Effectiveness of Three Desensitizing Dentifrices on Cervical Dentin Hypersensitivity: A Pilot Clinical Trial

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Abstract

Aim: Cervical dentin hypersensitivity (CDH) is defined as an acute pain of short duration that occurs in dentin exposed to the oral environment. The aim of this study was to evaluate the efficacy of three desensitizing toothpastes (Sensodyne® Rapid-Relief, Colgate® Sensitive Pro-Relief, Nano P®) for immediate and intermediate-term relief of CDH, when compared with a control toothpaste (Cocoricó®).

Materials and methods: Eight patients were enrolled in this clinical study. One hundred thirty-eight hypersensitive teeth were randomized into four groups according to the composition of the desensitizing toothpaste tested: Group I) strontium acetate and calcium carbonate; II) calcium carbonate and arginine 8%; III) calcium phosphate nanoparticles; and IV) a control toothpaste. A split mouth design was used for one application each of the desensitizing dentifrices. Assessment of CDH was done by evaporative and cold stimuli at baseline, immediately, 24 hours and 30 days after the treatment.

Results: The toothpastes presented similar effectiveness and statistically significant improvement in 30 days compared to baseline. Group III showed statistically significant relief for cervical dentin hypersensitivity immediately after the treatment.

Conclusions: The only toothpaste that presented immediate relief effect was the paste containing calcium phosphate nanoparticles in the form of hydroxyapatite.

Key words: Pain, dentin sensitivity, toothpaste, clinical trial

Introduction

Dentin is made up of tiny tubules (or dental canaliculi) which, if exposed to the oral environment, are vulnerable to cold, acidic substances, candy or to mechanical touch (Shiau, 2012; Marini *et al.*, 2000). This may cause cervical dentin hypersensitivity (CDH), a painful clinical condition that is relatively common in permanent dentition, manifesting itself in an uncomfortable way for the patient (Marini *et al.*, 2000).

The etiology of dentin or cementum exposure is multifactorial. The most common causes include incorrect methods of tooth brushing, occlusal trauma, periodontal treatments, and cemento-enamel junction defects. In addition, attrition, abrasion or erosion are non-carious cervical lesions caused by dental changes that induce loss of dental components (enamel, cementum, dentin; Shiau, 2012).

The mechanism of dentin hypersensitivity has been widely discussed in the literature (Brännström and Aström, 1972; Vaitkeviciene *et al.,* 2006; Kawabat *et al.,* 2008; Douglas de Oliveira *et al., 2013;* Pashley, 2013; Mantzourani and Sharma, 2013), and at present the hydrodynamic theory is the most accepted one (Kramer, 1995; West *et al.*, 2012).

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According to this theory the movement of intratubular fluids is the factor responsible for modulating various stimuli (tactile, thermal, osmotic and evaporative) of electrical activity in nerves (Porto *et al.*, 2009; Pashley, 2013; Magno *et al.,* 2015).

Several desensitizing agents have been clinically tested over the course of decades in an attempt to relieve the discomfort caused by cervical dentin hypersensitivity (Silverman *et al.*, 1996; Arrais *et al.*, 2003). The therapeutic agents can be classified into various groups: nerve stimulus blockers, anti-inflammatory drugs, protein-precipitating agents (that promote occlusion and sealing of the dentinal tubules) and lasers (Dababneh *et al.*, 1999). However, none of these have been shown to be consistently effective (Duran and Sengun, 2004). In the composition of desensitizing toothpastes, there are substances that obliterate the open tubules by the precipitation of protein and calcium crystals inside the tubules (Dababneh *et al.*, 1999; Duran and Sengun, 2004).

At present, there are several products that help to reduce dentinal hypersensitivity. Further, some products promise immediate pain relief (Ishikawa *et al.*, 1994; Duran and Sengun, 2004). The challenge is to find a substance that effectively eliminates this painful sensation, and decreases the chances of recurrence. Unfortunately, up to now, it has not yet been possible to find a fully effective treatment (Porto *et al.*, 2009; Mason *et al.*, 2010). The aim of this study was to evaluate the effectiveness of three desensitizing toothpastes for immediate and intermediate-term relief of CDH, when compared to a control toothpaste. The secondary objectives were to determine the teeth most associated with dentinal hypersensitivity in the selected sample and the occurrence of adverse effects.

