrush. At baseline, we randomly assigned participants who continued to meet the inclusion criteria to 1 of the 2 treatment groups: a 1.4% KO mouthrinse or placebo mouthrinse with a formulation similar to the test mouthrinse without KO and other ingredients to support the availability and functioning of KO. For the next 4 weeks, participants brushed with the provided toothpaste twice daily. After toothbrushing, participants rinsed with water, then with 10 mL of their assigned mouthrinse for 60 seconds. Throughout the study, participants who regularly used dental floss could continue to use floss.

We evaluated participants at screening, baseline, week 2, and week 4 for air sensitivity (cold air stimulus response test) by using a VAS and tactile sensitivity by using a Yeaple probe in grams of pressure and via VAS. At baseline, week 2, and week 4, participants evaluated their subjective perception of pain or discomfort by using the global subjective VAS. Investigators assessed safety by means of oral examination and query of each participant at each visit for any new or continuing symptoms since the previous visit and through the tabulation of AEs.

Participants conducted their first toothbrushing and mouthrinsing under supervision at the test centers. Each participant received a standard toothbrush and toothpaste, the assigned mouthrinse in blinded packaging, marked dosage cups, and diaries to document compliance with the home care regimen. The investigators checked the diaries and weighed the mouthrinse containers at each visit to monitor compliance.

Random assignment, conducted by the Biometrics and Clinical Data Systems Department at Johnson & Johnson, was stratified according to site; within each site, the random assignment involved variable block size with blocks of sizes 6 and 8 in random order. Each participant sequentially received a participant identifier and a unique random assignment number that determined that participant's treatment assignment according to the random assignment schedule. The examiners were blinded to participants' treatments, and personnel dispensing the test products or supervising their use did not participate in the examination of participants. The 10-mL dose of mouthrinse was based on the typical dose range of 10 to 20 mL for over-the-counter mouthrinses.

Assessments and outcomes

Dental clinical examiners, who were trained in the data collection methods used in the study, performed the clinical assessments throughout the study at each site. The same examiner examined each participant throughout the study. The examiners conducted the assessments in the order presented here.

VAS

Participants read the VAS instructions before each use. The VAS is a horizontal line labeled *no pain or discomfort* at 0 mm, and *intense pain or discomfort* at 100 mm. Participants marked the line at the point they felt represented their perception of the intensity of their pain or discomfort. For the global subjective VAS, participants marked the line to indicate their perception of the dentinal hypersensitivity pain or discomfort they experienced during their daily routines for the previous 2 weeks.

Oral Examination

At oral examinations, the examiners monitored oral soft and hard tissues for tolerability of study products. They recorded any clinically significant signs or symptoms that appeared or worsened after screening as AEs.

Tactile Sensitivity

The examiners placed the Yeaple probe perpendicular to the cervical labial surfaces of the study teeth and applied tactile pressure starting at 10 g. They then increased the pressure in 10-g increments (up to 80 g) until the participant indicated he or she felt discomfort.[13-16]

VAS After Yeaple Probe Stimulation

Participants rated their perception of their dentinal hypersensitivity pain or discomfort from the Yeaple probe application on the VAS. Participants who did not experience discomfort at the maximum force of 80 g received a 0-mm VAS.

Cold Air Stimulus Response Test

Ten minutes after Yeaple probe application, the examiner administered a 1-second application of cold air from a dental air syringe (approximately 65°F-70°F at 60 pounds per square inch of pressure) to exposed root surfaces of study teeth. Thereafter, participants indicated their level of pain or discomfort on the VAS.

Safety assessments

A qualified dental professional conducted intraoral examinations at all study visits. This professional recorded any findings or spontaneously reported or observed AEs and monitored all AEs throughout the study.

AEs

For all AEs, the investigators collected information to determine the outcome of the AE and to assess whether it met the criteria for classification as a serious AE and whether the AE had a suspected causal relationship to the investigational product. The primary efficacy variable was success (yes or no) for the participant on the basis of the change from baseline in the participant's mean cold air stimulus VAS score (averaged across study teeth) at week 4. We considered a participant an individual success if the participant's mean cold air stimulus VAS score was at least 30% lower than his or her mean baseline cold air stimulus VAS score.

