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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

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Abstract

Background and Aim: Several dentifrices have shown to be effective in reducing dentine hypersensitivity (DH), but more effective products are needed. The aim of the study was to evaluate the desensitizing efficacy of a new dentifrice based on zinc–carbonate hydroxyapatite (CHA) nanocrystals.

Methods and Materials: Using a double-blind, randomized design, the new dentifrice was compared with potassium nitrate/fluoride dentifrice (active control). The participant's DH was evaluated at baseline and after 4 and 8 weeks using airblast (primary outcome), tactile, cold water and subjective tests (secondary outcomes).

Results: The final sample consisted of 70 subjects with baseline DH; 36 received the new dentifrice and 34 the control one. Both dentifrices were largely effective; the percentage of score reduction from baseline to 8 weeks was greater than 28% for all tests (and greater than 55% for the cold water test) in both groups. As compared with controls, experimental subjects had a significantly greater improvement in the airblast test score (mean percentage of reduction of 46.0% *versus* 29.4% in controls) and the subjective test score (47.5% *versus* 28.1%, respectively), with both differences already being significant after 4 weeks. In contrast, there was no significant difference between groups for either the tactile or cold water tests at any time point and with any outcome.

Conclusions: This study documented that the new dentifrice containing zinc–CHA nanocrystals significantly reduced dentinal hypersensitivity after 4 and 8 weeks, supporting its utility in clinical practice.

Key words: carbonate hydroxyapatite nanocrystals; dentifrice; dentine hypersensitivity; potassium nitrate; RCT

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Conflict of interest and source of funding statement

All authors declare that they have no conflicts of interests.

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Dentine hypersensitivity (DH) is characterized by a short, sharp pain 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 (Addy 1992, Holland et al. 1997). The condition can arise as a result of enamel loss caused by attrition, abrasion or erosion and can be often associated with exposed root surfaces of canines and premolars (Orchardson & Collins 1987).

DH is a common problem with prevalence varying widely, affecting between 3% and 57% of adults (Addy 1990, Rees & Addy 2004). The most widely accepted theory of the mechanism of DH is the hydrodynamic theory proposed by Brannström (1963). According to this theory, stimuli cause a rapid displacement of fluid within exposed, open tubules, which in turn excite nerve terminals at the inner ends of the tubules or in the periphery of the pulp. In support of this theory, clinical evidence shows that individuals with DH have dentinal tubules that are patent from the pulp to the oral environment and sensitive dentine surfaces have wider and more numerous tubules than non-sensitive surfaces, which are mostly covered by a smear layer (Absi et al. 1987).

A number of treatment regimens have been recommended over the years, and particular attention has been focused on ''home use'' dentifrices containing various ''active'' compounds, either blocking the hydrodynamic mechanism or the neural response (Yates et al. 2005). Variations in DH symptoms occur according to the extent of opened dentinal tubules (Lee et al. 2008). Therefore, an effective method to occlude patent dentinal tubules may prove to be beneficial in treating DH. At one time, strontium salts were the most common desensitizing agents (Pearce et al. 1994), after which potassium salts became the most popular active ingredients of dentifrices licensed for use in DH treatment (Orchardson & Gillam 2000, Poulsen et al. 2006, Bellamy et al. 2009). Most of the products and devices used to contrast DH and enamel and dentine erosion, behave by reducing stimuli conduction and apatite dissolution rather than aiming to promote mineralization through apatite crystallization or the replacement of the lost mineral (Young et al. 2006, Roveri et al. 2009a, b). Hydroxyapatite (HA), in bone as well, is responsible for the mechanical behaviour of the calcified tissues. Unlike bone, in enamel and dentine, when HA is dissolved or abraded, it cannot spontaneously re-mineralize because enamel contains no cells and dentine apposition occurs only toward the pulp tissues (Roveri et al. 2009a, b). Recently, synthetic carbonate HA (CHA) biomimetic nanocrystals have been shown to produce in vitro re-mineralization of the altered enamel surfaces and to be effective in closing dentinal tubules, thus showing a potential use in desensitizing dentifrices (Rimondini et al. 2007, Lee et al. 2008, Roveri et al. 2008, 2009a, b). However, no clinical studies have shown the effectiveness of CHA-based dentifrice in reducing DH.

