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An evaluation of 10 percent and 20 percent benzocaine gels in patients with acute toothaches:

Efficacy, tolerability and compliance with label dose administration directions

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Abstract

Background—The authors evaluated the efficacy and tolerability of 10 percent and 20 percent benzocaine gels compared with those of a vehicle (placebo) gel for the temporary relief of toothache pain. They also assessed the compliance with the label dose administration directions on the part of participants with toothache pain.

Methods—Under double-masked conditions, 576 participants self-applied study gel to an open tooth cavity and surrounding oral tissues. Participants evaluated their pain intensity and pain relief for 120 minutes. The authors determined the amount of gel the participants applied.

Results—The responders' rates (the primary efficacy parameter), defined as the percentage of participants who had an improvement in pain intensity as exhibited by a pain score reduction of at least one unit on the dental pain scale from baseline for two consecutive assessments any time between the five- and 20-minute points, were 87.3 percent, 80.7 percent and 70.4 percent, respectively, for 20 percent benzocaine gel, 10 percent benzocaine gel and vehicle gel. Both benzocaine gels were significantly ($P \leq .05$) better than vehicle gel; the 20 percent benzocaine gel also was significantly ($P \leq .05$) better than the 10 percent benzocaine gel. The mean amount of gel applied was 235.6 milligrams, with 88.2 percent of participants applying 400 mg or less.

Conclusions—Both 10 percent and 20 percent benzocaine gels were more efficacious than the vehicle gel, and the 20 percent benzocaine gel was more efficacious than the 10 percent benzocaine gel. All treatments were well tolerated by participants.

Practical Implications—Patients can use 10 percent and 20 percent benzocaine gels to temporarily treat toothache pain safely.

Keywords

Benzocaine; toothache; pain; topical anesthetic; methemoglobinemia; double stopwatch

Topical benzocaine is marketed in 10 percent and 20 percent formulations (regular [10 percent] and maximum [20 percent] strength Orajel [Church & Dwight, Princeton, N.J.] and Anbesol [Pfizer Consumer Healthcare. Madison, N.J.]) for the temporary relief of toothache pain and has been used widely since 1903.[1] The U.S. Food and Drug Administration (FDA) assigned this product category I monograph status (generally recognized as safe and effective) as an external anesthetic or analgesic for the temporary relief of pain due to minor irritation or injury of the mouth and gingivae, minor dental procedures, dentures, orthodontic appliances, canker sores, teething, sore mouth and sore throat.[2] However, the FDA concluded that the available data were not adequate to establish the effectiveness of benzocaine for the temporary relief of toothache pain and assigned category III status (judged to be safe but efficacy data not confirmative) in the over-the-counter (OTC) monograph for this indication, noting that the FDA would consider reclassifying benzocaine as category I if additional data were received from well-controlled studies.[2] We conducted a study with the intention of meeting this requirement.

Investigators in several small vehicle- (placebo-) controlled studies published results supporting the effectiveness of 7.5 to 20.0 percent benzocaine gels in relieving toothache pain.[3-5] In these studies, the benzocaine and polyethylene glycol vehicle gels were applied by the investigators[3,4] or the study participants[5] to both the open tooth cavity and the surrounding soft tissue; significant differences in favor of benzocaine were achieved. In another study, investigators placed a mucoadhesive patch containing 12 milligrams of benzocaine or a vehicle apical to the mucogingival junction of the symptomatic tooth, and a significantly greater percentage ($P < .05$) of participants in the benzocaine group reported meaningful pain relief (PR) than did participants in the vehicle group by the 30-minute point.[6] The results of these studies show that the ability of benzocaine to anesthetize the surrounding soft tissue may contribute to its effectiveness in temporarily relieving toothache pain. Label dose administration directions for one 20 percent benzocaine gel product stated that it should be applied to both the symptomatic open tooth cavity and around the gingivae surrounding the teeth.[7] We designed our study to incorporate application to both the tooth and the soft tissue.

Despite benzocaine's long history of safe use, it has been associated in rare instances with methemoglobinemia, a condition in which the oxygen-carrying capacity of the blood is reduced (ferric state). Although most of the cases of methemoglobinemia in the literature involve benzocaine spray application in a hospital environment for diagnostic procedures such as intubation, endoscopy, bronchoscopy and transesophageal echocardiography,[8-44] case reports of methemoglobinemia associated with OTC use of benzocaine have been published.[11,45-55] Only two of these cases involved benzocaine self-application for toothache, and both of these cases involved significant overdoses.[54,55]

In 2011, the FDA issued a safety communication noting the potential for OTC benzocaine products to cause methemoglobinemia on rare occasions.[56] Most reports of methemoglobinemia involved children. Thus, although cases of methemoglobinemia involving self-application by adult patients with toothache are rare and typically involve significant overdoses of the drug, it is important to evaluate patients' compliance with label

dose administration directions in patients as young as 12 years (12 years is the youngest age recommended for benzocaine self-application in patients with an acute toothache[7]).