For testing purposes, we ordered the key secondary efficacy variables, each measurement averaged across study teeth, as follows:

- mean cold air stimulus VAS score at week 4;
- mean tactile sensitivity (Yeaple probe in grams of pressure) score at week 4;
- mean cold air stimulus VAS score at week 2;
- mean tactile sensitivity (Yeaple probe in grams of pressure) score at week 2.

Other secondary efficacy variables were as follows:

- participant's individual success on the basis of the mean cold air stimulus VAS score at week 2;
- mean tactile sensitivity VAS score at weeks 2 and 4;
- global subjective VAS score at weeks 2 and 4.

Statistical analyses

We based the estimation of the sample size on estimates of success rates, as defined earlier, on the basis of previous study data. We assumed the underlying true success rates at week 4 for this calculation to be 0.63 and 0.35 for experimental and placebo treatment, respectively, with a dropout rate no higher than 5%. A study with 360 participants completing the study (180 per group) would provide greater than 90% power for the statistical comparison and greater than 90% probability that the experimental group success rate would be at least 20% higher than the placebo group success rate on the basis of the normal approximation to the binomial distribution.

We based the efficacy analysis on all participants who were randomly assigned according to the intention-to-treat principle. We managed missing data as follows:

- For dichotomous variables, such as the primary efficacy variable, we imputed failure to change from baseline if a participant had no data value at a visit.
- For continuous data analyses, we carried baseline values forward to week 2 if week 2 was missing, and then we applied a repeated measures mixed model analysis.

The efficacy analysis included all participants. Of the 14 participants who were discontinued from the study, 7 had week 2 data, and 7 had no postbaseline data. Of the 10 participants in the placebo group who did not complete the study, 4 had week 2 data, and 6 had no postbaseline data. Of the 4 participants in the KO group who did not complete the study, 3 had week 2 data, and 1 had no postbaseline data.

We tested the primary efficacy variable and the 4 key secondary efficacy variables in a hierarchical order. We started with the analysis of the primary efficacy variable and thereafter proceeded with key secondary variable 1, followed by key secondary variable 2, followed by key secondary variables 3 and 4 by using the Hochberg method.[17] If any step in this hierarchical procedure resulted

