Michele Vano

Effectiveness of nano-hydroxyapatite toothpaste in reducing dentin hypersensitivity: A double-blind randomized controlled trial

Michele Vano, DDS, PhD[1]/Giacomo Derchi, DDS, PhD, MSc[2]/Antonio Barone, DDS, PhD[1]/Ugo Covani, DMD[3]

Objective: The present double-blind randomized clinical trial aimed to compare the efficacy in reducing dentin hypersensitivity of a dentifrice formulation containing nano-hydroxyapatite with a fluoride dentifrice and a placebo. **Method and Materials:** 105 subjects were recruited to participate in the study. A computer-generated random table with blocking to one of the three study treatments was used in order to have 35 subjects per group: 1) nano-hydroxyapatite 15% toothpaste, fluoride-free; 2) fluoride toothpaste; 3) placebo. Groups 1, 2, and 3 were instructed to brush their teeth for 2 minutes twice a day with the provided toothpaste. The participant's dentin hypersensitivity was evaluated at baseline and after 2 and 4 weeks using airblast and tactile tests. In addition, a subjective evaluation using a visual analog scale (VAS) was used. **Results:** Significantly lower values of cold air sensitivity and tactile sensitivity ($P < .001$) were found for the test group at 2 weeks and 4 weeks. In addition, statistically significantly ($P < .001$) lower values of sensitivity were reported for group 1 compared to groups 2 and 3, at 2 and 4 weeks respectively. The VAS scores were significantly lower ($P < .001$) in the test group at 2 and 4 weeks compared to baseline and to the control groups. **Conclusion:** The findings of the present study encourage the application of nano-hydroxyapatite in fluoride-free toothpaste as an effective desensitizing agent providing quick relief from symptoms after 2 and 4 weeks. *(doi: 10.3290/j.qi.a32240)*

Dentin hypersensitivity is a common dental clinical condition in permanent teeth and has been defined as acute pain for a short duration arising from the exposed dentin in response to thermal, evaporative, tactile, osmotic, or chemical stimuli, which cannot be ascribed to any other form of dental defect or pathology by the presence of open dentinal tubules on an exposed dentinal surface.[1,2]

Several theories have been used to explain the mechanisms of dentin hypersensitivity. The most widely accepted is the "hydrodynamic theory" proposed by Brännström in 1963.[3,4] According to this theory, open tubules of exposed dentin allow the movement of dentinal fluid within the dentinal tubules indirectly stimulating the pulp nerves. In support of this theory, individuals with dentin hypersensitivity show open dentinal tubules that are wider and more numerous than nonsensitive surfaces, which are mainly covered by a smear layer.[4-8]

[1] Assistant Professor, Department of Surgical Pathology, Medicine, Molecular and Critical Area, University of Pisa, University of Pisa, Pisa, Italy; and Tuscan Stomatologic Institute, Camaiore, Italy.

[2] Research Fellow, Department of Surgical Pathology, Medicine, Molecular and Critical Area, University of Pisa, University of Pisa, Pisa, Italy; and Tuscan Stomatologic Institute, Camaiore, Italy.

[3] Head Professor, Department of Surgical Pathology, Medicine, Molecular and Critical Area, University of Pisa, University of Pisa, Pisa, Italy; and Tuscan Stomatologic Institute, Camaiore, Italy.

Correspondence: Dr Michele Vano, Istituto Stomatologico Toscano, Centro di Odontoiatria, Ospedale Unico della Versilia, Via Aurelia, 335 -55043 Lido di Camaiore (LU), Italy. Email: michevano@hotmail.com

Table 1 Details of the toothpastes used in this study

Group	Product	Ingredients
Group 1: nano-hydroxyapatite toothpaste (test group)	PrevDent® toothpaste (PrevDent)	Water, hydrated silica, sorbitol, glycerin, xylitol, potassium nitrate, nano-hydroxyapatite 15%, magnesium aluminum silicate, *Mentha piperita* oil, sodium lauroyl sarcosinate, xanthan gum, phenoxyethanol, potassium chloride, sodium sulfate, sodium saccharin, CI 77891
Group 2: fluoride toothpaste (positive control)	Colgate Cavity Protection Regular (Colgate)	Sodium monofluorophosphate 0.76% (0.15% w/fluoride ion), dicalcium phosphate dihydrate, water, glycerin, sorbitol, sodium lauryl sulfate, cellulose gum, flavor, tetrapotassium pyrophosphate, sodium saccharin
Group 3: placebo	(PrevDent)	Glycerin, water

The management of dentin hypersensitivity through chemical and/or mechanical occlusion of patent tubules has been reported as an effective method for tooth sensitivity reduction.[9] Recent meta-analysis reported that active treatment options of dentin hypersensitivity (physical or chemical occlusion of open tubules) showed better results than placebo treatments.[10,11]

Dentifrices are common vehicles for desensitizing agents thanks to their low cost, ease of use, and home application.