The FDA has determined that the existing body of evidence supporting the use of topical benzocaine for the temporary relief of toothache pain is lacking.[2] For benzocaine to gain category I status for the treatment of toothache pain under the OTC monograph system, additional data are needed. We conducted a study to evaluate the efficacy and tolerability of 10 percent and 20 percent benzocaine gels compared with those of a vehicle gel in participants with toothache pain, as well as to assess the compliance of these participants with the benzocaine gel dose administration directions in a newly proposed product label developed by the manufacturers of Orajel and Anbesol.

METHODS

The institutional review boards at the participating research centers (University of Pennsylvania, Philadelphia; The State University of New York at Buffalo; University of Pittsburgh; Nationwide Children's Hospital, Columbus, Ohio; The Ohio State University, Columbus; University of Detroit Mercy; New York University, New York City; Tufts University, Boston; and University of Maryland, Baltimore) approved the protocol, informed consent forms and assent forms (for minors), and we listed the trial in ClinicalTrials. gov under the identifier NCT00474175. Male and female patients aged at least 12 years from all ethnic backgrounds were eligible to participate in the study. In the case of minors (those younger than 18 years), both a parental informed consent form and an adolescent assent form had to be read and signed by both the parent or guardian and the child. Study participants had to arrive at the research site with toothache pain of at least a moderate intensity on one permanent tooth with an open tooth cavity to be included in the study.

Participants rated their pain on an ordinal dental pain scale (DPS) on which 0 indicates no pain, 1 indicates slight pain, 2 indicates moderate pain, and 3 indicates severe pain. These results were corroborated by a score of at least 50 millimeters on a 100-mm visual analog scale on which 0 mm indicates no pain and 100 mm indicates the worst possible pain. We excluded patients from the study if they had pain from multiple hard-tissue or soft-tissue sites, had a periodontal abscess, did not have an open tooth cavity, reported having any allergies or contraindications to benzocaine or other local anesthetics, or had taken any short-acting systemic or topical analgesic within 120 minutes before the study visit or any long-acting systemic analgesic agent within 240 minutes before the study visit.

We randomly assigned those who qualified for the study to self-apply a single dose of the polyethylene glycol vehicle gel, 10 percent benzocaine gel or 20 percent benzocaine gel in a ratio of 1:2:2 stratified according to participants' baseline pain levels (moderate or severe). To assess compliance with dose administration directions, we gave participants the product label showing dose administration directions and a picture of how much gel to apply to their painful tooth and surrounding gingival tissue (Figure 1). We weighed the contents of each coded 7-milliliter study gel tube by using a digital balance immediately before and after participants self-applied the study gel with their fingers. Participants rated their pain intensity and PR levels by using the DPS and a five-level ordinal dental pain relief scale on which 0 indicated no relief, 1 indicated a little relief, 2 indicated some relief, 3 indicated a lot of relief, and 4 indicated complete relief. They rated their pain intensity and PR levels at five-minute intervals from zero to 30 minutes and at 10- minute intervals from 30 to 120 minutes after they applied the study gel.[5]

We recorded onset time of first perceptible relief and meaningful relief by asking the participants to press the buttons on two stopwatches when and if they experienced either event. The study coordinator activated both stopwatches at the time participants applied the study gel, and then he or she covered the stopwatch displays so that the participants could not see the elapsed time. We instructed the participants to "stop the first stopwatch when you first begin to feel any pain-relieving effect what-so-ever of the drug" and to "stop this second stopwatch when you have meaningful relief, that is, when the relief from the pain is meaningful to you," as in previous postsurgical dental pain studies.[57-59]

Participants completed a five-level ordinal global satisfaction assessment scale used frequently in postsurgical dental pain studies[58,59] at the conclusion of the 120-minute evaluation period or at the time they dropped out of the study owing to inadequate PR. (We encouraged participants with inadequate PR to wait at least 10 minutes before dropping out.) We asked participants, "How would you rate this medication for temporary relief of toothache pain?" Their choices were poor, fair, good, very good or excellent, and we assigned numeric values to each categorical response ranging from 0 for poor to 4 for excellent. We offered ibuprofen or acetaminophen to participants who requested a rescue analgesic. We encouraged these participants to remain in the research suite for the full 120 minutes.