The present randomized double-blind study aimed to compare the efficacy in reducing DH of a new dentifrice formulation containing zinc-substituted CHA nanocrystals with a commercially available desensitizing dentifrice containing potassium nitrate and sodium fluoride (KNO_3/NaF) in a silica base.

Methods

Study design and population

The study was carried out in the Department of Clinical Sciences and Stomatology of the Polytechnique University of Marche, Ancona, Italy. Inclusion criteria were hypersensitive area on facial surfaces of the teeth (incisors, cuspids, bicuspids and first molars with exposed cervical dentine) with at least two teeth scoring one or more at the airblast sensitivity test; good periodontal health (no probing depth >4 mm) with no other conditions that might explain their apparent DH; good physical health; age between 18 and 75 years; and provision of written informed consent. Exclusion criteria were chipped teeth, defective restorations, fractured undisplaced cuspids, deep dental caries or large restorations showing pulpal response, 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 drugs; ongoing treatment for tooth hypersensitivity; pregnancy or lactation (Singal et al. 2005); acute myocardial infarction within the past 6 months; use of a pace-maker; uncontrolled metabolic diseases; major psychiatric disorder; and heavy smoking and alcohol or drug abuse.

Eligible subjects were randomized to receive either a new dentifrice formulation (experimental group) or a commercially available desensitizing dentifrice (control group). The randomization process was made externally by the statistical unit using a computer-generated random table, and investigators were neither involved in the randomization process nor were they aware of the assigned group in all outcome evaluations. Randomly assigned identification codes for each subject were printed on sealed boxes containing either the experimental or the control dentifrices, and each subject had to use only the dentifrices contained in the assigned box during the follow-up. The appearance of the experimental and control dentifrices were identical (dentifrices were overwrapped to hide their identity), and although their colour had a slightly different tonality of white, no subject could reasonably guess the assigned dentifrice.

The final protocol of the study was approved by the Ethical Committee of the Polytechnique University of Marche, Ancona, Italy.

Dentifrices

The experimental group received the new dentifrice formulation containing nanocrystals of Zn–CHA, assembled in microparticles by means of the following formula: $Ca_{(10-x)}Zn_x(PO_4)_{(6-y)}(CO_3)_y(OH)_2$ ($Y = 4$–8% CO_3^{2-} substituted at PO_4^{3-}) ($X = 1\%$ Zn^{2+} substituted at Ca^{2+}) (BioRepair® Plus, Coswell S.p.A., Funo, Bologna, Italy).

The control group received a relatively new commercially available dentifrice (Sensodyne ProNamel™, GlaxoSmithKline Consumer Healthcare, Brentford, UK; authorized in the market since November 2007), containing 5% KNO_3 and NaF (with 1450 ppm F) in a silica base (in accordance with the requirements of the European Pharmacopoeia).

All subjects underwent scaling and polishing before the study; they were instructed to brush their teeth twice a day for at least 1 min. and not to use any other dentifrice or desensitizing agent.

Clinical examination

All subjects were visited at baseline, after 4 and after 8 weeks (end of the follow-up). 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 assessed using

the most common and validated stimuli tests: tactile test, airblast test and cold water test (Tarbet et al. 1979). The teeth were isolated with cotton rolls and stimuli were applied in each tooth. Stimuli tests were performed according to a standard methodology (Tarbet et al. 1979, Holland et al. 1997, Singal et al. 2005), briefly described as follows:

Tactile test: 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.

Airblast test: a blast of air was directed onto the affected area of the tooth for 1 s from a distance of 10 mm, while the adjacent teeth were isolated using cotton rolls, using a standard dental unit syringe of 40–65 psi at a temperature of 17–21°C.

Cold water test: a pre-cooled 1 cm^3 disposable syringe was filled with freshly melted ice-cold water. After isolating the specific tooth, 0.2 ml of the water was slowly expelled from the syringe onto the tooth surface.

The above stimuli tests were applied in the above order, with a minimum 5-min. gap between the application of different stimuli (Sowinski et al. 2001). For all stimuli tests, subject response was recorded on the following scale:

0 – no significant discomfort, or awareness of stimulus;
1 – discomfort but no severe pain;
2 – severe pain during application of stimulus;
3 – severe pain during and after application of stimulus.