Nano-hydroxyapatite (n-HA) is considered one of the most biocompatible and bioactive materials, and has gained wide acceptance in medicine and dentistry recently.[12]

Nano-sized particles have similarity to the apatite crystals of tooth enamel in morphology and crystal structure and have been studied as biomimetic materials for the reconstruction of tooth enamel suffering from mineral loss because of their unique potential for remineralization.[13-22]

Recently, n-HA paste has been used to reduce bleaching-related tooth sensitivity, with encouraging results.[23] However, evidence is still incomplete to prove that these products are effective in reducing dentin hypersensitivity.

The present randomized double-blind clinical trial aimed to compare the efficacy in reducing dentin hypersensitivity of a new dentifrice formulation containing n-HA, with a commercially available fluoride containing dentifrice and a placebo toothpaste. The present study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[24]

METHOD AND MATERIALS

This clinical investigation was designed as a single-site, double-blind, randomized, three-arm parallel group study involving subjects with hypersensitive teeth in accordance with the criteria described by Holland et al.[25]

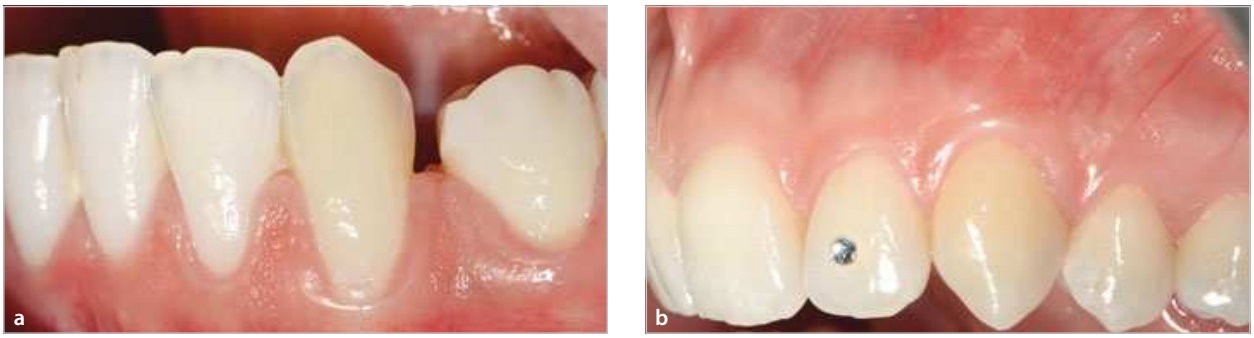
The study was carried out at the Istituto Stomatologico Toscano, Dentistry Department of Versilia Hospital, Italy (University of Pisa), from May 2013 to October 2013. The local ethical committee of Versilia Hospital independently reviewed and approved the conduct of this clinical study using human subjects (ethical approval form 433/2013, name of trial registry "Nano-Hap toothpaste and dental sensitivity"). The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000. The purpose of the study was explained to the patients, who gave written consent.

In total, 108 subjects were assessed for eligibility. Three subjects were excluded because they did not meet the inclusion criteria. Therefore 105 subjects, demonstrating two hypersensitive teeth that satisfied the tactile and airblast hypersensitivity enrolment criteria described below, qualified to participate in the study. Qualified subjects were randomly defined to one of the three study treatments in order to have 35 subjects per treatment group:

- Group 1: n-HA 15% toothpaste, fluoride-free (test group)
- Group 2: fluoride toothpaste (positive control group)
- Group 3: placebo group.

Table 1 summarizes the details of the toothpastes used in this study.

doi: 10.3290/j.qi.a32240



Figs 1a and 1b Clinical pictures illustrating patients with dentin hypersensitivity on *(a)* left mandibular canine and first premolar, and *(b)* left maxillary canine and first premolar.

All subjects received a scaling and polishing procedure before the study. After allocation all subjects were asked to cease using other desensitizing agents, such as desensitizing toothpastes and mouthrinses, for 2 weeks prior to the study and for the duration of the study. Subjects were provided with a standard nondesensitizing toothpaste for 2 weeks prior to the study as a '"wash-out" period. Groups 1, 2, and 3 were instructed to brush their teeth for 2 minutes twice a day with the provided toothpaste. The appearance of the experimental and control dentifrices were identical (dentifrices were over-wrapped to hide their identity). No additional oral hygiene product or method was allowed other than the provided toothpaste and toothbrush.

