Original Article

Effectiveness of a novel topical powder on the treatment of traumatic oral ulcers in orthodontic patients:

A randomized controlled trial

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ABSTRACT

Objective: To determine if 2-DeNT Oral Topical Powder is an effective treatment for traumatic oral ulcers.

Materials and Methods: Of the 46 patients who were randomly allocated, 20 patients from the experimental group and 17 from the placebo control group completed the study. The patients, operators, and evaluators were all blinded. Patients applied the powder twice a day and completed a diary twice a day for 10 days. The diary was used to monitor the size of the lesions and pain levels (using a 10-cm visual analog scale).

Results: By day 5, the ulcers in the experimental group had reduced in size by approximately 70%; and ulcers in the control group had reduced in size by 56%. The experimental-group ulcers were significantly ($P < .05$) smaller than the control-group ulcers from day 5 through day 9. Ulcers in the experimental group were completely resolved by day 8, whereas control-group ulcers were still present on day 10. Patients experienced a significant amount of stimulated pain until the night of day 2 in the experimental group and until the night of day 5 in the control group, but group differences in pain were not statistically significant.

Conclusions: The 2DeNT Oral Topical powder was more effective than the placebo powder at accelerating the healing of oral traumatic ulcers. (*Angle Orthod.* 2016;86:351–357.)

KEY WORDS: Traumatic oral ulcers; Treatment; Duration; Pain; Ulcer size

INTRODUCTION

Injury to the oral mucosa during orthodontic treatment is a common occurrence, and the most frequent patient complaints relate to brackets irritating the labial/buccal mucosa and distal wires extending into the retromolar area.[1] Oral ulcerations are the likely sequelae to such trauma. The damaged epithelium is replaced by a yellow fibrinopurulent membrane surrounded by erythema[2]; exposure of nerve endings can provoke a painful sensation.[3] The incidence of oral traumatic ulcers ranges between 60% and 81%.[4–7] Approximately 47% of adults report oral ulcerations as the most annoying aspect of orthodontic treatment[4]; 29% of adolescents report ulcers as the second most annoying aspect of treatment.[5]

Pain is part of the inflammatory phase of healing, which usually occurs within 24 hours after the injury.[8] Upon removal of the injurious agent, ulcers normally heal within 10–14 days.[9–12] Infection can prolong or delay healing by stimulating an inflammatory response.[13] Although saliva has antimicrobial properties,[14,15] the oral environment presents a challenge to healing because it includes a large commensal flora and oral pathogens that can induce an inflammatory infiltrate.[16]

Over-the-counter products indicated for oral ulcers include different formulations and various active com-

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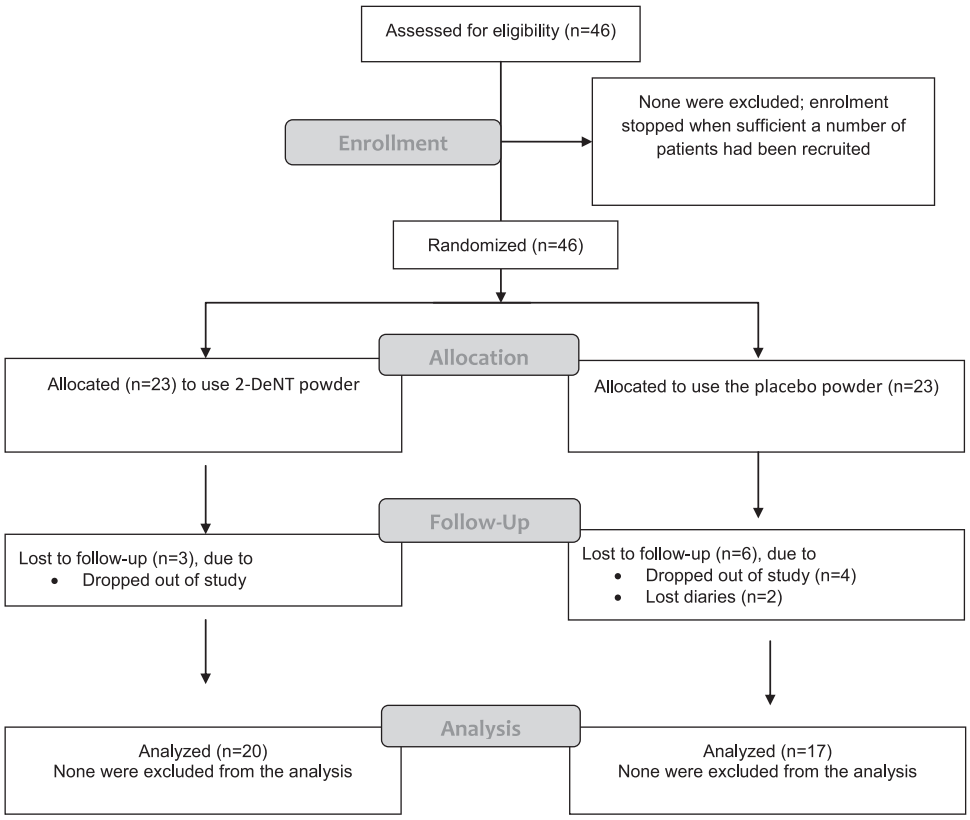