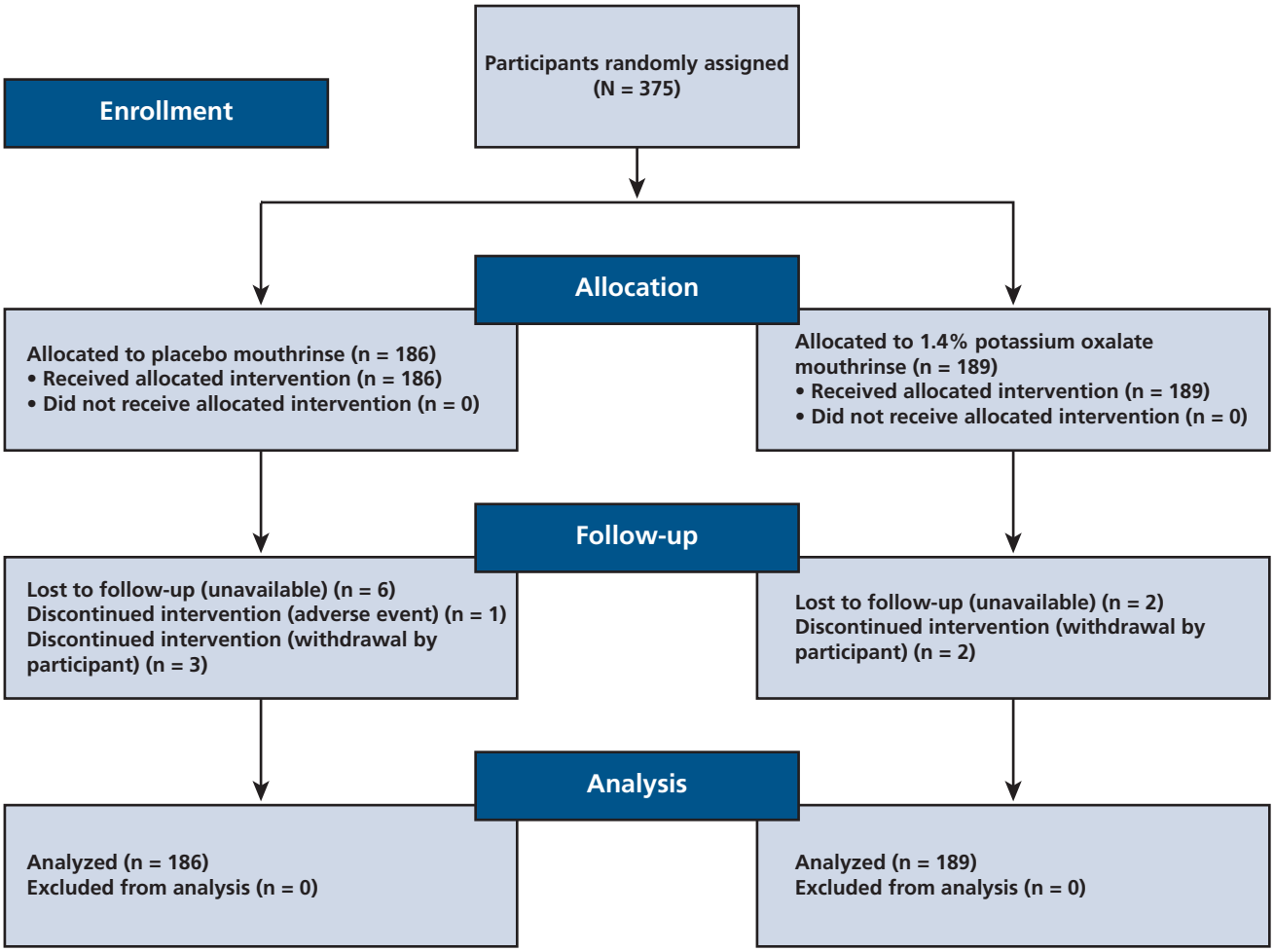

Figure 1. Disposition of participants.

in a nonsignificant finding, we considered all *P* values for any subsequently tested key secondary variables exploratory only. This procedure controls the familywise error at .05. We tested all other secondary efficacy variables as supportive analyses and evaluated them at the nominal .05 level, 2-sided, with no multiple comparison adjustment.

Analysis of Primary Efficacy Variable

We calculated observed success rates on the basis of imputing failures for missing data. We based the statistical comparison between the success rates in the 2 treatment groups at week 4 on a logistic regression model with study center and mean baseline cold air stimulus VAS score as covariates. We calculated model-based estimates and 95% confidence intervals (CIs) for odds ratios (ORs). We obtained model-based estimates of differences in success rates as estimated average causal effect.[18] In addition, we performed an analysis of the primary end point by using the statistical model specified for the analysis extended with a treatment-by-study center interaction term.

Analysis of Key Secondary Efficacy Variables

In the analysis for each of the key secondary variables, we based between-treatment comparisons on a repeated measures mixed model. We included data from weeks 2 and 4 in the analysis, as well as terms for treatment, visit, study center, and the corresponding baseline value as a covariate.

Analysis of Other Secondary Efficacy Variables

We analyzed individual success rates at week 2 analogously to the success rates at week 4. For tactile and global VAS scores, we based between-treatment comparisons on a repeated measures mixed model jointly including data from both week 2 and week 4, as specified for the analysis of the continuous key secondary efficacy variables.

Table 1. Participant demographic and baseline characteristics.