The randomization process was made using a computer-generated random table. Excel software (Microsoft) was used for randomization. The function=RAND was used in column A for 300 random numbers. In column B, the letters A, B, and C were put in groups of three, 100 times (ie, A, B, C, A, B, C). The cells were then blocked in groups of three and randomized by the random number in column A from smallest number to the largest number. Doing this in blocks of three ensured that the groups were evenly distributed. The entire study was blinded: investigators were neither involved in the randomization process nor were they aware of the assigned group in all outcome evaluations. To ensure the examiner remained blind, the study staff preparing and dispensing the over-wrapped blinded study treatments did so in a separate area.

The inclusion criteria were:

- hypersensitive areas on facial surfaces of the teeth (incisors, canines, premolars, and first molars with exposed cervical dentin) with at least two teeth scoring "pain (scale stimuli test, scores 2 and 3)" during application of stimulus (airblast and tactile sensitivity test)
- good periodontal health (no probing depth > 4 mm) with no other conditions that might explain their apparent dentin hypersensitivity (Fig 1)
- good overall physical health
- age between 20 and 70 years
- provision of written informed consent.

Exclusion criteria were:

- chipped teeth
- defective restorations
- fractured undisplaced canines
- deep dental caries
- deep periodontal pockets
- orthodontic appliances
- dentures or fixed dental prostheses that would interfere with the evaluation of hypersensitivity
- periodontal surgery within the previous 6 months
- ongoing treatment with antibiotics and/or anti-inflammatory drugs
- ongoing treatment for tooth hypersensitivity
- pregnancy or lactation
- heavy smoking
- alcohol or drug abuse.

All subjects were visited at baseline, after 2 and 4 weeks (end of the follow-up). The evaluations of the patients were carried out by two trained and calibrated dentists. Calibration of examiners was carried out on 10 subjects prior to the trial. Duplicate examinations were carried out on 10% of the subjects during the trial. Kappa statistic was used to assess the interexaminer reproducibility. At each visit, only (and all) the teeth identified as hypersensitive at baseline were reevaluated. During the visits, a minimum of two and up to four hypersensitive teeth were assessed using the most common and validated stimuli tests: tactile test and airblast test.

The teeth were isolated with cotton rolls and stimuli were applied to each tooth. Stimuli tests were performed according to a standard methodology,[25,26] briefly described as follows.

- Assessment of tactile sensitivity: A sharp dental explorer (EXD 11-12, Hu-Friedy) was passed across the facial area of the tooth, perpendicular to its long axis, at an approximated constant force. The test was repeated three times before a score was recorded.
- Assessment of evaporative (cold air) sensitivity: These assessments were performed by directing a 1-second application of compressed air from a triple air dental syringe at 60 psi (± 5 psi) with an operating temperature in the range 19°C (± 5°C), perpendicular to the exposed dentin surface, from a distance of approximately 1 cm while the adjacent teeth were isolated using cotton rolls. Two response measures were undertaken, a subjective assessment utilizing a visual analog scale (VAS) and an examiner-based Schiff assessment.[27]

VAS

Subjects were instructed on how to use a VAS and asked to complete a training exercise at the screening visit. At baseline and immediately after any time point, subjects were asked to rate the intensity of their response to the evaporative (cold air) test using the 100-mm line ranging from no pain, to worst imaginable pain.

Examiner assessment (Schiff sensitivity scale)

Prior to the subject recording their response to the air stimulus on the VAS, sensitivity was determined by the examiner using the Schiff Cold Air Sensitivity Scale as shown below; the higher the score, the higher the level of dentin hypersensitivity.

For all stimuli tests, subject responses were recorded on the following scale:

0. Subject does not respond to stimulus (no significant discomfort, or awareness of stimulus)
1. Subject responds to stimulus but does not request discontinuation of stimulus (discomfort but no severe pain)
2. Subject responds to stimulus and requests discontinuation or moves from stimulus (pain during application of stimulus)
3. Subject responds to stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus (severe pain during and after application of stimulus).

The above stimuli tests were applied in the above order, with a 5-minute pause between the applications of different stimuli.[28]

Sample size estimation

The main outcome was the difference across groups between the mean change in airblast test score from baseline to the end of the follow-up. According to previous studies,[29,30] the expected baseline mean airblast score was 2.1 ± 0.8 in both groups. The expected mean score at the end of the follow-up was 1.20 ± 0.7 in the experimental group; 1.60 ± 0.8 in the control group, with mean changes (from baseline to the end), respectively, of 0.90 (0.6) and 0.50 (0.50). Using an unpaired *t* test, and assuming an α error = .05 and an expected withdrawal/dropout rate of 15%, a minimum of 35 subjects per group was requested to achieve an 80% statistical power.