Subjective test

In addition to stimuli tests, the subject's subjective perception was investigated using an overall sensitivity score. Subjects were asked to rate their perception to hot/cold food and drink, air, tooth brushing and to sweet and sour food by providing a score of 0–10; where 0 = no pain and 10 = excruciating pain (Pereira & Chava 2001).

All assessments were made by two dentists with at least 5 years of practice, after receiving a 5-h specific training and were unaware of the subject's group. Each subject was evaluated by the same dentist throughout the trial. During each visit, the occurrence of potential adverse effects was assessed by investigators through both clinical survey and participant's enquiry.

Sample size estimation

Because of the recent debate on non-inferiority trials (Garattini & Bertele 2007), the study was conservatively planned with a superiority design. 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 (Pereira & Chava 2001, Singal et al. 2005), 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 (weeks 4 and 8) were assessed using *t*-test for normally distributed variables and Kruskal–Wallis test for non-normally distributed variables. Within each group, the differences in all scores between baseline and 4 weeks 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 4 or 8 weeks) were assessed using *t*-test and confirmed through the Kruskal–Wallis test.

In addition to the mean score changes during follow-up of the airblast (main outcome), tactile, cold water and subjective test (secondary outcomes), two measures were considered. Firstly, the response rate (decrease of at least one point in each test score – i.e. from 3 to 2 – during the follow-up) of the two groups was compared using Fisher's exact test, excluding those with a baseline level of 0. Secondly, the mean percentage of reduction in each score from baseline to the end of the follow-up was computed and compared across groups using the Kruskal–Wallis test.

A two-tailed *p*-value of 0.05 was considered significant for all analyses, which were carried out using Stata 10.1 (Stata Corp., College Station, TX, USA, 2007).

Results

Characteristics of the sample

The study was carried out between July and November 2009. The detailed flow of participants through each stage of the trial is shown in Fig. 1. Of a total of 86 eligible subjects, 75 accepted to participate and were thus randomized (38 in the experimental group; 37 in the control group). The 11 individuals refusing to participate were not different from the participants in terms of age and gender distribution (42 years on average and 36% of males).

In the control group, one individual refused to participate immediately after randomization; another one discovered her pregnancy a week after the first visit. All other subjects attended all examinations. Three additional subjects were excluded from the final analysis – two in the experimental and one in the control group – because they did not satisfy inclusion criteria (they scored zero at baseline airblast test) and were erroneously included. Therefore, the final sample consisted of 36 subjects in the experimental group and 34 in the control group.

The mean age and gender distribution of the final sample are shown in Table 1 and were not different across groups. Similarly, at baseline, experimental and control subjects were balanced with respect to all test scores, indicating that the randomization process was effective.

Efficacy of the dentifrices

The average scores of each test at any time point, by group, are also reported in Table 2, together with the mean changes in each discomfort test score between baseline and weeks 4 and 8.

Both dentifrices were largely effective; the percentage of score reduction from baseline to 8 weeks ranged from a minimum mean value of 28.1% (controls, subjective test) to a maximum of 62.9% (controls, cold water test). With one exception (controls, tactile test), the mean percentage of score reduction was

