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ORIGINAL ARTICLE

Reducing dentine hypersensitivity with nano-hydroxyapatite toothpaste: a double-blind randomized controlled trial

M. Vano[1] · G. Derchi[1,2] · A. Barone[3] · R. Pinna[4] · P. Usai[4] · U Covani[1,2]

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Abstract
Objectives The present randomized double-blind 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.
Methods and materials One hundred and five 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 2% gel toothpaste fluoride free; (2) fluoride gel toothpaste; (3) placebo. Groups 1, 2, and 3 were instructed to treat their teeth for 10 min twice a day with the provided toothpaste gel. 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 analogue scale was used.
Results Significant lower values of cold air sensitivity and tactile sensitivity ($p < 0.05$) were found for the test group at 2 weeks and 4 weeks. In addition, statistically significant ($p < 0.05$) lower values of sensitivity were reported for group 1 compared to those for groups 2 and 3 at 2 and 4 weeks, respectively. The VAS scores were significantly lower ($p < 0.05$) in the test group at 2 and 4 weeks compared to those at baseline and in the control groups.
Conclusion The application of nano-hydroxyapatite in gel toothpaste fluoride free is an effective desensitizing agent providing relief from symptoms after 2 and 4 weeks.

Keywords Dentine hypersensitivity · Nano-hydroxyapatite · Fluoride · Desensitizing agents

Clinical Relevance
Based on the clinical study results, a daily application of a toothpaste containing nano-hydroxyapatite can effectively reduce dentin hypersensitivity.

✉ P. Usai
rpinna@uniss.it

[1] Dept of Surgical Pathology, Medicine, Molecular and Critical Area, University of Pisa, Pisa, Italy

[2] Tuscan Stomatologic Institute, Viareggio, Italy

[3] Dept of Oral Surgery, University of Geneva, Genève, Switzerland

[4] Dept of Biomedical Sciences, University of Sassari, Viale San Pietro 43/C, 07100 Sassari (SS), Italy

Introduction

Dentine hypersensitivity has been defined as acute pain for a short duration arising from the exposed dentine 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].

The "hydrodynamic theory" proposed by Brännström M in 1963 is still the most accepted theory used to explain the mechanisms of dentin hypersensitivity [3, 4].

According to this theory, open tubules of exposed dentine 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 non-sensitive surfaces, which are mainly covered by a smear layer [4–8].

Mechanical and/or chemical occlusion of patent tubules has been reported as an effective method for tooth sensitivity reduction [9]. Studies reported that active treatment options of dentine showed better results than placebo treatments [10, 11].

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Recently, nano-hydroxyapatite (n-HAp) toothpaste showed interesting results in reducing dentin hypersensitivity and post bleaching-related tooth sensitivity [12, 13].

Nano-sized particles of hydroxyapatite are similar to the apatite crystals of tooth enamel in morphology and crystal structure and has been studied as a biomimetic material for the reconstruction of tooth enamel suffering from mineral loss because of its unique potential for remineralization [14–23].

However, evidence is still incomplete especially regarding the amount of n-HAp necessary to make these products effective in reducing dentin hypersensitivity.

The present randomized double-blind clinical trial aimed to compare efficacy in reducing dentin hypersensitivity of a new gel toothpaste formulation containing n-HAp with that of a commercially available gel fluoride and placebo toothpaste.

Methods 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. [24].

The study was carried out at the Dental Clinic of the University of Sassari. The protocol and informed consent forms were approved by the ethics committee of the University of Sassari (n° DH 2362CE). 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 their written consent. The experimentation followed CONSORT guideline [25] and was registered at the US National Institutes of Health (ClinicalTrials.gov) # NCT02895321.

One hundred and fifteen subjects were assessed for eligibility. Ten subjects were excluded because they did not meet the inclusion criteria. Therefore, 105 subjects, who demonstrated 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. Nano-hydroxyapatite 2% toothpaste gel fluoride free (test group)
Group 2. Fluoride toothpaste (positive control group)
Group 3. Placebo group

Table 1 summarizes the details of the gel toothpastes used in this study and their clincial application.