PARAMETER	PLACEBO MOUTHRINSE	POTASSIUM OXALATE MOUTHRINSE	TOTAL	OVERALL
	(n = 186)	(n = 189)		*P* VALUE
Age, y, Mean (SD*)	38.9 (12.1)	38.0 (12.0)	38.5 (12.0)	.455†
Sex, No. (%)				.570‡
Male	48 (25.8)	44 (23.3)	92 (24.5)	
Female	138 (74.2)	145 (76.7)	283 (75.5)	
Race, No. (%)				.049§
White	114 (61.3)	124 (65.6)	238 (63.5)	
Black or African American	42 (22.6)	45 (23.8)	87 (23.2)	
Asian	11 (5.9)	1 (< 1.0)	12 (3.2)	
Native Hawaiian or Other Pacific Islander	2 (1.1)	2 (1.1)	4 (1.1)	
American Indian or Alaska Native	3 (1.6)	1 (< 1.0)	4 (1.1)	
Other	14 (7.5)	16 (8.5)	30 (8.0)	
Smoker, No. (%)				.950‡
No	153 (82.3)	155 (82.0)	308 (82.1)	
Yes	33 (17.7)	34 (18.0)	67 (17.9)	
Baseline Score, Mean (SD)				
Cold air stimulus response VAS¶	59.3 (9.9)	59.7 (9.7)	59.5 (9.8)	.741†
Tactile sensitivity (Yeaple probe)	11.5 (4.3)	11.6 (4.2)	11.5 (4.2)	.772†
Tactile sensitivity VAS	53.7 (8.9)	54.9 (9.3)	54.3 (9.1)	.225†
Global subjective VAS	47.2 (17.1)	49.1 (18.3)	48.2 (17.7)	.290†

* SD: Standard deviation. † *P* values are based on analysis of variance model with term for treatment. ‡ *P* values are based on χ^2 test. § *P* value is based on Fisher exact test. ¶ VAS: Visual analog scale.

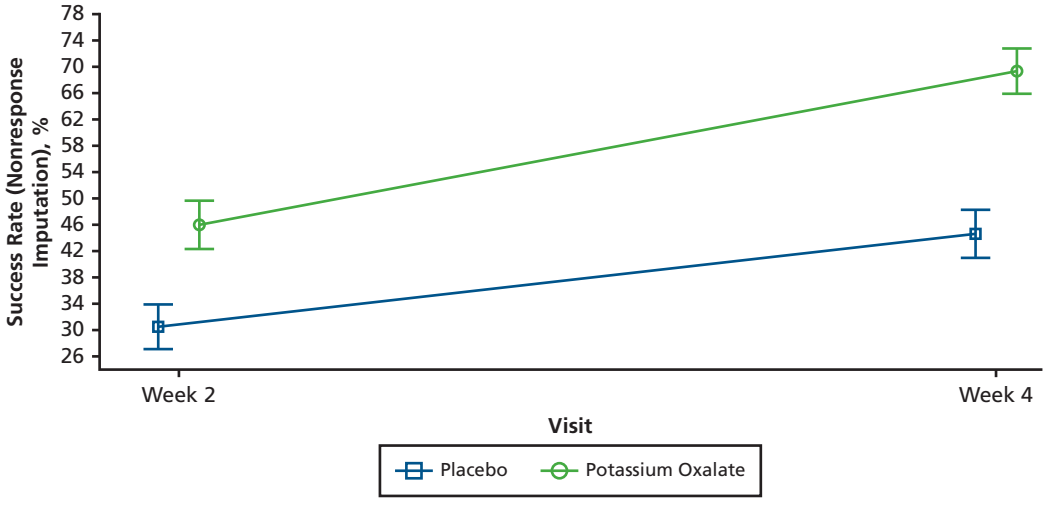

Figure 2. Success rate (standard error), according to visit: full analysis set (primary end point).

RESULTS

Of the 375 enrolled participants who were randomly assigned, 361 completed the study; 14 withdrew or were lost to follow-up (Figure 1). The mean (standard deviation) age of participants was 38.5 (12.0) years, and most were female (75.5%), white (63.5%), and nonsmokers (82.1%). All participant characteristics, except race, were comparable between the 2 groups. Race distributions were statistically significantly different between treatment groups ($P = .049$), primarily because of the imbalance of participants of Asian origin in the placebo group (11 of 186) compared with a single Asian participant in the KO group (1 of 189).

Table 2. Participants' individual success on the basis of the mean cold air stimulus visual analog scale score.

PARAMETER	PLACEBO MOUTHRINSE	POTASSIUM OXALATE MOUTHRINSE
	(n = 186)	(n = 189)
Week 2 Estimated Success Rate, No. (%)	57 (30.6)	87 (46.0)
Week 2 Comparison Versus Placebo		
Estimated success rate difference	NA*	15.4%
Estimated odds ratio		1.945
95% confidence interval		1.271 to 2.975
P value		.002
Week 4 Estimated Success Rate, No. (%)	83 (44.6)	131 (69.3)
Week 4 Comparison Versus Placebo		
Estimated success rate difference	NA	24.7%
Estimated odds ratio		2.817
95% confidence interval		1.843 to 4.307
P value		< .001

* NA: Not applicable.