Materials and methods

Sample size

To determine the sample size, a calculation for the comparison of means was used. Calculations with a 95% level of significance, 80% power and an additional 10% to compensate for losses determined that 30 hypersensitive teeth in each group would be sufficient to detect a difference of 1 cm on the visual analogue scale (VAS) between the groups. The standard deviation was obtained in a similar previous study (Sethna *et al.*, 2011).

Ethical principles

This randomized, controlled and triple blind pilot study was approved by the Ethics Committee of the Federal University of Jequitinhonha and Mucuri Valleys (UFVJM), protocol 119/11. The study was conducted from October 15th 2012 to December 10th 2012, in the Periodontics Clinic of the Dentistry Department (UFVJM), in accordance with the Helsinki Declaration of 1975, revised in 2008. Trial Identifier in ClinicalTrials.gov is NCT02018783.

All participants were informed about the objective of the research as well as the risks and benefits of participating in the study. Before the start of the trial, the participants signed a term of free and informed consent.

Eligibility criteria

Inclusion criteria were: subjects 18 years or older; in good general and oral health; complaint of CDH in teeth distributed in all four quadrants; not making use of desensitizing agents; not having undergone periodontal treatment over the past 3 months; response to evaporative stimulus. The exclusion criteria were: restorations and caries near the exposed dentin of the hypersensitive teeth; frequent use of painkillers, anti-inflammatory and antidepressants drugs.

Training and calibration

The researchers (VHUP and VOB) in charge of implementing the treatment with desensitizing toothpastes were trained to standardize the manner, time interval and pressure of application. The researchers (AFMM and ESO) in charge of making the readings of the visual analog scale of pain were trained and calibrated as regards intra- and inter-examiner reproducibility. The intraclass correlation coefficient was 0.99.

Evaluation of cervical dentin hypersensitivity

In each patient, the hypersensitive teeth of each quadrant were submitted to application of an air blast (evaporative stimulus) for 5 seconds, 0.5 cm away from the cervical region of the teeth. The teeth were isolated from their neighbors with utility wax. Tetrafluoroethane (Endo-Ice®, Maquira, Paraná, Brazil) spray (cold stimulus) was applied with a cotton swab on each hypersensitive tooth in each quadrant for 5 seconds. The stimuli were removed ahead of time when the patient considered the stimulus as unbearable pain.

Participants were instructed to brush their teeth with a soft brush using the modified Stillman technique, use dental floss afterwards, and avoid acidic foods. They were recommended not to use desensitizing toothpastes and fluoride toothpaste during the trial period.

The pain was measured using a 10 cm long visual analogic scale (VAS), which represented "no pain" on one end, and "unbearable pain" on the other. After each stimulus, patients were asked to mark the level of pain on the scale. Then this markup was quantified with a caliper, containing two decimal places. These data were evaluated before application of the desensitizing agent (baseline); immediately, 24 hours and 30 days after treatment.

Randomization, concealment of allocation and masking

Restricted randomization was done by an independent researcher (DWDO), who assigned a letter to each treatment and a number to each quadrant of the patient's mouth. Each treatment and each quadrant were randomly selected. This allocation was kept secret within opaque, sealed envelopes. Only at the time of application of desensitizing toothpastes were the envelopes opened. Each patient received all four types of treatment.

The masking of the patients was facilitated by the fact that the toothpastes had a similar color, consistency and taste, making it impossible for participants to know which treatment they had received in each quadrant. The operator was also blinded to the desensitizing toothpaste. To achieve this, he received a sufficient quantity of pastes for application, provided on wooden spatulas, without any identification, and was only informed about the protocol and application site.

Interventions

The in-office desensitizing toothpastes were used according to the manufacturer's instructions. In the control group (Group IV), a toothpaste without fluoride and low abrasiveness was used, according to a protocol similar to that of one of the tested pastes, in order to facilitate masking. Information about the groups, commercial name of the products, manufacturer and application protocols used are shown in *Table 1*. All desensitization procedures were performed after initial evaluation (baseline) of CDH.

At the end of the study, participants were informed about the results. The patients who presented with residual hypersensitivity received a new application of the desensitizing toothpaste that showed better results.