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 mouth rinses for 2 weeks prior to the study and for the duration of the study. Subjects were provided with a standard non-desensitizing toothpaste for 2 weeks prior to the study as a 'wash-out' period. Groups 1, 2, and 3 were instructed to treat their teeth for 10 min twice a day with the provided toothpaste gel. The appearance of the experimental and control dentifrices were identical (dentifrices were overwrapped 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, Redmond, VA, USA) 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 (i.e., 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 the smallest number to the largest number. Doing it 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 overwrapped blinded study treatments did so in a separate area.

The inclusion criteria were the following: hypersensitive areas on facial surfaces of the teeth (incisors, cuspids, bicuspids, and first molars with exposed cervical dentine) with at least two teeth scoring "pain (Scale stimuli test: score 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; good overall physical health; age between 20 and 70 years; and provision of written informed consent.

Exclusion criteria were the following: chipped teeth, defective restorations, fractured undisplaced cuspids, deep dental caries, or deep periodontal pockets, orthodontic appliances, dentures, or bridgework that would interfere with the evaluation of hypersensitivity; periodontal surgery within the previous 6 months; ongoing treatment with antibiotics and/or anti-inflammatory and/or analgesic drugs; ongoing treatment for tooth hypersensitivity, pregnancy, or lactation; heavy smoking and alcohol or drug abuse.

All subjects were visited at baseline and 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 ten 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 inter-examiner reproducibility. At each visit, only (and all) the teeth identified as hypersensitive at baseline were re-evaluated. During the visits, a minimum of two and up to four hypersensitive teeth were

Table 1 Desensitizing agents used in the study (manufacturer's data)

Group	Product	Ingredients	Batch no.	Mode of application
Group 1: Nano-hydroxyapatite gel toothpaste (test group)	Cavex Bite&White ExSense, Cavex Holland BV	Aqua 56% sorbitol 19% glycerin 12% erythritol 5% lithium magnesium sodium silicate 5% hydroxyapatite 2% potassium choride	150702	• Dispense a small amount of Cavex Bite&White ExSense onto a clean finger. • Gently apply gel on all surfaces of the sensitive teeth. • Allow gel to remain on tooth for 10 min. • Spit out any excess gel and rinse mouth with water.
Group 2: Fluoride gel toothpaste (positive control)	Colgate Cavity Gel Protection (Colgate-Palmolive, USA)	Sodium monofluorophosphate 0.76% (0.15% with fluoride ion). Dicalcium phosphate dihydrate, water, glycerin, sorbitol, sodium lauryl sulfate, cellulose gum, flavor, tetrapotassium pyrophosphate, sodium saccharin	151050	• Dispense a small amount of Colgate Cavity Gel Protection onto a toothbrush. • Gently apply gel on all surfaces of the sensitive teeth. • Allow gel to remain on tooth for 10 min. • Spit out any excess gel and rinse mouth with water.
Group 3: Placebo	Placebo	Glycerin, water		• Dispense a small amount of placebo onto a toothbrush • Gently apply gel on all surfaces of the sensitive teeth. • Allow gel to remain on tooth for 10 min. • Spit out any excess gel and rinse mouth with water.

assessed using the most common and validated stimuli tests: tactile test and airblast test.

The teeth were isolated with cotton rolls and stimuli was 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, Chicago, IL, USA) 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-s 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 dentine 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 analogue scale and an examiner-based Schiff assessment [27].

Visual analogue scale (VAS)

Subjects were instructed on how to use a VAS and were 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 in the subsequent paragraph; the higher the score, the higher the level of dentine 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-min 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 = 0.05 and an expected withdrawal/dropout rate of 15%, a minimum of 35 subjects per group were requested to achieve an 80% statistical power.

Statistical analysis

The normality distribution of all scores was assessed using the Shapiro–Wilk test. Differences across groups 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-rank 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. *p* value of 0.05 was considered significant for all analyses, which were carried out using SPSS 17.0 statistical software.