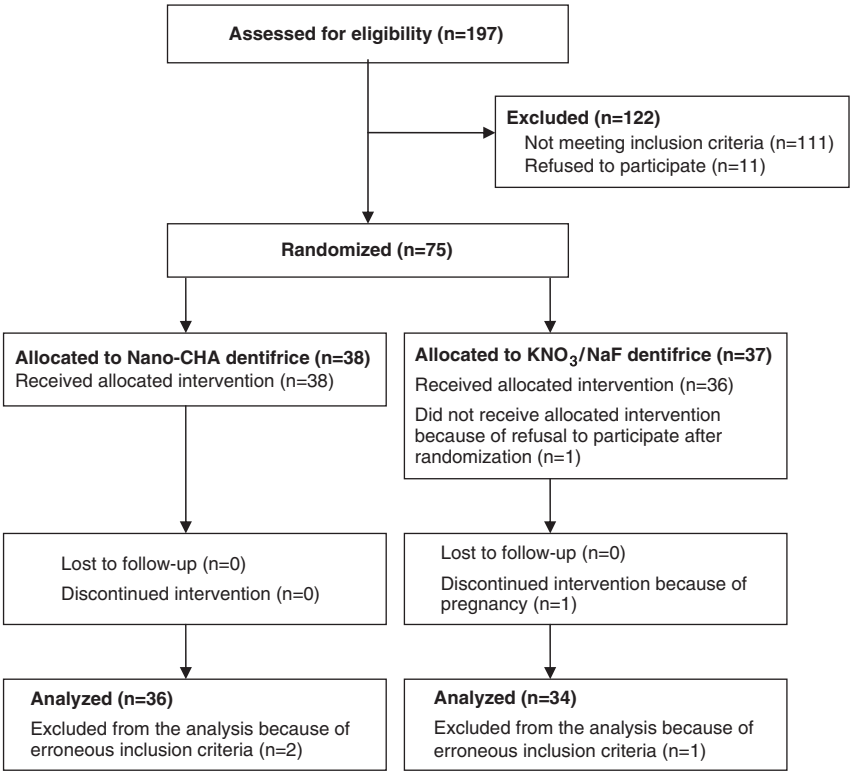

Fig. 1. Flow of participants through each stage of the trial.

Table 1. Demographic characteristics of the sample, by group

	Nano-CHA dentifrice ($n = 36$)	KNO_3/NaF dentifrice ($n = 34$)	p^*
Male gender, %	27.8	26.4	0.9
Mean age in years (SD)	43.7 (11.8)	46.6 (14.4)	0.4

*χ^2-test for categorical variables; *t*-test for continuous ones.
CHA, carbonate hydroxyapatite; KNO_3, potassium nitrate; NaF, sodium fluoride.

greater than 25% even after 4 weeks for all tests. Indeed, a highly significant ($p < 0.001$) improvement from baseline to the end of the follow-up (week 8) was observed in each group for all mean test scores, and the corresponding *p*-values were thus not reported in the table (all $p < 0.001$).

Comparison between dentifrices

At the end of the follow-up, experimental subjects, in comparison with controls, had a significantly greater improvement in airblast test and subjective test scores; the mean differences from baseline almost doubled (airblast score: 1.00 ± 0.53 *versus* 0.59 ± 0.50, respectively; subjective score: 2.14 ± 1.40 *versus* 1.24 ± 0.60, respectively). Notably, both differences were already significant after 4 weeks.

Also, the mean percentage reductions in airblast and subjective test score from baseline to week 8 were significantly greater in the experimental group and airblast test score was reduced of 46.0% on average in experimental subjects *versus* 29.4% in controls, and a 47.5% decrease in the subjective score was observed in the experimental group, *versus* a 28.1% mean reduction among controls (all $p < 0.01$).

Similar results were also observed when the rate of responses was considered (Table 3); subjects whose airblast test score decreased at least one level during the follow-up were almost doubled in the experimental group as compared with the control group (66.7% *versus* 35.3%, respectively; $p < 0.01$). Concerning the subjective test, 80% of the experimental subjects showed a response, 55.9% of controls ($p = 0.026$).

Conversely, with regard to tactile test and cold water test scores, no differences were observed between the groups at any time point and with any outcome (all $p > 0.05$).

Discussion

The present double-blind, randomized trial investigated the efficacy in reducing DH of two dentifrices: a newly developed dentifrice containing nano-sized Zn–CHA crystals, and an active control represented by an NaF/KNO_3 dentifrice.

After 8 weeks of follow-up, no adverse events were reported by participants of both groups. Conversely, a large and significant improvement of DH was apparent from all tests – airblast, tactile, cold water and subjective – confirming the efficacy of the control dentifrice and highlighting the potential of the new preparation. In fact, the dentifrice based on CHA nanocrystals was found to be comparable with the control preparation in decreasing DH, showing even larger benefits when DH was measured using airblast and subjective tests. In particular, the most promising finding concerns the rates of response with respect to the above tests, which were as high as 66.7% and 80.6%, respectively, using the new formulation.