Statistical analysis

Statistical analysis was performed using statistical software (SPSS version 20.0, IBM, Armonk, NY). Exploratory analysis of the data from the 138 teeth provided frequencies, means and standard deviations. The evaluation of data normality was checked by the Shapiro-Wilk test. As the distribution of the data was not normal, the Kruskal-Wallis test was used for comparison among groups, and the Friedman test for intra-group comparison with the Wilcoxon post-hoc test. The level of significance adopted was 5%. Bonferroni correction was used in the post-hoc tests, with a p value < 0.012 being considered significant.

To check the magnitude of the differences obtained between the baseline and 30 days post-treatment, the effect size was analyzed for each group according to the stimulus. The Cohen's d was used to calculate the effect size for two dependent groups. The results were categorized as having a small ($0.20 < d$), medium ($0.21 < d < 0.50$), or large ($d > 0.51$) effect (Cohen, 1988).

Results

Eight patients participated in the study (4 male, 4 female) with ages ranging between 22 and 48 years (mean age 29.5 years). One hundred and thirty-eight hypersensitive teeth were included in the study (*Figure 1*). The teeth were allocated as follows: in Group I there were 33 teeth (23.91%); in Group II, 31 teeth (22.47%); in Group III, 39 teeth (28.26%); and in Group IV, 35 teeth (25.36%). Among the total number of teeth, there were 33 incisors (23.91%), 23 canines (16.67%), 46 premolars (33.32%) and 36 molars (26.10%). No adverse effects were observed.

Table 1. Characteristics of desensitizing toothpastes used in the study.

Group	Desensitizing Toothpaste	Manufacturer	Therapeutic Agent	Application Time	Application Protocol
I	Sensodyne® Rapid-Relief	GlaxoSmithKline Ltda, Brazil	Strontium acetate and calcium carbonate	60 seconds	Digital application
II	Colgate® Sensitive Pro-Relief	Colgate-Palmolive Company, Brazil	Calcium carbonate and 8% arginine	3 seconds by repeating (1 time) the procedure	Slow-speed handpiece with a Robson brush
III	Nano P®	FGM Ltda, Brazil	Calcium phosphate nanoparticles in the form of hydroxyapatite	10 seconds with rest of 5 minutes	Slow-speed handpiece with a Robson brush
IV	Cocoricó®	Bitufo Ltda, Brazil.	Toothpaste without fluoride and low abrasiveness	60 seconds	Digital application