Results

One hundred and fifteen subjects were assessed for eligibility. Ten subjects were excluded because they did not meet the inclusion criteria. Therefore, 105 subjects were enrolled: 65 females (average age 39 years) and 40 males (average age 45 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 2.97 (baseline) to 1.72 and 1.64 for the experimental group at 2 weeks and 4 weeks, respectively (Fig. 1). Significant lower values of cold air sensitivity ($p < 0.05$) were found for the experimental group at 2 weeks and 4 weeks. In addition, statistically significant ($p < 0.05$) lower values of sensitivity were reported for the experimental group compared to those for the positive control group and negative control group 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-week assessments.

Tactile sensitivity

The tactile test sensitivity data are summarized in Table 2. Mean values ranged from 3.17 (baseline) to 1.98 and 1.83 for the experimental group at 2 and 4 weeks, respectively (Fig. 1). Significant lower values of tactile test sensitivity ($p < 0.05$) were found for the experimental group at 2 weeks and 4 weeks. In addition, statistically significant ($p < 0.05$) lower values of tactile sensitivity were reported for the experimental group compared to those for the positive control group (2.65 and 2.57) and for the negative control group (2.58 and 2.73) 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-week 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 ($p < 0.05$) in the experimental group

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

Assesment/treatment	Airblast sensitivity				Tactile sensitivity		
		Number	Mean	SD	Number	Mean	SD
Baseline	Experimental group	35	2.97 a	0.42	35	3.17 a	0.495
	Positive control	35	3.05 a	0.44	35	2.94 a	0.48
	Negative control	35	2.87 a	0.36	35	2.5 a	0.52
2 weeks	Experimental Group	35	1.72 b	0.56	35	1.98 b	0.73
	Positive control	35	2.65 a	0.48	35	2.69 a	0.6
	Negative control	35	2.58 a	0.35	35	2.83 a	0.65
4 weeks	Experimental group	35	1.64 b	0.43	35	1.83 b	0.63
	Positive control	35	2.57 a	0.63	35	2.72 a	0.53
	Negative control	35	2.73 a	0.58	35	2.92 a	0.49

Different letters indicate statistically significant differences (*t* test $p < 0.05$)

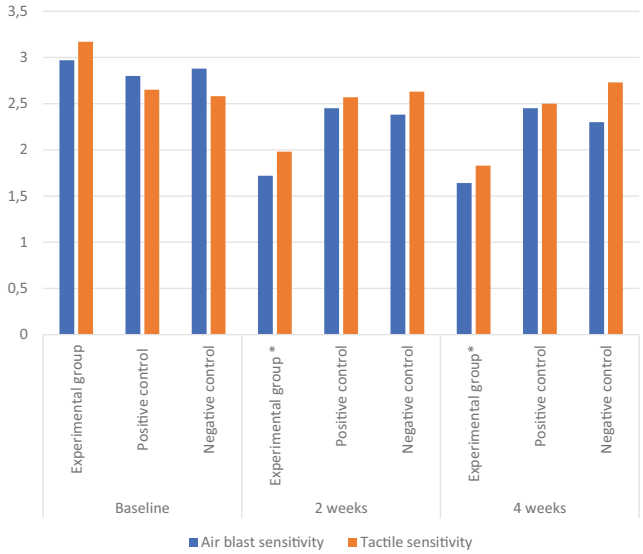

Fig. 1 Histogram showing the mean airblast scores and mean tactile scores at baseline, 2 weeks, and 4 weeks. *Asterisk* indicates statistically significant differences (*t* test $p < 0.05$)

at 2 and 4 weeks compared to those at baseline. On the other hand, no significant reduction of sensitivity was reported within the 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 gel dentifrice containing 2% n-HAp. The nano-hydroxyapatite is proving to be a suitable material for the treatment to reduce the pain. The results showed a significant reduction of dentin hypersensitivity for the test group both at airblast, tactile tests, and subjective evaluation (VAS). These results are in accordance with those of recent published studies [12, 13] in which a different percentage of n-HAp was contained in the experimental dentifrice. In particular, in a previous study [12] following the same protocol, we have observed the effectiveness of a dentifrice containing 15% of n-HAp. In the present study, we have found that the reduction of dentin hypersensitivity determined by an n-HAp dentifrice gel is also observed when the active ingredient is present at lower concentrations. Again, the mechanism of the n-HAp can be explained 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]. Different studies show the progressive closure of the tubular openings of the dentine with n-HAp [14–22].