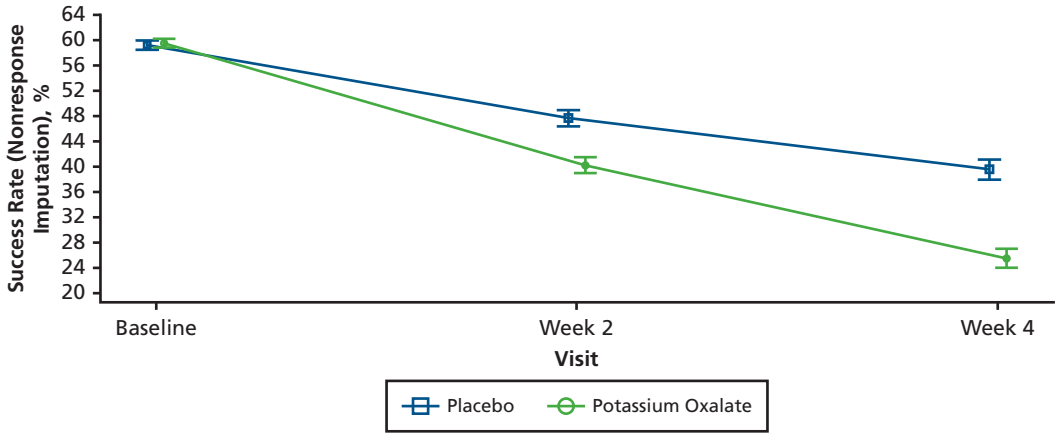

Figure 3. Mean (standard error) cold air stimulus visual analog scale score, according to visit: observed cases.

Overall, mean (standard deviation) baseline scores for cold air stimulus response test VAS, tactile sensitivity with Yeaple probe, tactile sensitivity VAS, and global subjective VAS were comparable between the 2 groups (Table 1). The mean number of study teeth per participant was 2.2, the number of study teeth per participant ranged from 2 to 4, and 85% of the participants had 2 study teeth.

Efficacy

Primary End Point

The KO mouthrinse had a statistically significantly higher success rate compared with the placebo mouthrinse (69.3% versus 44.6%; estimated OR, 2.817; 95% CI, 1.843 to 4.307; $P < .001$). Furthermore, we estimated the success rate difference between treatments to be 24.7%, thus exceeding the 20% needed to conclude superiority of the KO mouthrinse on the basis of American Dental Association (ADA) criteria (Figure 2, Table 2).[19]

A preplanned analysis of the primary end point by using the statistical model specified for the primary analysis extended with a treatment-by-study center interaction term indicated a possible deviation from homogeneity in the magnitude of treatment differences, ($P = .036$). The interaction was of a quantitative nature, with higher success rates observed for the KO mouthrinse at both sites. The observed success rates for the KO mouthrinse on the basis of imputing missing data for failures were 61.7% for site 1001 and 76.8% for site 1002. The corresponding rates in the placebo mouthrinse group were 46.8% for site 1001 and 42.4% for site 1002.

Table 3. Mean cold air stimulus response test visual analog scale score.

PARAMETER	PLACEBO MOUTHRINSE	POTASSIUM OXALATE MOUTHRINSE
	(n = 186)	(n = 189)
Baseline, Mean (SD*)	59.3 (9.9)	59.7 (9.7)
Week 2, Adjusted Mean (SE†)	48.0 (1.3)	40.4 (1.3)
Week 2 Comparison Versus Placebo	NA‡	
Estimated mean difference		−7.67
SE		1.809
95% confidence interval		−11.23 to −4.11
Estimated improvement		16.0%
P value		< .001
Week 4, Adjusted Mean (SE)	40.0 (1.6)	25.8 (1.6)
Week 4 Comparison Versus Placebo	NA	
Estimated mean difference		−14.27
SE		2.239
95% confidence interval		−18.68 to −9.87
Estimated improvement		35.6%
P value		< .001

* SD: Standard deviation. † SE: Standard error. ‡ NA: Not applicable.