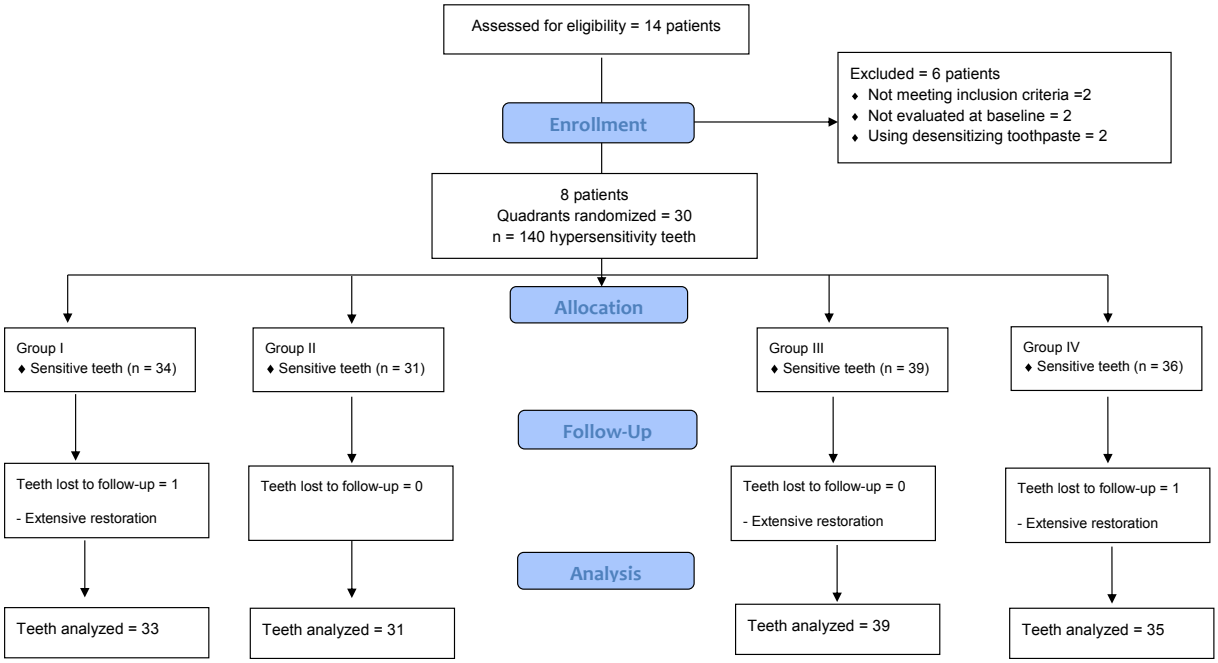

Figure 1. CONSORT diagram of the study.

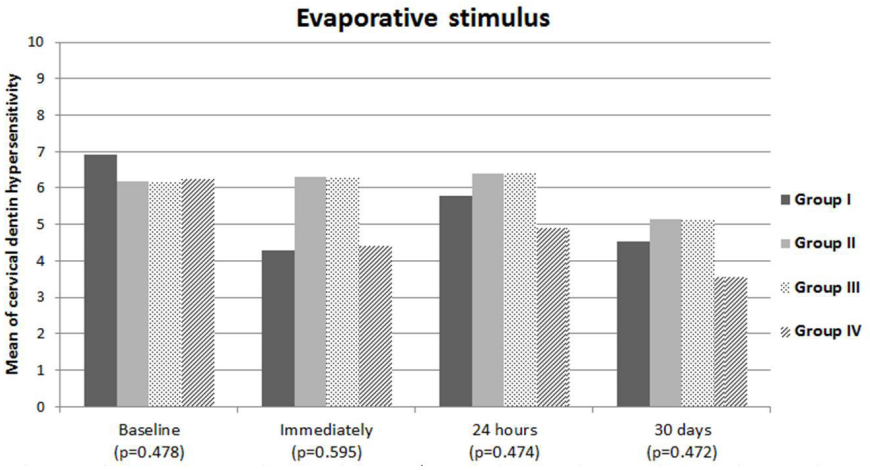

Figure 2. Intergroup analysis for evaporative stimulus according to time interval.

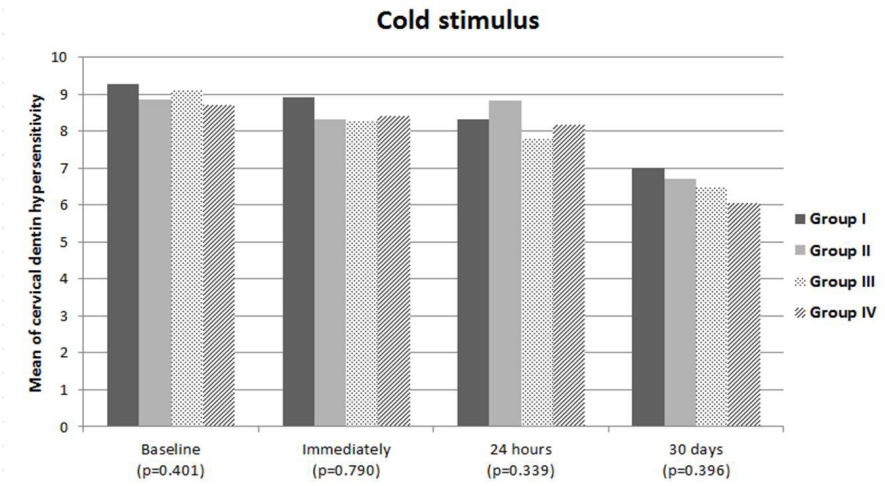

Figure 3. Intergroup analysis for cold stimulus according to time interval.

Table 2. Intragroup test for evaporative stimulus according to time interval.