Roveri et al. [19, 20] have described a layer deposition of nano-sized zinc carbonate nano-crystals (Zn–CHA) on the enamel and dentin surfaces, which fills the enamel scratches and seals the exposed dentin tubules. n-HAp 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 those of a randomized controlled trial showing the efficacy of CHA nano-crystals-based dentifrice in reducing dentin hypersensitivity [31].

The rationale behind the use of n-HAp 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 marketplace that have been formulated specifically for their dentine tubule-occluding abilities in order to reduce the pain of dentine hypersensitivity [32–34].

Another explanation for 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 intra-dental nerve excitability and could cause depolarization of the pulpal sensory nerves, interrupting the transmission of pain stimuli [35–39].

Tooth sensitivity was measured in three ways in this study: through evaporative stimuli (Schiff Score) followed by visual analogue scale 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 that 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 a short time period.

n-HAp contained in the tested toothpaste could penetrate and occlude the exposed dentin tubules which are responsible

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	59.58 a	18.52	39–78	57.12 a	14.79	40–72	55.65 a	13.09
2 weeks	15–66	43.21 b	16.22	37–76	53.25 a	15.23	35–70	57.51 a	11.41
4 weeks	12–57	41.38 b	13.85	38–77	52.33 a	12.39	40–70	53.44 a	10.39

Different letters indicate statistically significant differences (*t* test $p < 0.05$)

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

Among other treatments for dentin hypersensitivity, laser therapy and iontophoresis have gained some popularity [30, 41, 42].

However, those treatments have several disadvantages, including high cost, complexity of use, and decreasing effectiveness over time.

The frequency of treatment 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 apply the treatment twice daily using only the provided material.

This clinical trial included a positive control group which used a standard fluoridated gel 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 a toothpaste and its efficacy in decay prevention has been shown both in vivo and in vitro [44]. On the other hand, the effectiveness of fluoride as the only active agent in a toothpaste, for the reduction of dentin hypersensitivy, gave conflicting results.

Recently, Sharma et al. [45] 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 fluoride toothpaste [26].

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

Also, the placebo group did not provide any significant reduction in dentin hypersensitivity despite the psychological interactions which occur in response to placebo treatments. The pathological conditions that have shown to be most influenced by the "placebo effect" are chronic pain, depression, and impaired motor function [46].

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, we could speculate that the absence of clinical effects in the placebo group in the present investigation could be explained by the acute and temporary nature of the pain that characterized 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," for example, doctors, nurses, hospitals, syringes, pills, and so forth [47].

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 who will show a response to placebo and which is the right context able to generate placebo effects [48].

Conclusion

Two percent nano-hydroxyapatite gel dentifrice was effective in reducing dentin hypersensitivity. Thanks to its safety, ease of use, and home application, n-HAp dentifrice can be considered a prime choice treatment for managing dentin hypersensitivity. Its mechanism of action could be explained thanks to the occlusion of the exposed dentin tubules which are responsible for dental sensitivity through the irritation of the nerves. However, it must keep in mind that the causative factors of dentin hypersensitivity must be eliminated in order to achieve a long-term resolution of this condition. Therefore, further long-term follow-up studies with a larger sample size are needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Funding The authors declare that no financial relationships exist regarding any of the products involved in this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The protocol and informed consent forms were approved by the ethics committee of the University of Sassari (n° DH 2362CE).

Informed consent Informed consent was obtained from all individual participants included in the study.

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