Statistical analysis

The normality of distribution of all scores was assessed using the Shapiro-Wilk test. Differences across groups

doi: 10.3290/j.qi.a32240

Table 2 Mean airblast scores and mean tactile scores at baseline, 2 weeks, and 4 weeks for each treatment group

Assessment/treatment		Air blast sensitivity			Tactile sensitivity		
		n	Mean	SD	n	Mean	SD
Baseline	Experimental group	35	2.82[a]	0.35	35	2.54[a]	0.52
	Positive control	35	2.80[a]	0.41	35	2.6[a]	0.59
	Negative control	35	2.88[a]	0.32	35	2.5[a]	0.62
2 weeks	Experimental group	35	1.1[b]	0.56	35	1.35[b]	0.55
	Positive control	35	2.45[a]	0.38	35	2.4[a]	0.6
	Negative control	35	2.38[a]	0.28	35	2.5[a]	0.65
4 weeks	Experimental group	35	1.2[b]	0.49	35	0.95[b]	0.59
	Positive control	35	2.45[a]	0.53	35	2.5[a]	0.60
	Negative control	35	2.3[a]	0.47	35	2.5[a]	0.50

[a,b], Different letters indicate statistically significant differences (*t* test, $P < .001$); SD, standard deviation.

at baseline and at each time point (2 weeks and 4 weeks) were assessed using *t* test for normally distributed variables. Within each group, the differences in all scores between baseline and 15 days or the end of the follow-up were evaluated using paired *t* test and confirmed through Wilcoxon matched pairs signed ranks test. The differences across groups between the mean change in each test score (between baseline and 2 weeks or 4 weeks) were assessed using *t* test and confirmed through the Kruskal-Wallis test. A *P* value of .05 was considered significant for all analyses, which were carried out using SPSS 17.0 statistical software.

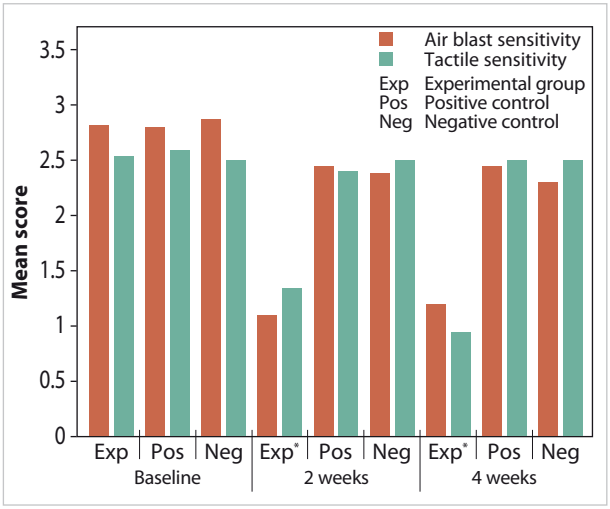


Fig 2 Histogram showing the mean airblast scores and mean tactile scores at baseline, 2 weeks, and 4 weeks (*statistically significant difference: *t* test, $P < .001$).

RESULTS

In total, 108 subjects were assessed for eligibility. Three subjects were excluded because they did not meet the inclusion criteria. Therefore, 105 subjects were enrolled: 57 females (average age 41 years) and 48 males (average age 43 years). All the subjects enrolled completed the entire study. The average scores of each test at any time point, by group, are reported in Table 2. The three groups were evenly balanced with no statistically significant differences for the baseline values.

Evaporative (cold air) sensitivity

The evaporative (cold air) sensitivity data are summarized in Table 2. Mean values ranged from 2.82 (baseline) to 1.1 and 1.2 for the experimental group at 2 weeks and 4 weeks respectively (Fig 2). Significantly lower values of cold air sensitivity ($P < .001$) were found for the experimental group at 2 weeks and 4 weeks. In addition, statistically significantly ($P < .001$) lower values of sensitivity were reported for the experimental group compared to the positive control group (2.8 and 2.45) and negative control group (2.88 and 2.38) at 2 and 4 weeks respectively. On the other hand, there was no statistical difference between the control groups at any time point. Within each group no statistically sig-

Table 3 Mean VAS scores at baseline, 2 weeks, and 4 weeks for each treatment group

	Experimental group			Positive control group			Placebo group		
	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD
Baseline	42–76	56.25[a]	14.56	39–78	54.77[a]	10.76	40–72	57.45[a]	10.02
2 weeks	15–66	39.45[b]	11.24	37–76	51.25[a]	11.05	35–70	56.21[a]	8.81
4 weeks	12–57	36.08[b]	10.35	38–77	50.11[a]	9.99	40–70	54.24[a]	8.47

[a,b], Different letters indicate statistically significant differences (*t* test, $P < .001$); SD, standard deviation.

nificant difference was noted between 2- and 4-week assessments.