Figure 1. Diagram of patient flow throughout the trial.

pounds.[17] Benzydamine hydrochloride and chlorhexidine are no better than a placebo mouthwash if the traumatic etiology has not been removed.[6,18] Experiments have shown that active gels increase healing of mucosal ulcerations faster than inactive gels.[12] Ulcers treated with benzydamine hydrochloride gel were reduced 33% more than ulcers in control groups, but they were still not healed until the 12th day.

The objective of the present study was to determine if, after the traumatic etiology has been removed, 2-DeNT Oral Topical Powder accelerates healing and decreases the duration of oral traumatic ulcers compared with an inactive placebo powder. This is important because traumatic ulcers are a major problem that has yet to be resolved.

MATERIALS AND METHODS

This was a parallel randomized controlled trial. It is based on a power of 90%, a type I error of 5%, and an effect size of 1; thus, 36 subjects were required. To account for potential dropouts, a sample of 46 consecutive orthodontic patients who developed oral traumatic ulcers in the buccal mucosa was enrolled. Most of their ulcers were due to orthodontic wires extending too far into the vestibule or to brackets rubbing against the cheek. Microsoft Excel and simple random allocation procedures were utilized; one investigator prepared lists used by another investigator to assign patients to either the experimental (23 patients) or control (23 patients) groups (Figure 1). Nineteen male subjects (9 control group, 10 experimental group) and 18 female subjects (10 experimental group, 8 control group) completed the study. Ages ranged from 12 to 29 years. Subjects were orthodontic patients in the Texas A&M University Baylor College of Dentistry Orthodontic Clinic. The study was approved by the Institutional Review Board at the Texas A&M University System Health Science Center, and informed consent was obtained from patients' parents before enrollment.

The selection criteria for this study included the following: (1) orthodontic patients older than 12 years, (2) patients in good general health and free of any systemic illness, (3) patients with pain/ulceration in the oral mucosa, and (4) patients willing and able to cooperate with all aspects of the protocol and able to communicate effectively and give informed written consent. Exclusion criteria included the following: (1) taking drugs that may influence the pattern of oral ulceration; (2) cigarette smoking; (3) history of oral mucosal disease, in particular recurrent aphthous ulcers; (4) history of skin or systemic diseases with which oral lesions may be expected; (5) oral ulcerations with unknown etiology that are not traumatic