Groups	Evaluation time	Mean (SD)	*p* value*	*p* value**
I	**Baseline**	6.92 (2.94)	< 0.001	Baseline x immediately = 0.017 Baseline x 24 hours = 0.038 Baseline x 30 days < 0.001 Immediately x 24 hours = 0.583 Immediately x 30 days = 0.066 24 hours x 30 days = 0.020
	Immediately	4.30 (3.28)		
	24 hours	5.79 (2.93)		
	30 days	4.54 (3.66)		
II	**Baseline**	6.18 (3.54)	0.026	Baseline x immediately = 0.737 Baseline x 24 hours = 0.976 Baseline x 30 days = 0.054 Immediately x 24 hours = 0.527 Immediately x 30 days = 0.009 24 hours x 30 days = 0.014
	Immediately	6.31 (3.15)		
	24 hours	6.40 (3.26)		
	30 days	5.15 (4.05)		
III	**Baseline**	6.23 (2.72)	< 0.001	Baseline x immediately = 0.002 Baseline x 24 hours = 0.013 Baseline x 30 days < 0.001 Immediately x 24 hours = 0.282 Immediately x 30 days = 0.006 24 hours x 30 days = 0.003
	Immediately	4.40 (3.39)		
	24 hours	4.90 (3.47)		
	30 days	3.54 (3.72)		
IV	**Baseline**	6.82 (3.12)	< 0.001	Baseline x immediately = 0.026 Baseline x 24 hours = 0.178 Baseline x 30 days = 0.002 Immediately x 24 hours = 0.224 Immediately x 30 days = 0.049 24 hours x 30 days = 0.056
	Immediately	5.42 (3.77)		
	24 hours	5.96 (2.89)		
	30 days	4.96 (4.13)		

*Friedman test ($p < 0.05$). **Wilcoxon post-hoc test (Bonferroni correction: $p < 0.012$).

Intergroup equality test

There was no statistically significant difference among the four groups regarding evaporative and cold stimuli in the different time intervals of assessment (*Figures 2 and 3*).

Intra-group equality test (evaporative stimulus)

With air blast stimulus, all groups presented results with statistically significant differences between the tests performed at baseline and after 30 days, except for Group II. Group III was the only one that showed statistically significant relief for cervical dentin hypersensitivity immediately after the treatment (*Table 2*).

Intra-group equality test (cold stimulus)

With tetrafluoroethane stimulus, all four groups showed statistically significant differences between baseline assessment and after 30 days. Groups I and II presented with statistically significant reduction of CDH after 24 hours. The only group that demonstrated a statistically significant immediate relief effect was Group III (*Table 3*).

Effect size

For the evaporative stimulus, the effect size was large for Groups I and III, and medium for Groups II and IV. For the cold stimulus, all groups had a large effect size (*Table 4*).

Discussion

Cervical dentin hypersensitivity is characterized as an acute pain that cannot be explained by other pathologies (Shiau, 2012). Despite being a common clinical complaint, the difficulty of its treatment is expressed by the huge number of techniques and therapeutic alternatives, including both in-office and home treatment (Silverman *et al.*, 1996; Arrais *et al.*, 2003; Dababneh *et al.*, 1999; Duran and Sengun, 2004).

Table 3. Intragroup test for cold stimulus according to time interval.

Groups	Evaluation time	Mean (SD)	*p*-value*	*p*-value**
I	**Baseline**	9.28 (1.57)	< 0.001	Baseline x Immediately = 0.100 Baseline x 24 hours = 0.001 Baseline x 30 days <0.001 Immediately x 24 hours = 0.195 Immediately x 30 days = 0.001 24 hours x 30 days = 0.026
	Immediately	8.91 (1.65)		
	24 hours	8.31 (2.16)		
	30 days	7.02 (3.18)		
II	**Baseline**	8.87 (1.76)	0.002	Baseline x Immediately = 0.225 Baseline x 24 hours = 0.983 Baseline x 30 days = 0.002 Immediately x 24 hours = 0.309 Immgediately x 30 days = 0.004 24 hours x 30 days = 0.004
	Immediately	8.33 (2.89)		
	24 hours	8.83 (2.18)		
	30 days	6.71 (3.70)		
III	**Baseline**	9.14 (1.37)	< 0.001	Baseline x Immediately <0.001 Baseline x 24 hours = 0.001 Baseline x 30 days <0.001 Immediately x 24 hours = 0.422 Immediately x 30 days = 0.007 24 hours x 30 days = 0.021
	Immediately	8.26 (2.04)		
	24 hours	7.80 (2.84)		
	30 days	6.51 (3.65)		
IV	**Baseline**	8.72 (2.08)	0.010	Baseline x Immediately = 0.133 Baseline x 24 hours = 0.248 Baseline x 30 days = 0.002 Immediately x 24 hours = 0.564 Immediately x 30 days = 0.005 24 hours x 30 days = 0.007
	Immediately	8.42 (1.90)		
	24 hours	8.18 (2.39)		
	30 days	6.07 (4.01)		

*Friedman test ($p < 0.05$). **Wilcoxon post-hoc test (Bonferroni correction: $p < 0.012$).