We recorded the participants' blood pressure and heart rates before they applied the study gel and again at 60 and 120 minutes after application. We recorded all adverse events (AEs) when they occurred, as well as the time the participant dropped out of the study during the 120-minute evaluation period if he or she dropped out. At the end of the evaluation period, we asked any participant who used 1 gram or more of the study gel (100 mg and 200 mg of 10 percent and 20 percent benzocaine, respectively) what the possible reason was for overapplying the gel. We referred all study participants for definitive dental care (endodontic therapy or extraction) at the end of the study.

Statistical analyses

The primary efficacy parameter was the percentage of responders, defined as a participant who had an improvement in pain intensity as exhibited by a pain score reduction of at least one unit on the DPS from baseline for two consecutive assessments any time between the five- and 20-minute points. We considered an observed increase of 10 percentage points for each of the benzocaine gels compared with the vehicle gel to be a clinically meaningful difference. We considered the dose response to be established if we observed an increase of five percentage points for the 20 percent benzocaine group compared with the 10 percent benzocaine group.

For power analysis, we assumed a 50 percent response rate in the benzocaine groups and a 30 percent response rate in the vehicle group, and we expected sample sizes of 200 per benzocaine group and 100 in the vehicle group to provide at least 90 percent power. We used two-sided statistical tests for all analyses. We controlled the type I error rate at 5 percent for efficacy analyses by testing 20 percent benzocaine gel against the vehicle gel first, followed by testing 10 percent benzocaine gel against the vehicle if the results of the first test were significant.

We used the Mantel-Haenszel test to analyze participants' baseline DPS score, sex, race and age distribution. We analyzed the percentages of participants classified as responders in each group by using the Cochran-Mantel-Haenszel (CMH) test, controlling for site and baseline DPS score.

For the secondary efficacy parameters, we used the Kaplan-Meier method to estimate the distribution of the time elapsed before onset of confirmed first perceptible relief (time to pressing the button on the first stopwatch, provided that the participant also indicated meaningful relief by pressing the button on the second stopwatch[59]) and meaningful relief, duration of effect and time elapsed before dropping out owing to lack of efficacy for each treatment group. We used the Cox proportional hazards regression model, adjusting for site and baseline DPS score, to compare the treatment groups. We calculated pain intensity difference (PID) scores at each time point by subtracting each reported pain intensity score from the pain intensity score reported at baseline. We summed PR and PID scores at each time point to derive PR combined with PID (PRID) scores, and we plotted these scores across time. We also calculated the time-weighted sum of PRID (SPRID) scores at 60 and 120 minutes. We analyzed the PRID and SPRID scores by using an analysis of variance model with treatment, baseline DPS score and site terms in the model. We calculated duration of effect as the time difference between the onset of effect (the first of two consecutive periods in which pain intensity was reduced by at least one unit) and its offset (the first of two time points in which pain intensity returned to baseline levels or higher), and we compared these durations between treatments by using the Cox proportional hazards model. We also used the Cox proportional hazards model to analyze the time to dropping out of the study. We calculated all 95 percent confidence intervals on the basis of the corresponding fitted model. We analyzed the global satisfaction scores among treatments by using the CMH test and modified ridit scores.

We calculated the percentage of participants who applied no more than 400 mg of gel, and we graphed the amount of gel applied per participant in 200-mg intervals as a histogram.

RESULTS

A total of 577 participants enrolled in the study, and 576 self-applied study medication (Figure 2). One participant did not apply study medication and was excluded in the final analyses. Among all participants, 100 were minors (aged 12-17 years). Table 1 (page 520) illustrates the demographic characteristics and baseline pain scores for each treatment group. We found no significant differences among treatment groups.

Table 2 displays the percentage of responders, and Table 3 shows the overall observed differences and 95 percent confidence intervals calculated by using the CMH model, with *P* values comparing each pair of treatment groups. Both 10 percent and 20 percent benzocaine gels were statistically better than the vehicle gel ($P = .038$ and $P < .001$, respectively). We observed a dose-response relationship: the 20 percent benzocaine group had 6.6 percent more responders than did the 10 percent benzocaine group ($P = .047$).

Table 4 and Table 5 display a summary of the analyses for the secondary efficacy variables. Both 10 percent and 20 percent benzocaine gels had statistically more rapid median onset times than did the vehicle gel for first perceptible relief and meaningful relief ($P < .001$), with 20 percent benzocaine gel having a significantly more rapid median onset time than did the 10 percent gel for confirmed first perceptible relief ($P = .030$). In addition, 20 percent benzocaine gel was statistically better than the vehicle gel for SPRID at 60 minutes ($P = .035$). Figure 3 illustrates the time-effect curves for PRID for the three treatment groups through 120 minutes. Both benzocaine gels also were significantly ($P < .05$) more efficacious than the vehicle gel for mean global satisfaction scores. Figure 4 (page 524) illustrates the percentage of participants who rated their global satisfaction as poor, fair, good, very good or excellent for each treatment group. Seventy-nine percent of participants who received the 20 percent benzocaine gel and 80 percent of participants who received the

10 percent benzocaine gel assigned a global satisfaction score of good, very good or excellent compared with 61 percent of participants who received the vehicle gel.