These findings are in partial agreement with the meta-analysis of Poulsen et al. (2006), which showed a statistically significant effect, after 6–8 weeks of follow-up, of KNO_3 dentifrice on airblast (standardized mean difference between KNO_3 and control dentifrices $= -1.25$; $p < 0.001$) and tactile sensitivity (SMD = 1.19; $p < 0.001$), whereas the subjective assessment failed to show a significant effect ($p = 0.088$). However, only 216 individuals were included in the latter meta-analysis, in which a lack of statistical power was likely.

Current treatment regimens for DH are centred around two basic principles. First, according to the hydrodynamic theory based on the alteration of fluid flow in dentinal tubules (Brannström 1963), it can be suggested that if the tubules are occluded anywhere along their length, hydraulic conductance

Table 2. Comparison of mean discomfort scores at different time intervals between groups

	Nano-CHA dentifrice ($n = 36$)	KNO_3/NaF dentifrice ($n = 34$)	p^*
Airblast test (primary outcome)			
Score at baseline (T0)	2.16 ± 0.63	2.01 ± 0.60	0.3
Score after 4 weeks	1.39 ± 0.74	1.56 ± 0.74	0.3
Score after 8 weeks (end)	1.17 ± 0.70	1.42 ± 0.68	0.13
Difference between T0 and week 4 score	0.77 ± 0.57	0.46 ± 0.49	0.014
Difference between T0 and week 8 score	1.00 ± 0.53	0.59 ± 0.50	0.002
% reduction in mean from T0 to week 4	35.8 ± 26.5	22.6 ± 24.6	0.036
% reduction in mean from T0 to week 8	46.0 ± 27.4	29.4 ± 24.5	0.001
Secondary outcomes			
Cold water test			
Score at baseline (T0)	2.19 ± 0.68	2.00 ± 0.60	0.2
Score after 4 weeks	1.21 ± 0.81	1.18 ± 0.66	0.8
Score after 8 weeks (end)	0.97 ± 0.61	0.74 ± 0.65	0.13
Difference between T0 and week 4 score	0.97 ± 0.80	0.82 ± 0.49	0.3
Difference between T0 and week 8 score	1.22 ± 0.82	1.25 ± 0.62	0.7
% reduction in mean from T0 to week 4	44.5 ± 36.1	41.0 ± 24.3	0.6
% reduction in mean from T0 to week 8	55.7 ± 30.2	62.9 ± 29.4	0.3
Subjective test			
Score at baseline (T0)	4.52 ± 2.26	4.41 ± 1.99	0.8
Score after 4 weeks	3.26 ± 2.13	3.72 ± 1.96	0.4
Score after 8 weeks (end)	2.38 ± 1.66	3.17 ± 1.93	0.070
Difference between T0 and week 4 score	1.26 ± 0.74	0.69 ± 0.60	<0.001
Difference between T0 and week 8 score	2.14 ± 1.40	1.24 ± 0.60	<0.001
% reduction in mean from T0 to week 4	27.9 ± 21.8	15.6 ± 27.0	0.039
% reduction in mean from T0 to week 8	47.5 ± 28.5	28.1 ± 30.0	0.007
Tactile test[†]			
Score at baseline (T0)	0.69 ± 0.65	0.75 ± 0.75	0.8
Score after 4 weeks	0.39 ± 0.64	0.65 ± 0.69	0.10
Score after 8 weeks (end)	0.32 ± 0.44	0.51 ± 0.58	0.21
Difference between T0 and week 4 score	0.30 ± 0.65	0.10 ± 0.32	0.09
Difference between T0 and week 8 score	0.36 ± 0.54	0.24 ± 0.46	0.2
% reduction in mean from T0 to week 4	43.2 ± 90.8	13.7 ± 34.8	0.11
% reduction in mean from T0 to week 8	52.7 ± 53.2	32.0 ± 39.2	0.078

All values are expressed as mean and standard deviation (SD).

*T-test for normally distributed variables (airblast and cold water test and subjective score), and Kruskal–Wallis test for non-normally distributed variables (tactile test score).

[†]It must be observed that thirteen subjects in each group ($n = 26$ overall) scored zero at baseline tactile test; caution is thus required to interpret the results of these comparisons.

CHA, carbonate hydroxyapatite; KNO_3, potassium nitrate; NaF, sodium fluoride.