Table 4. Effect size pre- and post-treatment according to the stimulus.

Groups	Cohen's *d*	
	Evaporative	Cold
I	0.71	0.91
II	0.27	0.74
III	0.82	0.95
IV	0.50	0.82

The aim of this study was to analyze the effectiveness of three desensitizers with immediate action available on the market. Through this research it was found that all toothpastes, including the control, were able to reduce CDH.

The technology of the toothpaste containing arginine is called Pro-Argin®, which promotes the obliteration and formation of plugs inside the exposed dentinal tubules and is able to relieve CDH (Petrou, 2009). The mechanism associated with the use of strontium acetate is based on its chemical affinity for dentin, and its action of obliterating the dentinal tubules (Banfield and Addy, 2004). Strontium solution reacts with the phosphate ions present in the dentinal tubule fluid and forms strontium-apatite, which is insoluble and is deposited in the form of crystals (Mason *et al.*, 2010). The calcium phosphate precipitates quickly within the dentinal tubules, and is frequently used in toothpastes such as the one used in Group I (Ishikawa *et al.*, 1994; Sethna *et al.*, 2011).

Studies have shown that nanoparticles of 20 nm in size (the thickness of a human hair) mimic natural enamel blocks and are effective as an enamel repair material and anticarious agent (Allaker, 2010). Nanocomposites containing calcium phosphate nanoparticles are advantageous because of the small size and high surface area of nanoparticles (Xu *et al.*, 2010). It has been shown that the calcium phosphate nanocomposite has mechanical properties two times greater than those of traditional calcium phosphate composites (Moreau *et al.*, 2011).

The active agent has a diameter 20 times smaller than the diameter of the dentinal tubules, suggesting that there will be a larger amount of calcium phosphate per area within the tubular canaliculi, thus obliterating them more effectively for a prolonged period (Ishikawa *et al*., 1994; Yoshiyama *et al*., 1996; Martínez-Ricarte *et al*., 2008). In addition, studies have shown that in hypersensitive dentin there are dentinal tubules with a diameter of 0.83 micra, whereas dentinal tubules of 40 micra in diameter do not present CDH (Yoshiyama *et al*., 1996; Martínez-Ricarte *et al*., 2008). These facts may explain the ability of the nanoparticle desensitizing agent to penetrate into the hypersensitive dentin tubules, obliterating them and consequently reducing the hypersensitivity. Thus, the nanoparticles toothpaste presented highly significant and immediate pain relief in both tests used in this study.

Studies about the effectiveness of strontium acetate have demonstrated a 37.8% decrease in cases of hypersensitivity after 6 weeks of using this toothpaste (Mason *et al*., 2010; Magno *et al*., 2015). The strontium acetate acts through precipitation of proteins and denaturation of odontoblasts, forming a protective barrier that prevents intratubular fluid movement (Porto *et al*., 2009), *i.e.*, it decreases the permeability of the dentinal tubules. In the present study, it was found that this active agent was effective within 24 hours, extending to 30 days, as shown by thermal testing.

The new Pro-Argin® technology may result in the benefits of a quick and lasting relief of dentinal hypersensitivity (Petrou *et al*., 2009). Arginine and calcium carbonate work together to accelerate the natural mechanisms of dentinal tubule occlusion and formation of a protective layer on the dentin surface (Petrou *et al*., 2009). Clinical findings have suggested that toothpastes containing arginine and calcium carbonate are able to provide significant relief of dentinal hypersensitivity (Petrou *et al*., 2009; Ayad *et al*., 2009; Hamlin *et al*., 2009). In the present study, the group treated with the toothpaste that contained 8% arginine associated with calcium phosphate presented a significant improvement in CDH, and this result is therefore compatible with those in the literature reports (Petrou *et al*., 2009; Ayad *et al*., 2009; Hamlin *et al*., 2009). However, it was not possible to observe an immediate effectiveness of this product, which could only be confirmed 30 days after the single application (statistically significant decrease in CDH).