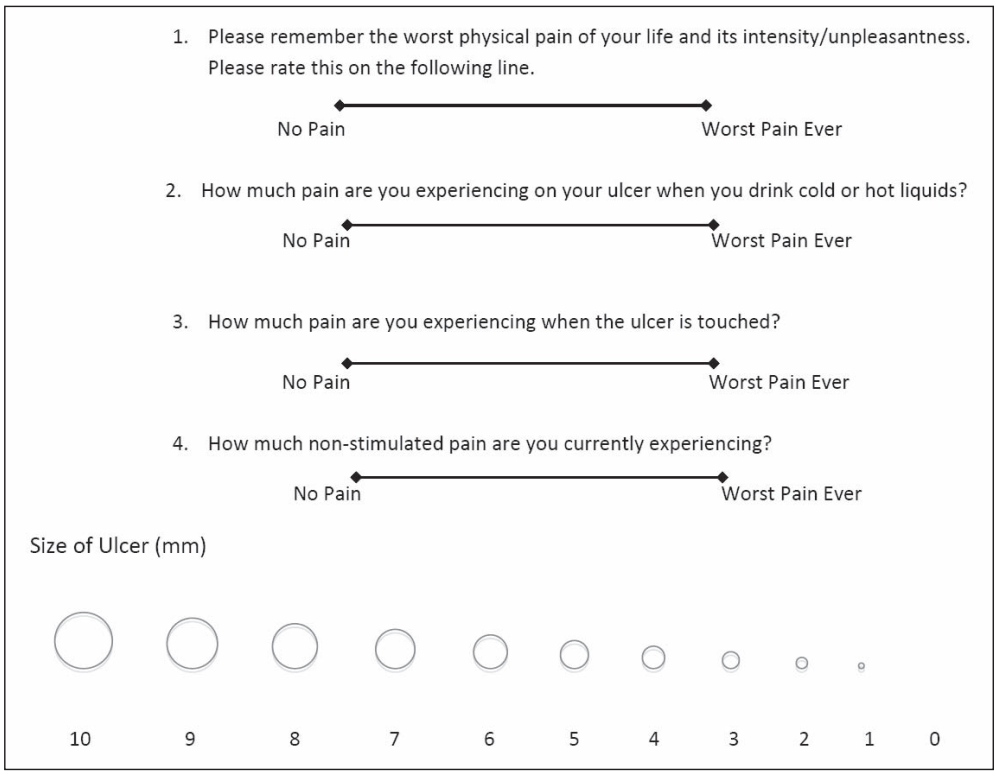


Figure 2. Record of lesion size and three questions pertaining to the pain.

in nature; (6) oral ulcerated lesions not located on the buccal mucosa (ie, lesions on the tongue); (7) pregnant and lactating women; and (8) patients with a known hypersensitivity to nystatin, tetracycline, metronidazole, dexamethasone, diphenhydramine, karaya gum, zinc oxide, or yellow dye.

For the orthodontic-related ulcers that occurred between monthly recall/adjustment visits, the healing period was considered to commence after the traumatic irritant had been removed. The patients with nonorthodontic injuries reported that they had occurred within 48 hours of starting the study.

Intraoral photographs (Canon Rebel T1i SLR Digital Camera, 100 mm Macro lens, Canon, USA, Melville, NY) were taken of each lesion. Using a transparent millimeter ruler, the principal investigator measured the initial size of the ulcer in order to demonstrate the procedures to the patients. Each patient was then asked to record the size of the lesion (primary outcome variable) and answer three questions pertaining to the pain (secondary outcomes) they were experiencing (Figure 2). The first question established a baseline for pain and was asked only once. The questions were piloted to ensure their validity. Pain was measured using a 10-cm visual analog scale, with no pain and worst pain ever as anchors. The first set of data was collected in the orthodontic clinic. Lesion size and pain questions were recorded daily for 10 days. A repeated measures design was used due to subjectivity and potential errors associated with the measurements.

The principal investigator then applied either the experimental or control power onto the lesion to demonstrate its application. The experimental 2DeNT Oral Topical Powder (Wedgewood Pharmacy, Swedesboro, NJ) consisted of nystatin (antifungal), tetracycline (antibiotic), metronidazole (sulfa drug antibiotic), dexamethasone (steroid), diphenhydramine (antihistamine),
karaya gum (mucoadhesive), and zinc oxide (protectant with some antimicrobial qualities). We chose 2-DeNT powder because it is untested. The placebo control powder consisted only of the karaya gum (used to enhance powder retention to mucosal tissue), yellow dye (coloring agent used to mimic the color of the active powder), and zinc oxide as a filler and stabilizer. Both the patients and investigators were blinded as to the contents of the bottles. Patients were instructed to avoid eating or drinking for 30 minutes after powder application and to avoid touching the lesion with their tongue. They were provided with a bottle of the powder and instructed to apply two or three “puffs” to cover the lesion twice a day (morning and night) until the lesion resolved.

The patients were instructed to measure the ulcer and answer the pain questions twice daily (ie, morning and night) at home. Data collection continued until the lesion had healed (ie, when it resembled the