Table 3. Rate of responses (reduction of at least one in the test score from baseline to the end of the follow-up) in each group

Test	Nano-CHA dentifrice ($n = 36$), %	KNO_3/NaF dentifrice ($n = 34$), %	p*
Airblast test (primary outcome)	66.7	35.3	0.009
Secondary outcomes			
Cold water test	63.9	82.3	0.083
Subjective test	80.6	55.9	0.026
Tactile test**	22.2	14.7	0.4

*χ^2-test.

**It must be observed that 13 subjects in each group ($n = 26$ overall) scored zero at baseline tactile test; caution is thus required to interpret the results of this comparison.

CHA, carbonate hydroxyapatite; KNO_3, potassium nitrate; NaF, sodium fluoride.

will be reduced. Although there are in vitro evidences demonstrating that occlusion of tubules can occur and hence reduce intra-tubular fluid movement (Absi et al. 1987, Pashley 1990, Lee et al. 2008), yet there are no unequivocal clinical data purporting that the active dentifrice ingredients consistently stop the pain of DH by occlusion of the tubules (Addy et al. 2007). The second theory is the modification or blocking of the pulpal nerve response with, for example, potassium ions, which may reduce intra-dental nerve excitability by raising the concentration of local extra-cellular potassium ions and causing depolarization of the pulpal sensory nerves, thereby interrupting the transmission of the pain stimuli (Markowitz et al. 1991, Peacock & Orchardson 1995).

According to this latter theory, the present report confirmed the data of pre-existent literature, thus supporting the

effectiveness of potassium ions, contained in the control dentifrice, for subjects experiencing DH and/or dental erosion (Tarbet et al. 1980, Silverman 1985, Nagata et al. 1994, Silverman et al. 1996, Sowinski et al. 2001, Poulsen et al. 2006). Moreover, sodium fluoride can also be indirectly beneficial for DH, because it is not only an anti-caries agent but also a chemical agent that protects against acid erosion by promoting the tooth re-mineralization/re-hardening and inhibiting tooth demineralization/enamel softening (Groeneveld et al. 1990, Richards & Banting 1996, Ren et al. 2009).

On the other hand, the potential desensitizing effect of biomimetic CHA nanocrystals, contained in the experimental dentifrice, is due to the progressive closure of the tubular openings of the dentine with plugs within a few minutes until the regeneration of a mineralized layer has occurred within a few hours (Rimondini et al. 2007, Lee et al. 2008, Roveri et al. 2008, 2009a, b). Roveri et al. (2008, 2009a, b) have described this layer as a deposition of CHA on the enamel and/or dentin surfaces, which is less crystalline than native carbonate apatite, and which fills the enamel scratches and pits and/or seals the dentin exposed tubules, respectively. Indeed, synthetic biomimetic CHA nanocrystals are very similar to biogenic CHA nanocrystals (constituents of the mineral phase of calcified tissues such as bone, dentin and enamel), which contain 4–8 wt% of carbonate anions, are approximately 25 nm wide, 2–5 nm thick and 60 nm in length and exhibit a non-stoichiometric composition and a low degree of crystallinity (reviewed in Roveri et al. 2009a, b). Patented synthetic CHA nanocrystals have been synthesized (according to the method of Liou et al. 2004, with some modifications), both of about 20 and 100 nm in size with an acicular and plate morphology, respectively, and subsequently aggregating in micro-sized crystal clusters (microparticles), with a nearly stoichiometric in bulk Ca/P molar ratio of about 1.6–1.7 and containing 4 ± 1 wt% of carbonate ions replacing prevalent phosphate groups (Coswell et al. 2006). In vitro studies have demonstrated that the dentine and enamel re-mineralizing action produced by synthetic CHA nanocrystals appears to be compatible with the development of dentifrices with a re-mineralizing effect and able to contrast DH (Roveri et al. 2009a, b). Recent clinical trials have reported the desensitizing efficacy of a novel dentifrice based on calcium carbonate containing 8% arginine and fluoride (Ayad et al. 2009, Docimo et al. 2009); however, to the authors knowledge, until now there have not been any clinical trials documenting the nanosized CHA crystal application to desensitizing dentifrices. The present RCT provides the first clinical evidence that a dentifrice based on CHA nanocrystals may reduce DH.