Participants applied a mean (standard deviation) of 235.6 (148.7) mg (median, 203; range, 18-1,026 mg) of study gel, with 88.2 percent of participants applying 400 mg or less. Only one participant, a 29-year-old man randomly assigned to the 20 percent benzocaine gel group, applied more than 1,000 mg of study gel. He stated he wanted "instant relief" from his pain, and when he placed more medication on his finger than the picture on the label, he knew he could not put it back, so he applied it all. Figure 5 (page 524) presents the distribution of the amount of study gel applied in 200-mg intervals.

Participants reported only 16 AEs in this study; four (3.5 percent) of 115 participants in the vehicle gel group, six (2.6 percent) of 233 participants in the 10 percent benzocaine gel group and six (2.6 percent) of 228 participants in the 20 percent benzocaine gel group. We rated all AEs as mild in intensity except for one AE in a participant in the vehicle gel group that was rated as moderate. The most common AEs were transient increases in blood pressure (n = 3) and gastrointestinal complaints (n = 2). We observed no cases of methemoglobinemia. There were no significant differences between treatment groups in the overall incidence of AEs or the incidence of any particular AE.

DISCUSSION

The results of our study demonstrated that for the primary efficacy endpoint of percentage of responders, both 10 percent and 20 percent benzocaine gels were significantly more efficacious than was the vehicle gel and the 20 percent benzocaine gel was significantly more efficacious than was the 10 percent benzocaine gel in the relief of toothache pain. To our knowledge, our study is the first with results demonstrating a dose response between the 10 percent and 20 percent benzocaine treatments. The dose-response relationship supports the availability of both regular strength (10 percent) and maximum strength (20 percent) formulations. The clinical importance of an increase of five percentage points in PR is supported by the results of a 2004 systematic review of the outcome difference between regular and extra-strength acetaminophen.[60] In that meta-analysis, the results showed a difference of five percentage points in the number of participants reaching the response threshold when investigators compared maximum strength and regular strength acetaminophen. Thus, a difference of five percentage points has been accepted as being a clinically significant difference. In our study, participants we randomly assigned to the 20 percent benzocaine gel group had a significantly quicker onset of confirmed first perceptible relief than did participants we randomly assigned to the 10 percent benzocaine gel group. Both 10 percent and 20 percent benzocaine gels also were statistically better than vehicle gel with regard to a number of secondary endpoints (Table 4, Table 5, Figure 3 and Figure 4).

There was a high percentage of positive responders in the vehicle group. A placebo response rate as high as 30 percent is not uncommon in studies of analgesics for a variety of reasons, including participant expectation. In topical application, there also may be a vehicle effect resulting from protection of the lesion from the environment. In addition, the vehicle composition might have an effect. Polyethylene glycol is used as the solvent in benzocaine solutions because the local anesthetic is poorly soluble in water.[61,62] In our study, the concentrations of polyethylene glycol in the 20 percent benzocaine, 10 percent benzocaine and vehicle gels were 77 percent, 87 percent and 97 percent, respectively. Results from laboratory experiments indicated that 40 percent polyethylene glycol completely abolishes compound action potentials with significant diminution of C-fiber nerve activity beginning at a concentration of 30 percent.[63] Thus, the vehicle used commercially to keep benzocaine in solution is likely to be active and may not be a "true placebo" per se. Investigators

reported analgesic response rates of 47 percent and 60 percent for polyethylene glycol gel and liquid, respectively, in study participants with toothaches.[5,64]

In our study, participants' compliance with label dose administration directions was good, with 88.2 percent applying 400 mg or less of study gel. The product label we gave participants in this study was evaluated first in a small 30-participant pilot study.[5] The picture depicting how much gel to apply is not on label directions for benzocaine gels, and we believe this graphic contributed to the favorable label dose administration direction compliance rates in our study and should be considered in future label directions for benzocaine gels. To our knowledge, our study is the first evaluation of compliance with label dose administration directions in a large cohort of participants, including adolescents as young as 12 years, who had moderate to severe toothache pain.

The fact that we did not evaluate the application of multiple doses of the study gels across a day was one of the limitations of our study. We have no data regarding whether participants who were assigned randomly to the benzocaine gel groups would have used the gel more than four times per day (the maximum dosage stated on the labels of benzocaine toothache products). Because our goal was to enroll participants in the study and have them receive definitive treatment for their symptomatic tooth the same day, conducting a multiple-dose study was not feasible or ethical.