Tactile sensitivity

The tactile test sensitivity data are summarized in Table 2. Mean values ranged from 2.54 (baseline) to 1.35 and 0.95 for the experimental group at 2 and 4 weeks respectively (Fig 2). Significantly lower values of tactile test sensitivity ($P < .001$) were found for the experimental group at 2 weeks and 4 weeks. In addition, significantly ($P < .001$) lower values of tactile sensitivity were reported for the experimental group compared to the positive control group (2.4 and 2.5) and negative control group (2.5 and 2.5) at 2 and 4 weeks respectively. On the other hand, there was no statistical difference between the control groups at any time point. Within each group no statistically significant difference was noted between 2 and 4 weeks assessments.

Subjective evaluation (VAS)

Mean VAS scores at baseline, 2 weeks, and 4 weeks for each treatment group are summarized in Table 3. The VAS scores were significantly lower ($P < .001$) in the experimental group at 2 and 4 weeks compared to baseline. On the other hand no significant reduction of sensitivity was reported within positive and negative control groups at any time points. Within each group no statistically significant difference was noted between 2- and 4-week assessments.

DISCUSSION

The present randomized clinical trial investigated the efficacy in reducing dentin hypersensitivity of a new toothpaste, a dentifrice containing n-HA as the main component. The results showed a significant reduction of dentin hypersensitivity for the test group both at airblast, tactile tests, and subjective evaluation (VAS). In addition, after 4 weeks of follow-up, no adverse events were reported by participants. The efficacy of the n-HA toothpaste may be explained considering two theories. The first is in accordance with the hydrodynamic theory[3] based on the alteration of fluid flow in dentinal tubules; If the dentinal tubules are obliterated anywhere along their length, hydraulic conductance will be reduced and pain consequently diminished.[4] Various studies show the progressive closure of the tubular openings of the dentin with n-HA.[13-22]

Roveri et al[19,20] have described a layer deposition of nano-sized zinc-carbonate HA nanocrystals (Zn–CHA) on the enamel and dentin surfaces, which fills the enamel scratches and seals the dentin exposed tubules. n-HA could determine a progressive closure of the tubular openings of the dentin with plugs but also the regeneration of a mineralized layer that would extend the desensitizing action.[17,19] The results reported in the present study are in accordance with a randomized controlled trial showing the efficacy of CHA nanocrystals-based dentifrice in reducing dentin hypersensitivity.[31]

The rationale behind the use of n-HA stems from the fact that it would obliterate the open dentinal tubules and blend with them because it is similar to the inorganic composition of the tooth. This principle is in accordance with the majority of desensitizing toothpastes recently introduced into the market place, which have been formulated specifically for their dentin tubule occluding abilities in order to reduce the pain of dentin hypersensitivity.[32-34]

doi: 10.3290/j.qi.a32240

The second principle, which could explain the efficacy of the tested toothpaste, can be related to the modification or blocking of the pulpal nerve response with potassium ions, which may diminish intradental nerve excitability and could cause depolarization of the pulpal sensory nerves, interrupting the transmission of the pain stimuli.[35-39]

Tooth sensitivity was measured in three ways in this study, through evaporative stimuli (Schiff score) followed by VAS and with tactile stimuli test. Two time points following treatment were recorded, after 2 and 4 weeks of treatment. Statistical significance was found at both time points and with more than one stimuli test. This proves the clinical efficacy of the experimental toothpaste in contrast with the control treatments. This randomized, double-blind study demonstrated that the experimental toothpaste was able to reduce dentin hypersensitivity over short time period.

n-HA contained in the tested toothpaste could penetrate and occlude the exposed dentin tubules which are responsible for dental sensitivity through the irritation of nerves. In accordance with the clinical results of the present trial, several in vitro studies showed that n-HA[13,40] toothpaste caused remineralization comparable to or even higher than a fluoride toothpaste, and inhibited caries development. Therefore n-HA dentifrice could be an effective alternative to fluoride toothpaste, and might help to promote remineralization.

Among the other treatments for dentin hypersensitivity, laser therapy and iontophoresis have gained some popularity.[30,41,42] However, these treatments have several disadvantages, including high cost, complexity of use, and decreasing effectiveness over time.

Brushing frequency was reported to significantly correlate with hypersensitivity.[43] In order to avoid any confounder, oral self-care was standardized as each participant was instructed to brush twice daily using only the provided material.