A further possible reason of the reduced DH experienced by the subjects using the CHA microparticles-based dentifrice is that the latter (without silica) exhibits an abrasion value in RDA of about 23 (Coswell data, not yet published), which is minor when compared with the one exhibited by the control (RDA $\cong$ 37,5), which indeed contains silica (Drisko 2007). In fact, it has been reported that the dentine appears more susceptible to dentifrice abrasion than enamel and its loss correlates with dentifrice abrasiveness (Hooper et al. 2003). For instance, simple tooth brushing using a non-abrasive dentifrice has been reported to prevent or reduce DH in the cervical regions by occluding the dentinal tubules with organic pellicle-containing minerals (Kuroiwa et al. 1994).

Another minor finding of the present report is that the new formulation tested, also presenting zinc substitution of CHA nanocrystals, does not interfere with the DH reduction effect. In fact, zinc has been widely documented to have an antibacterial effect, and Yates et al. (2005) have also suggested its potential additional role in adhering to and thus occluding dentine tubules, although this precipitate is labile in water. On the other hand, control dentifrice, although containing fluoride as an anti-caries agent, appeared not to have an effect in controlling and inhibiting plaque attack (Bellamy et al. 2009). Clearly, future clinical trials are needed in order to clarify the potential anti-plaque action of CHA nanocrystals-based dentifrice.

These findings further the knowledge on the application of nanotechnology in clinical dentistry. The advantage of choosing HA particles with the smallest possible dimensions was discovered more than two decades ago, at the beginning of nanotechnologies. Indeed, since 1976, Hefferren has shown that increased re-mineralization occurs, more especially with apatite particles sizes $< 4\,\mu$m. Although HA is commonly considered to be the main synthetic bone-filler biomaterial, only a few daily use products for dental health care have been patented (reviewed in Roveri et al. 2009a, b). This might be due to the fact that HA has been considered too expensive to be consistently utilized as an active agent in toothpastes or mouth washes. Only recently, the development of nanotechnologies has opened new opportunities in obtaining cheap HA micro-nanoparticles using the ''bottom up'' methods (Ogawa et al. 2008), in order to improve the biological responses of natural HA.

The main limitations of the study are the absence of a negative control, and the limited validity of the comparisons regarding the tactile test. Concerning the latter issue, subjects were enrolled based on the results of the airblast test (which was the main outcome of the study), and 26 individuals were included although they scored zero at baseline tactile test. Clearly, these subjects could not show improvements during the follow-up, and the results of the tactile test should therefore be interpreted with caution. Conversely, it is worth noting that none of the participants showed a baseline score of zero for any of the other sensitivity tests. With regard to the control group, the decision to use only an active control was mainly due to funding limitations. In fact, it is generally claimed that a negative control should also be used, because its absence may limit the assessment of the true efficacy of both dentifrices (Holland et al. 1997). It is also true, however, that the adoption of positive controls (such as potassium-containing dentifrices) are also possible when equivalence or superiority claims are anticipated (Holland et al. 1997), as it was in the present study as well as in several other recent trials on desensitizing products (i.e. Docimo et al. 2007, 2009, Ayad et al. 2009).

With these caveats, this trial represents the first clinical demonstration that nanostructured CHA microparticles may significantly reduce painful stimuli and could therefore be used as active ingredients for desensitizing dentifrices. Future studies are warranted in order to evaluate whether the in vitro action of CHA nanocrystals, based on the gradual sealing of the dentinal canaliculi by means of the deposition of the biomimetic HA coating (Rimondini et al. 2007, Roveri et al. 2009a, b), could be confirmed in vivo.

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Clinical Relevance

Scientific rationale for the study: Millions of patients suffer from the painful symptoms of DH, in which dentinal tubules are opened to the oral cavity allowing stimuli to trigger a neural response via hydrodynamic mechanisms. Clinical studies have demonstrated the efficacy of desensitizing dentifrices that are based on potassium salts. Only in vitro findings have shown that zinc–CHA nanocrystals may produce a mineralized coating, which seals dentinal tubules. Therefore, a RCT has been designed to establish whether dentifrices containing these latter components may be effective in leading to pain relief.

Principal findings: The present trial is the first clinical evidence demonstrating the efficacy of CHA nanocrystals-based dentifrice in reducing DH.

Practical implications: CHA nanocrystals-based dentifrice can be recommended in patients suffering from DH.