Although reports of methemoglobinemia associated with benzocaine administration are a growing concern to the FDA,[56] methemoglobinemia rarely occurs with the OTC use of benzocaine products for the temporary relief of toothache pain.[54,55] Drug-induced methemoglobinemia most often is an adverse event that occurs after an overdose of a strong oxidizing drug such as nitroglycerin, benzocaine, prilocaine, phenelzine (a monoamine oxidase inhibitor) or ciprofloxacin. When people have excessive levels of these drugs in their blood, the reduced form of hemoglobin (ferrous state) is converted into oxidized methemoglobin (ferric state), which has poor oxygen-carrying capacity.[5,13,65,66] Even the participant in our study who administered the greatest amount of gel (1,026 mg), which would translate to a 10 percent benzocaine dose of 103 mg and a 20 percent benzocaine dose of 205 mg, still would be sevenfold and 3.5-fold, respectively, below the reported methemoglobinemia threshold dose of 15 mg per kilogram in a person weighing as little as 50 kg.[15,49] The second highest amount of gel administered by any participant in our study was 870 mg, and only five participants (0.8 percent) administered 800 mg or more of gel.

CONCLUSION

Both 10 percent and 20 percent benzocaine gels were effective in the temporary relief of toothache pain and were well tolerated. Most participants were able to correctly self-apply doses of benzocaine that were at least 10-fold below the reported threshold that could lead to methemoglobinemia. All study gels were well tolerated.

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ABBREVIATION KEY

AE	Adverse event
DPS	Dental pain scale
FDA	Food and Drug Administration
OTC	Over the counter
PID	Pain intensity difference
PR	Pain relief
PRID	Pain relief combined with pain intensity difference
SPRID	Time-weighted sum of pain relief combined with pain intensity difference

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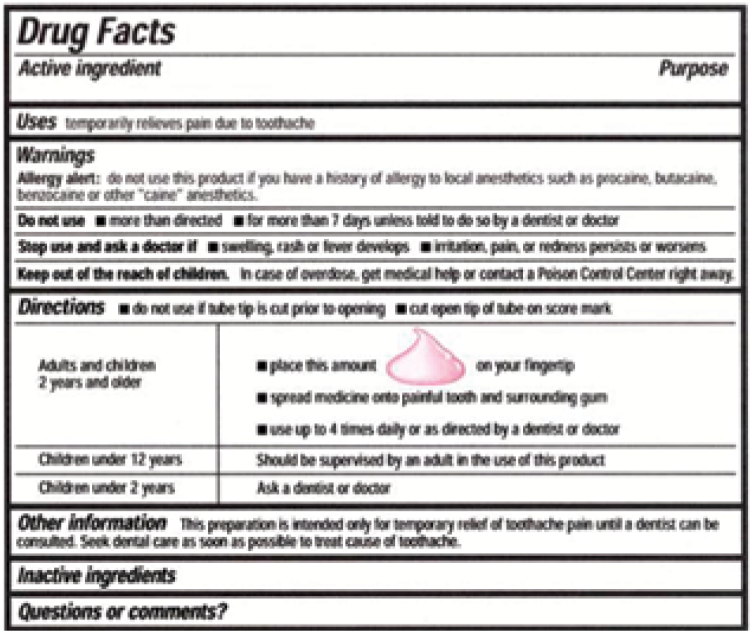

Drug Facts

Active ingredient	Purpose

Uses temporarily relieves pain due to toothache

Warnings

Allergy alert: do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine or other "caine" anesthetics.

Do not use ■ more than directed ■ for more than 7 days unless told to do so by a dentist or doctor

Stop use and ask a doctor if ■ swelling, rash or fever develops ■ irritation, pain, or redness persists or worsens

Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ do not use if tube tip is cut prior to opening ■ cut open tip of tube on score mark

Adults and children 2 years and older	■ place this amount on your fingertip ■ spread medicine onto painful tooth and surrounding gum ■ use up to 4 times daily or as directed by a dentist or doctor
Children under 12 years	Should be supervised by an adult in the use of this product
Children under 2 years	Ask a dentist or doctor

Other information This preparation is intended only for temporary relief of toothache pain until a dentist can be consulted. Seek dental care as soon as possible to treat cause of toothache.

Inactive ingredients

Questions or comments?

Figure 1.
Label showing dose administration directions presented to study participants.