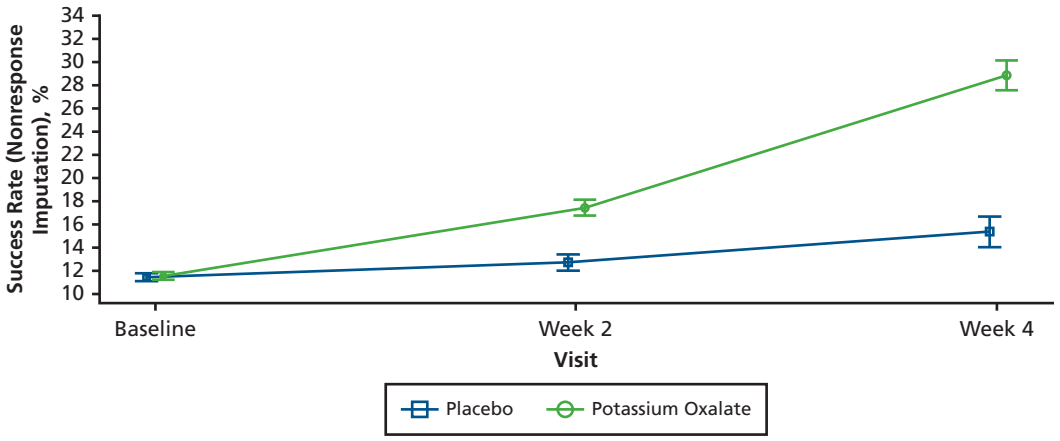

Figure 4. Mean (standard error) tactile sensitivity (Yeaple probe) score, according to visit: observed cases.

Key Secondary End Points

For mean cold air stimulus VAS score at week 4, the KO mouthrinse provided a statistically significant improvement relative to placebo mouthrinse (estimated difference, −14.27 mm; 95% CI, −18.68 to −9.87; 35.6% improvement; $P < .001$) (Figure 3, Table 3). For the mean tactile sensitivity with the Yeaple probe assessment at week 4, KO mouthrinse provided a statistically significant improvement relative to placebo mouthrinse (estimate difference, 13.45 g; 95% CI, 9.83 to 17.08; 88.0% improvement; $P < .001$) (Figure 4, Table 4). Finally, for the week 2 mean cold air stimulus VAS score and the mean Yeaple probe assessment, the KO mouthrinse showed statistically significant improvements relative to placebo mouthrinse for both measurements (estimated difference, −7.67 mm; 95% CI, −11.23 to −4.11; 16.0% improvement; for cold air stimulus VAS; 4.70-g estimated difference; 95% CI, 2.78 to 6.62; 37.0% improvement; for Yeaple probe assessment; $P < .001$ in both cases). See Figure 3 and Table 3 and Figure 4 and Table 4, respectively.

To summarize, in this study, we demonstrated the superiority of KO mouthrinse over placebo mouthrinse. We did so for both the primary and the 4 key secondary efficacy end points, controlling the overall, familywise error rate at 5%.

Table 4. Mean tactile sensitivity (Yeaple probe) score.

PARAMETER	PLACEBO MOUTHRINSE (n = 186)	POTASSIUM OXALATE MOUTHRINSE (n = 189)
Baseline, Mean (SD*)	11.5 (4.3)	11.6 (4.2)
Week 2, Adjusted Mean (SE†)	12.7 (0.7)	17.4 (0.7)
Week 2 Comparison Versus Placebo	NA‡	
Estimated mean difference		4.70
SE		0.975
95% confidence interval		2.78 to 6.62
Estimated improvement		37.0%
P value		< .001
Week 4, Adjusted Mean (SE)	15.3 (1.3)	28.7 (1.3)
Week 4 Comparison Versus Placebo	NA	
Estimated mean difference		13.45
SE		1.844
95% confidence interval		9.83 to 17.08
Estimated improvement		88.0%
P value		< .001

* SD: Standard deviation. † SE: Standard error. ‡ NA: Not applicable.