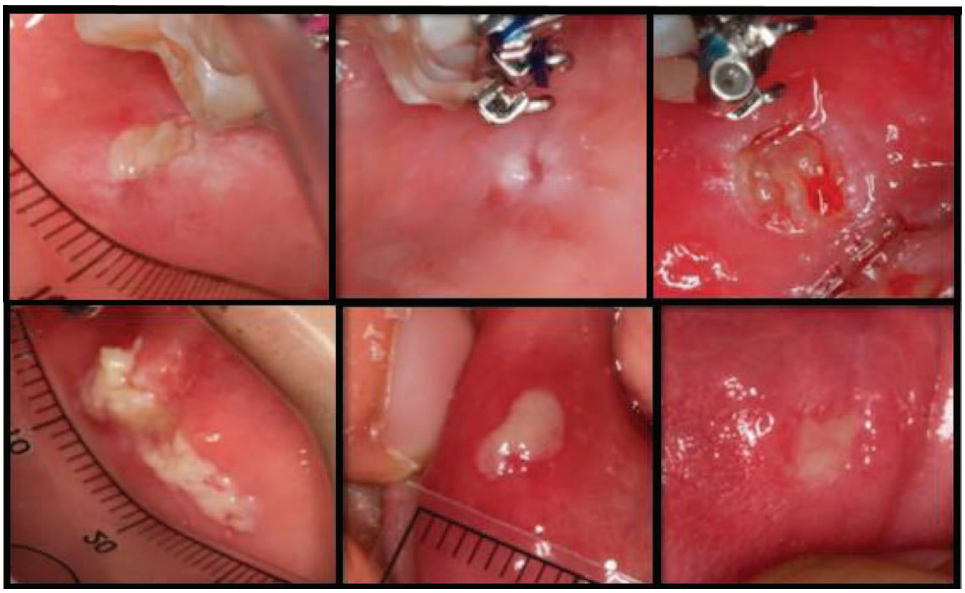


Figure 3. Clinical presentation of ulcers from wire pokes (top panel) and injuries other than wire pokes (bottom panel).

other healthy parts of their cheeks). The subjects, operators, or evaluators were all blinded. There were no changes to the methods after trial commencement.

Statistical Analysis

Multilevel modeling procedures were used to statistically evaluate the changes over time and to compare group differences in ulcer size and pain.[19,20] The order of each model was determined in the fixed part of each polynomial regression. Starting with fourth-order models, the highest-order term was compared with its standard error (estimates had to be $\geq$1.96 SE). If the term was not statistically significant, it was dropped, and the next highest-order term was tested. This process was repeated until significance was attained. The constant term provided estimates of size and pain at day 5. The time and time^2 terms estimated daily rates of change (linear term) and acceleration/deceleration (quadratic term). Rates of change in ulcer size were estimated by taking the first derivative of the polynomials. The basic model partitioned variation into two levels: subjects were at the higher level and the 20 measurement occasions, nested within subjects, were at the lower level.

Statistical Package for the Social Science (version 19, SPSS, Chicago, Ill) was used to estimate means and standard deviations for pain and ulcer size. The standard errors were used to determine whether the mean size and pain measures at each time point differed from zero. Group differences in the percentages of patients who had complete ulcer resolution were tested using a χ^2 test. All tests were performed based on a $P < .05$.

RESULTS

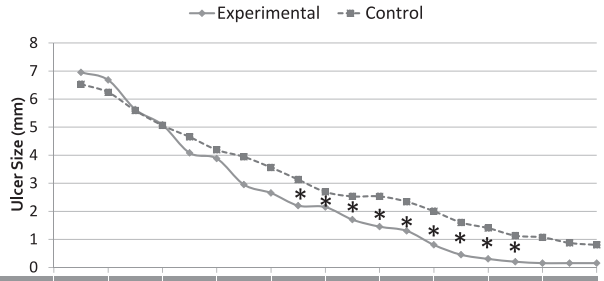
The majority of the ulcers were irregular in shape and had a yellow fibrin clot in the center of the lesion. Some of the lesions appeared deeper and had a thicker fibrin clot, while others were continuous with or raised above the level of the adjacent mucosal tissue (Figure 3). Others were surrounded by a white area of hyperkeratosis or had an erythematous border. The control and experimental groups had similar proportions of orthodontically and nonorthodontically related injuries (Table 1).

Ulcer size

The ulcers were initially similar in size and showed no statistically significant group differences (Figure 4). Ulcer size decreased over time in both groups. The multilevel models showed that the decrease followed a curvilinear healing pattern that was best described by a quadratic polynomial (Table 2). By day 5, the ulcers showed significant group differences in size and in the rates at which the ulcers changed size (ie, time effect)

Table 1. Percentages of the Various Types of Traumatic Injuries

	Experimental Group	Placebo Control Group
Wire poking	50	70.6
Forsus	10	0
Bracket	15	0
Ligature tie abrasion	10	5.9
Sports injury to mouth	5	11.8
Lip biting	5	11.8
Miscellaneous mouth injury	5	0
Total	100	100



Day	1		2		3		4		5		6		7		8		9		10	
Time	M	N	M	N	M	N	M	N	M	N	M	N	M	N	M	N	M	N	M	N
Exp	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	NS	NS	NS	NS	NS
Control	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S

Figure 4. Ulcer size recorded each morning (M) and night (N), along with significant ($P < .05$) intergroup differences (*) as well as significant intragroup differences from zero (S).

as well as rate changes (time^2). Statistically significant group size differences were evident through day 9. At day 5, the ulcers in the experimental group were decreasing significantly faster (0.76 mm/day) than the ulcers in the control group (0.60 mm/day) (Figure 5).