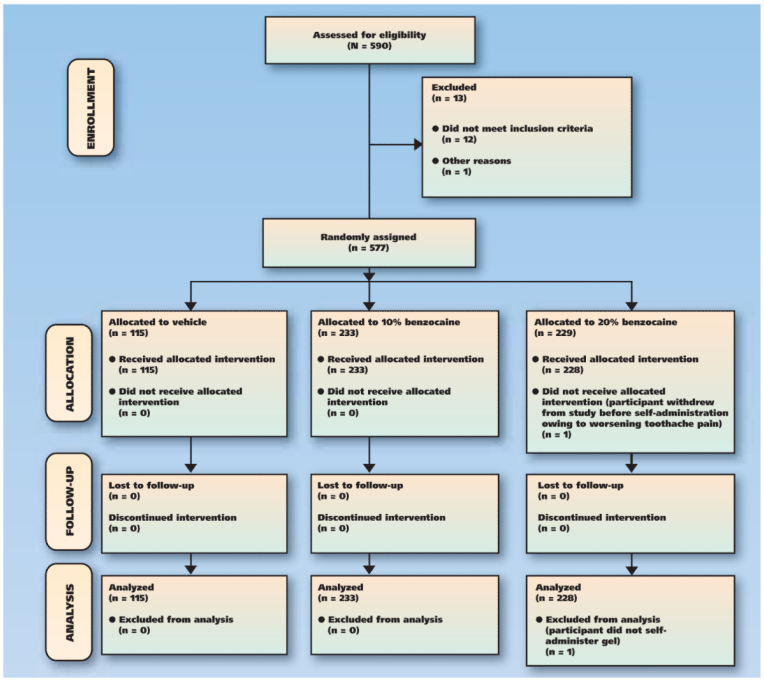

Figure 2.
Flow diagram of participant study inclusion and exclusion.

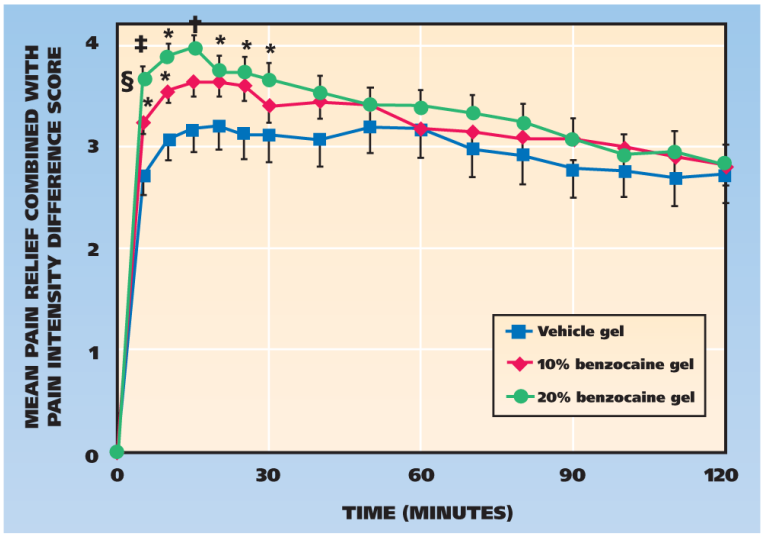

Figure 3.

Time-effect curves for pain relief combined with pain intensity difference (PRID) (standard error of the mean) through 120 minutes after self-application. * Significantly better than vehicle gel ($P \leq .05$). † Significantly better than vehicle gel ($P \leq .01$). ‡ Significantly better than vehicle gel ($P \leq .001$). § Significantly better than 10 percent benzocaine gel ($P \leq .05$).

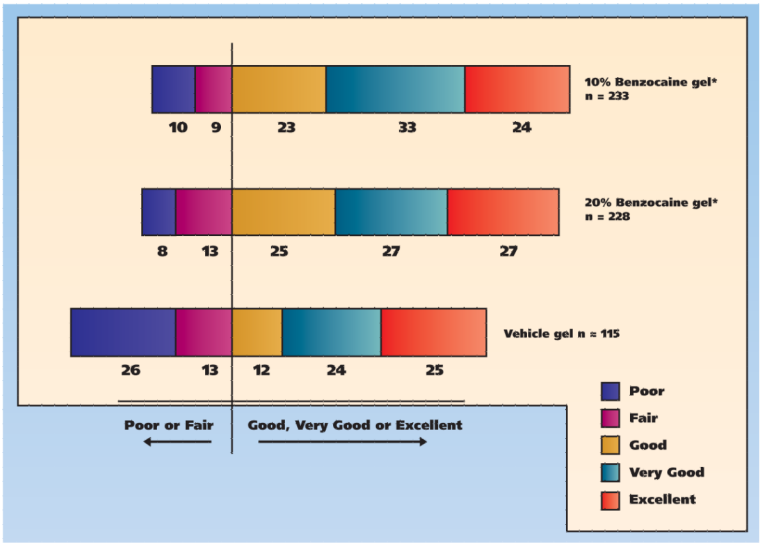

Figure 4.