This clinical trial included a positive control group which used a standard fluoridated toothpaste containing sodium monofluorophosphates 0.76%, and a placebo group to provide a baseline against which the effectiveness of the active treatment could be measured. In the present trial, the fluoride toothpaste did not provide any significant reduction in dentin hypersensitivity. Fluoride is a very important component in toothpaste and its efficacy in decay-prevention has been shown both in vivo and in vitro.[44,45] On the other hand, the effectiveness of fluoride as the only active agent in a toothpaste, for the reduction of dentin hypersensitivity, gave conflicting results.

Recently, Sharma et al[46] in a randomized clinical trial tested the same fluoride toothpaste without any significant reduction in dentin hypersensitivity. Similar results were reported in another randomized clinical trial that failed to show any reduction of dentin hypersensitivity using a fluoride toothpaste.[26]

Kielbassa et al[47] reported that among the fluoride toothpastes those containing sodium fluorides or monofluorophosphates, as the positive control group in the present trial, showed lower remineralizing and cariostatic effects compared to those containing amine fluorides.

Another possible explanation for the lack of desensitizing effect provided by the fluoride toothpaste used as control group in this study could be found in the amount of fluoride contained (0.15% w/fluoride ion) which may be too low to provide any reduction of dentin hypersensitivity.

The placebo group did not provide any significant reduction in dentin hypersensitivity despite the psychologic interactions that occur in response to placebo treatments. The pathologic conditions that have shown to be most influenced by the "placebo effect" are chronic pain, depression, and impaired motor function.[48]

Dentin hypersensitivity can be defined as temporary pain or an exaggerated response in exposed dentin to different stimuli which cannot be explained as arising from other forms of dental defect or pathology. Therefore, it could be speculated that the absence of clinical effects in the placebo group in the present investigation can be explained by the acute and temporary nature of the pain that characterizes dentin hypersensitivity. In addition, different studies indicate that the context in which the medical treatment is carried out plays an important role in the outcome of

treatment. The "context of treatment" is the "atmosphere around the treatment," including for example doctors, nurses, hospitals, syringes, and pills.[49]

In the present investigation, the medical treatment was basically carried out by the patient at home, therefore the "context of treatment" could not play a major role in this case. The placebo effect is a complex psychophysiologic response; it is not possible to identify in advance the patients that will show response to placebo and which is the right context able to generate placebo effects.[50]

CONCLUSION

n-HA is well known and commonly used as synthetic bone-filler biomaterial but is not yet widespread in dental health care products. The findings of the present study encourage the application of nanotechnology in toothpaste. Thanks to its low cost, ease of use, and home application, n-HA dentifrice is a valid treatment with definite potential as an effective desensitizing agent providing quick relief from symptoms. Its mechanism of action could be explained due the occlusion of the exposed dentin tubules, which are responsible for dental sensitivity through the irritation of nerves. The n-HA toothpaste tested in the present study did not contain fluoride; however, n-HA toothpastes showed remineralizing effects comparable to or even higher than those of fluoride toothpastes. None of the patients reported any adverse responses to the agent. Although the results are encouraging, this study could be considered limited by its short-term follow up. The positive control group (fluoride toothpaste) and the placebo group did not provide any significant reduction in dentin hypersensitivity. Desensitizing agents only play a part in achieving symptom relief and are not the sole approach in managing this condition. In order to obtain long-term success, the underlying causative factors of dentin hypersensitivity must be eliminated. Therefore, further long-term follow up studies with a larger sample size are needed.