The experimental-group ulcers healed earlier than the control-group ulcers. By day 8, the average size of ulcers in the experimental group was not significantly different from zero, whereas ulcer size in the control group was significant through the day 10. More patients in the experimental than the placebo group experienced complete ulcer resolution (Figure 6), but group differences were statistically significant only on the night of day 9.

Pain

Unstimulated pain and pain upon drinking hot/cold liquids were not significantly different from zero throughout the study course, and there was no pattern of pain resolution for either of the two measures. Pain upon touching the ulcer was low in both groups (Figure 7). It was significantly different from zero throughout day 1 and the morning of day 2 in the experimental group and until the morning of day 5 in the control group. The multilevel analysis (Table 2) showed no statistically significant group differences.

DISCUSSION

The experimental 2-DeNT powder accelerated the rate of healing. By the morning of day 5, the experimental-group ulcers had been reduced by ~ 5 mm, whereas the control-group ulcers were only ~ 3 mm smaller. The experimental-group ulcers exhibited greater size reductions than the control-group ulcers throughout the first eight days. Tetracycline, one of the powder's active components, has been shown to prevent or reduce the size of inflammatory lesions induced by bacteria within the first four days of treatment.[21] This could explain why group differences were evident as early as day 5.

Bacterial and fungal contamination of wounds can prolong wound healing by stimulating the inflammatory response.[13,22–24] Biopsies of recurrent aphthous ulcers have revealed high levels of collagenase in the connective tissue adjacent to the ulcer.[25] Tetracycline inhibita host-derived collagenases in patients with recurrent aphthous stomatitis.[26] Therefore, in addition to the antibacterial properties of tetracycline, its anticollagenolytic effects may also have improved the healing in the experimental group. Nystatin decreases the inflammatory stimulus by reducing fungal colonization of wounds.[27] Dexamethasone and diphenhydramine, the anti-inflammatory and antihistamine components of the powder, also modulate the inflammatory response.[28,29]

Metronidazole, another active component of the 2-DeNT powder, could also have accelerated ulcer healing. Peripheral areas of re-epithelialization have been shown to be significantly greater in rats treated with topical metronidazole than in untreated rats.[30] Topical metronidazole gel used on dorsal wounds of

Table 2. Multilevel Estimates and Standard Errors (SEs) of Ulcer Size and Discomfort at Day 5[a]

	Constant			Time			Time^2		
	Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*
Experimental group									
Size	1.953	0.352	<.001	–0.760	0.027	<.001	0.080	0.010	<.001
Discomfort	–0.096	0.199	NS	–0.063	0.051	NS	0.082	0.016	<.001
Differences between experimental and placebo control groups									
Size	1.047	0.523	<.05	0.161	0.040	<.001	–0.040	0.015	<.01
Discomfort	0.231	0.288	NS	–0.021	0.075	NS	–0.037	0.024	NS

[a] NS indicates not significant.

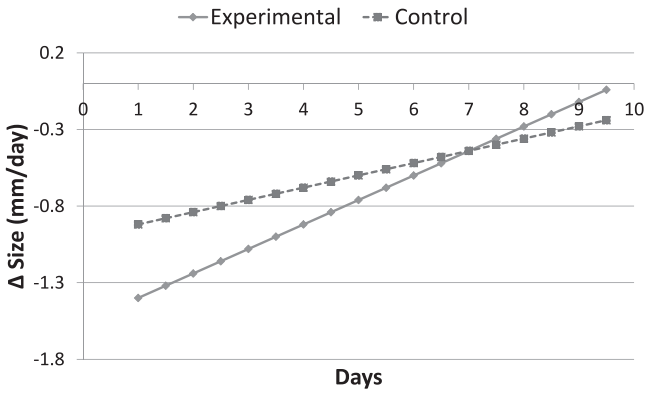


Figure 5. Rates of ulcer size change based on the multilevel estimates.

rats also produced significantly higher concentrations of type I collagen and greater angiogenesis.[31] Since healing depends on vascularization and the ability to produce collagen, metronidazole may also have contributed to early healing of the ulcers and to their earlier re-epithelialization.