Percentage of participants who rated the global satisfaction of each treatment gel as poor, fair, good, very good or excellent. * Significantly better than vehicle ($P \leq .05$). The percentages for 10 percent benzocaine total 99 percent owing to rounding.

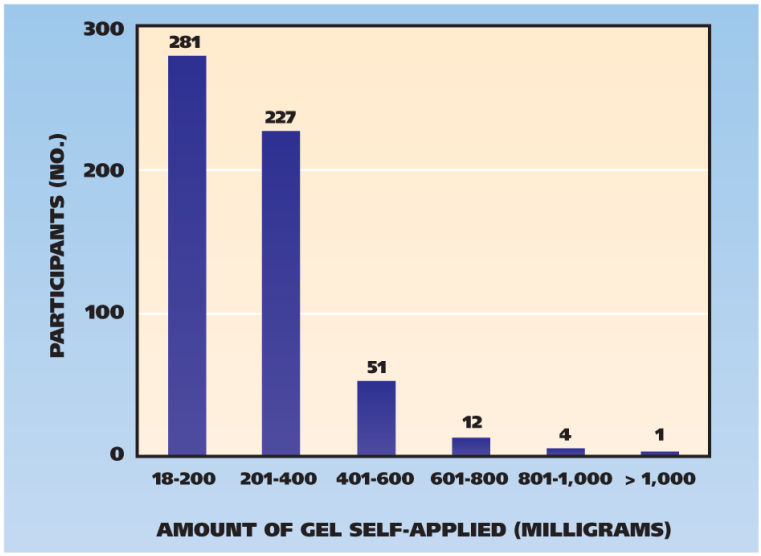

Figure 5.
Number of participants self-applying various amounts of study gel in 200-milligram increments.

TABLE 1

Demographic characteristics of and baseline pain scores for the three treatment groups.[*†]

CHARACTERISTIC	OVERALL STUDY POPULATION (N = 576)	VEHICLE (n = 115)	10 PERCENT BENZOCAINE (n = 233)	20 PERCENT BENZOCAINE (n = 228)
Sex, No. (%)				
Male	276 (47.9)	53 (46.1)	113 (48.5)	110 (48.2)
Female	300 (52.1)	62 (53.9)	120 (51.5)	118 (51.8)
Age, Years				
Mean (SD[‡])	31.1 (12.7)	31.2 (12.6)	30.8 (12.7)	31.3 (12.8)
Range	12-82	12-65	12-82	13-70
Adolescents, No. (%)				
12-14 years	31 (5.4)	7(6.1)	13 (5.6)	11 (4.8)
15-17 years	69 (12.0)	13 (11.3)	33 (14.2)	23 (10.1)
Race, No. (%)				
Black	365 (63.4)	78 (67.8)	145 (62.2)	142 (62.3)
White	180 (31.3)	31 (27.0)	73 (31.3)	76 (33.3)
Asian	14 (2.4)	3 (2.6)	7 (3.0)	4 (1.8)
Other (mixed racial origins)	10 (1.7)	2(1.7)	5(2.1)	3(1.3)
American Indian/Alaskan Native	5 (0.9)	1 (0.9)	3(1.3)	1 (0.4)
Native Hawaiian/ other Pacific Islander	1 (0.2)	0 (0)	0 (0)	1 (0.4)
Not reported	1 (0.2)	0(0)	0(0)	1 (0.4)
Ethnicity, No. (%)				
Non-Hispanic or non-Latino	537 (93.2)	108 (93.9)	218 (93.6)	211 (92.5)
Hispanic or Latino	39 (6.8)	7(6.1)	15 (6.4)	17 (7.5)
Weight, Pounds				
Mean (SD)	179.3 (51.2)	184.8 (54.4)	179.5 (54.2)	176.4 (46.1)
Range	66-410	104-366	83-410	66-350
Baseline Pain Dental Pain Scale Score, No. (%)				
Moderate	354 (61.5)	71 (61.7)	144 (61.8)	139 (61.0)
Severe	222 (38.5)	44 (38.3)	89 (38.2)	89 (39.0)
Baseline Pain Visual Analog Scale Score, Millimeters				
Mean (SD)	73.5 (14.3)	74.1 (13.4)	73.3 (14.5)	73.5 (14.7)
Range	49-100	51-100	49-100	50-100

[*] Not all percentage totals equal 100 percent owing to rounding.

[†] Treatment groups were comparable with respect to their demographic and baseline characteristics.

[‡] SD: Standard deviation.

TABLE 2

Responders, according to treatment type.