REFERENCES

1. Addy M. Bristol. Tooth brushing, tooth wear and dentine hypersensitivity: are they related? Int Dent J 2005;55:261–267.
2. Rees JS, Addy M. A cross-sectional study of dentine hypersensitivity. J Clin Periodontol 2002;29:997–1003.
3. Brännström M. A hydrodynamic mechanism in the transmission of pain producing stimuli through dentine. In: Anderson DJ (ed). Sensory Mechanisms in Dentine. Oxford: Pergamon Press, 1963:73–79.
4. Chung G, Jung SJ, Oh SB. Cellular and molecular mechanisms of dental nociception. J Dent Res 2013;92:948–955.
5. Absi EG, Addy M, Adams D. Dentine hypersensitivity. A study of the patency of dentinal tubules in sensitive and non-sensitive cervical dentine. J Clin Periodontol 1987;14:280–284.
6. Pashley D. Mechanisms of dentin sensitivity. Dent Clin North Am 1990;34:449–474.
7. Chidchuangchai W, Vongsavan N, Matthews B. Sensory transduction mechanisms responsible for pain caused by cold stimulation of dentine in man. Arch Oral Biol 2007;52:154–160.
8. Han SY, Jung HI, Kwon HK, Kim BI. Combined effects of Er:YAG laser and nanocarbonate apatite dentifrice on dentinal tubule occlusion: in vitro study. Photomed Laser Surg 2013;31:342–348.
9. Markowitz K, Pashley DH. Personal reflections on a sensitive subject. J Dent Res 2007;86:292–295.
10. Lin PY, Cheng YW, Chu CY, Chien KL, Lin CP, Tu YK. In-office treatment for dentin hypersensitivity: a systematic review and network meta-analysis. J Clin Periodontol 2013;40:53–64.
11. da Rosa WL, Lund RG, Piva E, da Silva AF. The effectiveness of current dentin desensitizing agents used to treat dental hypersensitivity: a systematic review. Quintessence Int 2013;44:535–546.
12. Hannig M, Hannig C. Nanomaterials in preventive dentistry. Nature Nanotech 2010;5:565–569.
13. Najibfard K, Ramalingam K, Chedjieu I, Amaechi BT. Remineralization of early caries by a nano hydroxyapatite dentifrice. J Clin Dent 2011;22:139–143.
14. Vandiver J, Dean D, Patel N, Bonfield W, Ortiz C. Nanoscale variation in surface charge of synthetic hydroxyapatite detected by chemically and spatially specific high-resolution force spectroscopy. Biomaterials 2006;26:271–283.
15. Huang SB, Gao S, Cheng L, Yu H. Combined effects of nano-hydroxyapatite and *Galla chinensis* on remineralisation of initial enamel lesion in vitro. J Dent 2010;38:811–819.
16. Huang S, Gao S, Yu H. Remineralization potential of nano-hydroxyapatite on initial enamel lesions: an in vitro study. Caries Res 2011;45:460–468.
17. Lee S, Kwon H, Kim B. Effect of dentinal tubule occlusion by dentifrice containing nano-carbonate apatite. J Oral Rehabil 2008;35:847–853.
18. Roveri N, Battistella E, Bianchi CL, et al. Surface enamel remineralization: biomimetic apatite nanocrystals and fluoride ions different effects. J Nanomater 2009:746383.
19. Roveri N, Battistella E, Foltran I, et al. Synthetic biomimetic carbonate-hydroxyapatite nanocrystals for enamel remineralization. Adv Mater Res 2008;47–50:821–824.
20. Roveri, N, Foresti E, Lelli M, Lesci IG. Recent advancements in preventing teeth health hazard: the daily use of hydroxyapatite instead of fluoride. Recent Patents Biomed Eng 2009:197–215.
21. Rimondini L, Palazzo B, Iafisco M, et al. The remineralizing effect of carbonate-hydroxyapatite nanocrystals on dentine. Mater Sci Forum 2007;539–543;602–605.
22. Yuan P, Shen X, Liu J, et al. Effects of dentifrice containing hydroxyapatite on dentinal tubule occlusion and aqueous hexavalent chromium cations sorption: a preliminary study. PLoS One 2012;7:e45283.
23. Browning WD, Cho SD, Deschepper EJ. Effect of a nano-hydroxyapatite paste on bleaching-related tooth sensitivity. J Esthet Restor Dent 2012;24:268–276.