Other Secondary End Points

For participants' individual success at week 2, the KO mouthrinse had a statistically significantly higher success rate than did the placebo mouthrinse (46.0% versus 30.6%; estimated OR, 1.945; 95% CI, 1.271 to 2.975; $P = .002$) (Figure 2, Table 2). Results of VAS assessment of tactile sensitivity, averaged over study teeth, after application of the Yeaple probe also demonstrated a statistically significant improvement for the KO mouthrinse compared with the placebo mouthrinse at week 2 (estimated difference, −6.67; 95% CI, −9.92 to −3.43; 15.0% improvement; $P < .001$) and week 4 (estimated difference, −11.52; 95% CI, −15.30 to −7.75; 30.1% improvement; $P < .001$).

For the global subjective VAS, KO mouthrinse users rated dentinal sensitivity and discomfort statistically significantly lower than did placebo mouthrinse users. KO mouthrinse users rated global sensitivity 7.2% lower ($P = .023$; 95% CI, −6.04 to −0.45) at week 2 and 19.5% lower ($P < .001$; 95% CI,−11.29 to −3.93) at week 4 than did placebo mouthrinse users.

Safety

Fifteen participants experienced at least 1 AE during the study: 8 participants in the placebo group and 7 in the KO group. The investigators classified 9 of these AEs as probably or very likely related to study treatment. The investigators documented all AEs and followed them to resolution. Treatment-related AEs included oral mucosal exfoliation (5 in the KO group; 1 in the placebo group) and gingival ulceration (3 in the placebo group). One participant in the placebo group experienced moderate gingival ulceration and withdrew from the study. This AE resolved after the participant withdrew from the study. All other participants with AEs considered related to product use completed the study, and the AEs resolved without a change in study product use or treatment. The 3 observations of gingival ulceration in the placebo group appeared to be superficial and near a canine eminence or frenulum, which are common locations for toothbrush abrasion or trauma. All resolved at follow-up. There were no serious AEs during the study. We considered the AEs in this study to be within normal expectations for participation in a mouthrinse study. We identified no safety issues in this study.

DISCUSSION

Dentinal hypersensitivity is a common problem, but measuring it to show clinically meaningful improvements when using a product to reduce and control it is a challenge. Results from a literature

review on pain and consultation with subject matter experts indicated that a 30% reduction on the 11-point pain intensity numerical rating scale represented a clinically important and relevant difference from baseline.[20-22] Effect size criteria indicate that 30% reductions from most of the cold air stimulus VAS 40- to 80-mm range equal large effect sizes (where effect size is the difference in treatment means divided by the standard deviation), and all are closer to large than to medium.[21] Finally, the investigators' consensus from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommended that the percentages of patients responding with pain relief of 30% or more be reported in clinical trials of chronic pain treatments.[22] We applied this patient-success threshold to this study to ensure we considered only clinically meaningful reductions success.

In addition, the ADA guidelines for testing products for dentinal hypersensitivity require a statistically significant difference of at least 20% between control and experimental groups for 1 sensitivity index to receive the ADA Seal of Acceptance as a dentinal hypersensitivity product.[19] We applied this criterion to indicate study success. On the basis of these criteria, the experimental KO mouthrinse provided a clinically meaningful reduction in dentinal hypersensitivity compared with placebo mouthrinse in the primary end point, participants' individual success at week 4 on the basis of the mean cold air stimulus VAS score averaged across study teeth. This result builds on results from previous in vitro and in vivo studies that demonstrate the effect of KO on dentinal hypersensitivity.[23-25]

The placebo success rate, although significantly lower than the KO success rate, was also in the 30% or greater range for decreased sensitivity. This finding was not unexpected because investigators often see effects from placebo in pain studies,[26] and the KO mouthrinse, even with the placebo effect, exceeded the 20% criterion of pain reduction compared with placebo. The difference in the magnitude of treatment differences between the 2 study centers also was not unexpected, given that there were 2 examiners. Nevertheless, we observed higher success rates for the KO mouthrinse at both sites. Other than a few incidents of transient, superficial mucosal irritation and exfoliation in a small number of participants, the participants tolerated the mouthrinses in this study well.

CONCLUSIONS

Our study's results demonstrated that the experimental KO mouthrinse used twice daily as an adjunct to toothbrushing provided statistically significant and clinically relevant reduction in and control of dentinal hypersensitivity compared with results with a placebo mouthrinse. ■

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The data sets used or analyzed during the study are available from the corresponding author on reasonable request.

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