The toothpaste that was used as control also presented positive results with respect to the reduction of dentin hypersensitivity, having an effectiveness similar to that of the desensitizing toothpastes tested in this research. This result suggests that there may be other factors besides the desensitizing therapeutics agents capable of contributing to the reduction of CDH. These lower levels of sensitivity can be attributed to the treatment received by the participants, which could influence the patient's emotions and expectations, considering human suggestibility and the Hawthorne effect (Ayada *et al*., 2009; Hamlin *et al*., 2009; Pansky *et al*., 2011; West *et al*., 1997; França *et al*., 2015; Magno *et al*., 2015).

The placebo effect may also be involved, as it can occur when there are excellent relations between the dentist and patient. The positive motivation and emotional stimuli could activate pain inhibitors at a central level, *i.e.*, they cause the release of endorphins in the central nervous system, modulated by the peripheral nervous system. Approximately 20 to 45% of patients who do not receive treatment or are treated with placebos get relief from pain (Levin *et al*., 1973; França *et al*., 2015; Magno *et al.,* 2015).

The teeth most commonly associated with CDH were the premolars. Studies suggest that this group of teeth is at risk for developing non-carious cervical lesions caused by attrition, abrasion and erosion (Bernhardt *et al*., 2006; Smith *et al*., 2008). These cervical defects of enamel loss may cause cervical dentin hypersensitivity.

The split-mouth design used in the present study is a highly effective model of study. It makes comparisons within each patient rather than comparing patients to each other (parallel design; Koch, 1997). In this case, the error variance of the experiment can be reduced, obtaining a more powerful statistical test (Hoang-Dao *et al*., 2009). In order to use a split-mouth design, more than one location in the mouth must be affected by the investigated disease (Lesaffre *et al*., 2007). In this study, hypersensitive teeth in the same quadrant received only one desensitizing toothpaste. Therefore, leakage of low viscosity desensitizing agents to adjacent teeth was not a concern and thus avoided the "carry-across" effect (Lesaffre *et al*., 2007; Schwarz *et al*., 2002; Duran and Sengun, 2004).

The present study used evaporative and thermal stimuli for CDH assessment, which are very accurate in reproducing the pain experienced by the patient in daily activities and are easy to apply. Furthermore, these tests are often used to evaluate cervical dentin hypersensitivity in clinical trials (Gentile and Greghi, 2004; Addy *et al*., 2007). Liu *et al.* (1998) reported that a tactile stimulus does not exactly reproduce the stimuli received from day to day by the patient; thus, the reliability of the results may be questioned. Therefore, the tactile stimulus was avoided in the study.

In dentistry studies, the sample size can be specified in the average number of sites examined (Koch and Paquette, 1997; Liu *et al*., 1998). This fact allows the maximization of accuracy of the search results while the cost of the study is minimized (Liu *et al*., 1998; Hujoel and Loesche, 1990; Hujoel and DeRouen, 1992). In addition, the pain experience in CDH is different for different teeth in the same patient. Therefore, this clinical trial used the tooth as sampling unit.

The effect size is an additional measure to the traditional statistical test of the null hypothesis, aimed to determine the clinical significance of the effect, and not limited to dichotomous (significant or non-significant) results (Cohen, 1988). Treatment with the Nano P® and Sensodyne® toothpastes showed a large effect size for both stimuli, suggesting that the reduction in CDH after both treatments was large and probably improved the day-to-day living dentin hypersensitivity in terms of severity. Moreover, all other groups exhibited a clinical effect in reducing dentin hypersensitivity after treatment (effect of size ranging from medium to large). These results suggest that the desensitizing toothpaste used has variable clinical efficacy in the treatment of CDH.

Although well delineated, this clinical trial has some limitations. For instance, the short follow-up of participants, and numerous teeth were examined in only eight patients. Also, the data from this study arose from heterogeneity in relation to the desensitizing toothpastes and protocol application.

Conclusions

It could be concluded that: 1)All desensitizing toothpastes tested demonstrated similar efficacy for relief of cervical dentin hypersensitivity when assessed in the 30 day time interval; 2) The groups treated with toothpastes composed of strontium acetate and calcium carbonate, or calcium phosphate nanoparticles in the form of hydroxyapatite, presented with statistically significant relief after 24 hours, when tests were performed with cold spray; 3) The only desensitizing toothpaste that provided an immediate relief effect after both stimuli was that composed of calcium phosphate nanoparticles in the form of hydroxyapatite.

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