doi: 10.3290/j.qi.a32240

24. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. Trials 2010;11:32.
25. Holland GR, Narhi MN, Addy M, Gangarosa L, Orchardson, R. Guidelines for the design and conduct of clinical trials on dentine hypersensitivity. J Clin Periodontol 1997;24:808–813.
26. Plagmann HC, König J, Bernimoulin JP, Rudhart AC, Deschner J. A clinical study comparing two high-fluoride dentifrices for the treatment of dentinal hypersensitivity. Quintessence Int 1997;28:403–408.
27. Schiff T, Dotson M, Cohen S, De Vizio W, McCool J, Volpe A. Efficacy of a dentifrice containing potassium nitrate, soluble pyrophosphate, PVM/MA copolymer, and sodium fluoride on dentinal hypersensitivity: a twelve-week clinical study. J Clin Dent 1994;5:87–92.
28. Sowinski J, Ayad F, Petrone M, et al. Comparative investigations of the efficacy of a new toothpaste containing potassium nitrate and triclosan 57 desensitising efficacy of a new dentifrice. J Clin Periodontol 2001;28:1032–1036.
29. Pereira R, Chava V. Efficacy of a 3% potassium nitrate desensitizing mouthwash in the treatment of dentinal hypersensitivity. J Periodontol 2001;72:1720–1725.
30. Singal P, Gupta R, Pandit N. 2% sodium fluoride-iontophoresis compared to a commercially available desensitizing agent. J Periodontol 2005;76:351–357.
31. Orsini G, Procaccini M, Manzoli L, Giuliodori F, Lorenzini A, Putignano A. A double-blind randomized-controlled trial comparing the desensitizing efficacy of a new dentifrice containing carbonate/hydroxyapatite nanocrystals and a sodium fluoride/potassium nitrate dentifrice. J Clin Periodontol 2010;37:510–517.
32. Earl J, Leary R, Muller K, Langford R, Greenspan D. Physical and chemical characterization of dentin surface following treatment with NovaMin technology. J Clin Dent 2011;22:62–67.
33. Mason S, Hughes N, Sufi F, et al. A comparative clinical study investigating the efficacy of a dentifrice containing 8% strontium acetate and 1040 ppm fluoride in a silica base and a control dentifrice containing 1450 ppm fluoride in a silica base to provide immediate relief of dentine hypersensitivity. J Clin Dent 2010;21:42–48.
34. Hughes N, Mason S, Jeffery P, et al. A comparative clinical study investigating the efficacy of a test dentifrice containing 8% strontium acetate and 1040 ppm sodium fluoride versus a marketed control dentifrice containing 8% arginine, calcium carbonate, and 1450 ppm sodium monofluorophosphate in reducing dentinal hypersensitivity. J Clin Dent 2010;21:49–55.
35. Seong J, Macdonald E, Newcombe RG, et al. In situ randomised trial to investigate the occluding properties of two desensitising toothpastes on dentine after subsequent acid challenge. Clin Oral Investig 2013;17:195–203.
36. Peacock JM, Orchardson R. Effects of potassium ions on action potential conduction in A- and C-fibers of rat spinal nerves. J Dent Res 1995;74:634–641.
37. Waraaswapati N, Krongnawakul D, Jiraviboon D, Adulyanon S, Karimbux N, Pitiphat W. The effect of a new toothpaste containing potassium nitrate and triclosan on gingival health, plaque formation and dentine hypersensitivity. J Clin Periodontol 2005;32:53–58.
38. Kim SY, Kim EJ, Kim DS, Lee IB. The evaluation of dentinal tubule occlusion by desensitizing agents: a real-time measurement of dentinal fluid flow rate and scanning electron microscopy. Oper Dent 2013;38:419–428.
39. Frechoso C, Menendez M, Guisasola C, Arregui I, Tejerina J, Sieilsa A. Evaluation of the efficacy of two potassium nitrate bioadhesive gels (5% and 10%) in the treatment of dentinal hypersensitivity: A randomized clinical trial. J Clin Periodontol 2003;30:315–320.
40. Tschoppe P, Zandim DL, Martus P, Kielbassa AM. Enamel and dentine remineralization by nano-hydroxyapatite toothpastes. J Dent 2011;39:430–437.
41. Sgolastra F, Petrucci A, Gatto R, Monaco A. Effectiveness of laser in dentinal hypersensitivity treatment: a systematic review. J Endod 2011;37:297–303.
42. Sgolastra F, Petrucci A, Severino M, Gatto R, Monaco A. Lasers for the treatment of dentin hypersensitivity: a meta-analysis. J Dent Res 2013;92:492–429.
43. Gillam D, Newman H, Davies E, Bulman J. Clinical efficacy of a low abrasive dentifrice for the relief of cervical dentinal hypersensitivity. J Clin Periodontol 1992;19:197–201.
44. Walsh T, Worthington HV, Glenny AM, Appelbe P, Marinho VC, Shi X. Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. Cochrane Database Syst Rev 2010;20:CD007868.
45. Itota T, Nakabo S, Torii Y, Narukami T, Doi J, Yoshiyama M. Effect of fluoride-releasing liner on demineralized dentin. Quintessence Int 2006;37:297–303.
46. Sharma D, McGuire JA, Amini P. Randomized trial of the clinical efficacy of a potassium oxalate-containing mouthrinse in rapid relief of dentin sensitivity. J Clin Dent 2013;24:62–67.
47. Kielbassa AM, Tschoppe P, Hellwig E, Wrbas KT. Effects of regular and whitening dentifrices on remineralization of bovine enamel in vitro. Quintessence Int 2009;40:103–112.
48. Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? Nat Rev Neurosci 2005;6:545–552.
49. Di Blasi Z, Harkness E, Ernst E, Georgiu A, Kleijnen J. Influence of context effect on health outcomes. A systemic review. Lancet 2001;375:757–762.
50. Barrett B, Muller D, Rakel D, Rabago D, Marchand L, Scheder JC. Placebo, meaning, and health. Perspect Biol Med 2006;49:178–198.

doi: 10.3290/j.qi.a32240