TREATMENT	RESPONDERS, NO. (%)
Vehicle (n = 115)	81 (70.4)
10 Percent Benzocaine (n = 233)	188 (80.7)
20 Percent Benzocaine (n = 228)	199 (87.3)

TABLE 3

Differences in participants receiving 10 percent benzocaine, 20 percent benzocaine or vehicle gel.

TREATMENT	PAIRWISE COMPARISONS	
	Observed Treatment Differences, % (95 Percent CI*)	*P* Value†
20 Percent Benzocaine Versus Vehicle	16.8 (7.2-25.7)	< .001‡
10 Percent Benzocaine Versus Vehicle	10.3 (0.3-19.3)	.038‡
20 Percent Benzocaine Versus 10 Percent Benzocaine	6.6 (0.2-13.3)	.047‡

*The 95 percent confidence interval (CI) was calculated on the basis of the Cochran-Mantel-Haenszel weighted percentages and corresponding standard errors.

†*P* values are from the Cochran-Mantel-Haenszel test, controlling for site and baseline dental pain scale score.

‡The first treatment was significantly better than was the second treatment at the .05 level.

TABLE 4

Summary of the time elapsed from baseline to the event efficacy parameters for the three treatment groups.

PARAMETER	TREATMENT			HAZARD RATIO (95 PERCENT CONFIDENCE INTERVAL; *P* VALUE*)		
	Vehicle (n = 115)	10 Percent Benzocaine (n = 233)	20 Percent Benzocaine (n = 228)	20 Percent Benzocaine Versus Vehicle	10 Percent Benzocaine Versus Vehicle	20 Percent Benzocaine Versus 10 Percent Benzocaine
Median Time Elapsed From Baseline to Meaningful Relief, Minutes	8.5	4.4	3.2	2.0† (1.6 to 2.7†; < .001‡)	1.7† (1.3 to 2.3†; < .001‡)	1.2† (1.0 to 1.4†; .100)
Median Time Elapsed From Baseline to Confirmed First Perceptible Relief, Minutes	2.0	1.4	1.1	2.0† (1.6 to 2.6†; < .001‡)	1.6† (1.3 to 2.1†; < .001‡)	1.2† (1.0 to 1.5†; .030‡)
Median Duration of Effect, Minutes	> 115	> 115	> 115	0.9† (0.6 to 1.2†; .492)	0.9† (0.7 to 1.3†; .649)	1.0† (0.7 to 1.3†; .773)
Median Time Elapsed Before Dropping Out, Minutes	> 120	> 120	> 120	1.2† (0.7 to 2.1†; .484)	1.1† (0.6 to 2.0†; .653)	1.1† (0.7 to 1.7†; .752)

** P* values for meaningful relief, confirmed first perceptible relief, duration of effect and time elapsed before dropping out were derived from the Cox proportion hazards model with terms for treatment, site and baseline dental pain scale score.

† The hazard ratio of the first treatment relative to the second treatment and corresponding 95 percent confidence intervals were based on the Wald statistic.

‡ The first treatment was significantly better than was the second treatment at the $P \leq .05$ level.

Table 5

Summary of SPRID[*] scores for the three treatment groups.

PARAMETER	TREATMENT			OBSERVED TREATMENT DIFFERENCE (95 PERCENT CONFIDENCE INTERVAL; *P* VALUE)		
	Vehicle (n = 115)	10 Percent Benzocaine (n = 233)	20 Percent Benzocaine (n = 228)	20 Percent Benzocaine Versus Vehicle	10 Percent Benzocaine Versus Vehicle	20 Percent Benzocaine Versus 10 Percent Benzocaine
SPRID at 60 Minutes, Mean (SD[†])	3.1 (2.3)	3.4 (2.0)	3.6 (2.0)	0.5 (0.0 to 1.0[‡]; .035[§])	0.3 (−0.1 to 0.8[‡]; .173)	0.2 (−0.2 to 0.6[‡]; .358)
SPRID at 120 Minutes, Mean (SD)	5.9 (4.8)	6.4 (4.2)	6.7 (4.3)	0.8 (−0.2 to 1.7[‡]; .135)	0.5 (−0.5 to 1.5[‡]; .332)	0.3 (−0.5 to 1.1[‡]; .517)

[*] SPRID: Time-weighted sum of pain relief combined with pain intensity difference. *P* values for SPRID 60 and SPRID 120 were derived from the analysis of variance (ANOVA) model with treatment, site and baseline dental pain scale (DPS) score.

[†] SD: Standard deviation.

[‡] The 95 percent confidence intervals were calculated on the basis of the least squares means from the ANOVA model with treatment, site and baseline DPS score.

[§] The first treatment was significantly better than was the second treatment at the $P \leq .05$ level.