By the night of day 8, the ulcers in the experimental group had largely resolved. The ulcers in the control group were not completely resolved within the 10-day observation period. Earlier resolution may have occurred because the antimicrobial components of the powder have the capacity to reduce secondary infections, which can prevent or delay healing.[13,22] Tetracycline applied locally to periodontal pockets has been shown to significantly reduce bacterial counts.[32] Furthermore, cutaneous ulcers treated with topical metronidazole have shown significant reductions in anaerobic organisms.[33] Nystatin, another component of the active powder, exhibits similar reductions in microorganism colonization.[27]

It is also possible that the antimicrobial properties of zinc oxide may have aided ulcer healing in the placebo control group. Topical zinc stimulates wound

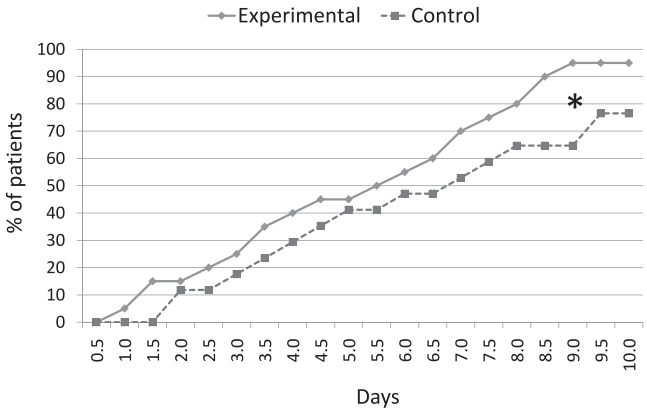
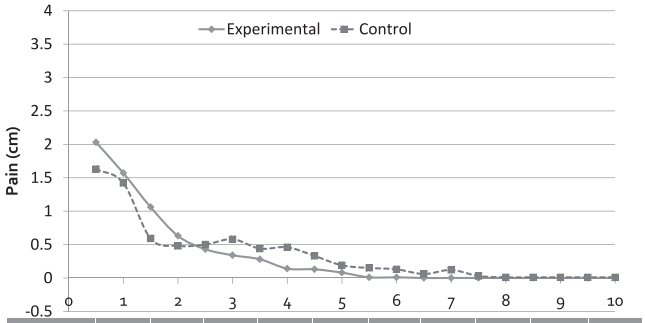


Figure 6. Percentages of patients with complete ulcer resolution, along with significant ($P < .05$) group differences (*).



Day	1		2		3		4		5		6		7		8		9		10	
Time	M	N	M	N	M	N	M	N	M	N	M	N	M	N	M	N	M	N	M	N
Exp	S	S	S	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Control	S	S	S	S	S	S	S	S	S	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Figure 7. Pain when the ulcer is touched as recorded each morning (M) and night (N), along with significant ($P < .05$) group differences (*) and differences from zero (S).

healing by enhancing re-epithelialization, decreasing inflammation, and decreasing bacterial growth of cutaneous wounds.[34] Moreover, the placebo powder covered and provided a protective layer over the lesion, acting as a barrier against infectious agents. Placebo treatments of oral ulcers have previously been shown to exhibit better healing rates than untreated controls.[12,35] Based on substantial size differences after five days, faster resolution of the ulcers, together with a possible placebo treatment effect, 2-DeNT powder was found to be clinically effective and significant.

In the present study, the initial pain reported when touching the ulcer (20% of the visual analog scale) was lower than previously reported for injuries caused by orthodontic appliances (53% to 63%).[1,36] This may have been due to not seeing the patient immediately after the injury, when the response was the greatest.[1,36] A study evaluating amlexanox oral paste for the treatment of recurrent minor aphthous ulcers showed that when the ulcers were touched, pain continued until the morning of day 2 in the experimental group and until the morning of day 5 in the control group.[35] In the present study, pain was also evident until day 2 and day 5 in the experimental and control groups, respectively. The lack of group differences was probably due to the small effect size and limited power of the present study. The decrease in the pain of oral ulcers is coincident with the formation of a fibrin clot, which usually occurs within the first few days after tissue injury.[37]

CONCLUSIONS

- The experimental 2-DeNT powder accelerated the rate of healing of oral traumatic ulcers.
- The experimental 2-DeNT powder resulted in earlier resolution of oral traumatic ulcers.

ACKNOWLEDGMENTS

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