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Tooth bleaching with hydrogen peroxide and nano-hydroxyapatite: a 9-month follow-up randomized clinical trial

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Abstract: *Objectives:* The aim of this study was to compare the amount of tooth colour change, rebound rate and tooth sensitivity in patients submitted to a bleaching technique with 6% hydrogen peroxide (HP) with or without 2% nano-hydroxyapatite (n-HA). *Methods:* Sixty subjects were included in this examiner-blinded, randomized clinical trial using a 6% HP gel with or without 2% n-HA. Tooth colour and tooth sensitivity were analysed before and after treatment. All data were analysed statistically. *Results:* After bleaching, both treatments demonstrated significant improvements in tooth shade ($P < 0.05$ for both groups). At the 9-month recall, tooth shade remained significantly lighter than at baseline ($P < 0.05$ for both groups). However, a relapse of the tooth shade was observed compared with the immediate post-bleaching result ($P < 0.05$). 6% HP with 2% n-HA produced significantly lower sensitivity ($P < 0.05$) than the bleaching product without n-HA. Colour change evaluation resulted in no difference between the two groups. *Conclusion:* Both treatments demonstrated significant improvements in tooth shade. The bleaching effectiveness of the tested products was comparable. The use of 6% HP with 2% n-HA reduced the incidence of sensitivity during the bleaching treatment compared to a bleaching agent that did not contain n-HA.

Key words: hydrogen peroxide; nano-hydroxyapatite; randomized controlled trial; tooth bleaching; tooth sensitivity

Introduction

Tooth whitening utilizing professional bleaching products has become widely used in daily clinical practice (1). Thanks to increased awareness of oral aesthetics many individuals are looking to enhance their appearance through 'whiter' teeth.

In-office bleaching and dentist-prescribed home-applied bleaching are the two most commonly utilized whitening procedures. The success of tooth whitening depends mainly on the combination of the peroxide concentration and the application period. The way of tooth whitening varies from in-office power bleaching with a higher concentration of peroxide for a short period to at-home bleaching with a much lower concentration of peroxide but over a longer period (2).

Compared with home bleaching, however, in-office bleaching has advantages in terms of clinician control, quick whitening results, reduced

Dates:

Accepted 4 December 2014

To cite this article:

Int J Dent Hygiene
DOI: 10.1111/ijdh.12123
Vano M, Derchi G, Barone A, Genovesi A, Covani U. Tooth bleaching with hydrogen peroxide and nano-hydroxyapatite: a 9-month follow-up randomized clinical trial.

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treatment time, and avoidance of material ingestion and discomfort from wearing trays (3).

The in-office bleaching can produce significant bleaching results after only one treatment, but may require longer application time or multiple treatments to obtain optimum results. However, longer application time or multiple treatments will increase the risk of tooth sensitivity (4). Indeed, a large percentage of patients in the first days of treatment show temporary tooth sensitivity (5). Tooth sensitivity during and after the treatment has been associated with microscopic surface defects and subsurface pores in enamel but may represent as well the degree of biological damage of tooth bleaching (3, 6, 7). It has been theorized that these defects allow rapid ingress of the whitening agent to the pulp and this results in sensitivity. A product that encourages repair of these microscopic defects can reduce sensitivity. Laboratory studies have shown these microscopic pores can be repaired using a paste containing nano-sized hydroxyapatite (n-HA) (8, 9). Nano-hydroxyapatite paste has been used to reduce bleaching-related tooth sensitivity, with encouraging results (10). Recently, the use of n-HA dentifrice proved to be a valid desensitizing agent providing quick relief from dentin hypersensitivity (11).

Many clinical studies (12) on various hydrogen peroxide products revealed good tooth whitening results. However, the whitening effect shows some relapse in colour after the cessation of active bleaching treatment (13).

In-office tooth bleaching is traditionally performed with high concentrations of hydrogen peroxide (35–38%) (14, 15). However, the American Dental Association only considers 10% carbamide peroxide (approximately equivalent to 3.5% hydrogen peroxide) to be a safe whitener (16). In addition, the new European regulations that follow as an amendment to the EU Directive 76/768/EEC concerning cosmetic products allow the use of hydrogen peroxide and other compounds or mixtures that release hydrogen peroxide, with a maximum concentration of 6% of hydrogen peroxide present or released (17).

Therefore, according to these regulations, this study evaluated colour change, stability and tooth sensitivity in patients submitted to an in-office bleaching technique with 6% hydrogen peroxide with or without 2% n-HA. The null hypothesis stated that there would be no difference between the two groups in terms of tooth sensitivity and no improvements compared to baseline with regard to tooth shade.

Study population and methodology

The study was conducted at the Istituto Stomatologico Toscano, Dentistry Department of Versilia Hospital, Italy (University of Pisa), from June 2013 to April 2014. The local ethical committee of Versilia Hospital, Italy, independently reviewed and approved to conduct this clinical study using human subjects; Ethical Approval Form 432/2013, name of trial registry 'Nano-Hap and Hydrogen peroxide effects on 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 a written consent.

The inclusion criteria were all six maxillary anterior teeth present and free from any signs of defects, caries, loss of vitality or restorations with an initial shade of A2 or darker according to a value-oriented Vitapan Classic shade guide (Vita Zahnfabrik). Subjects had to be willing to refrain from the use of tobacco products during the study period and be able to return for scheduled follow-up examinations.

The exclusion criteria were smoking, pregnancy or breastfeeding, history of previous bleaching treatment, dentin hypersensitivity caused by caries lesions, fracture of restorations, chipped teeth, marginal gaps, teeth with cervical fillings and recent use of desensitizing toothpaste or agents.

Sixty-six subjects were assessed for eligibility. Six subjects were excluded because they were not meeting the inclusion criteria. Therefore, 60 subjects (Table 1) who satisfied the inclusion criteria were enrolled in this study. Qualified subjects were randomly defined to one of the two study treatments in order to have 30 subjects per treatment group (Table 2): □

Group 1: 6% hydrogen peroxide (HP) and 2% nano-hydroxyapatite (n-HA) (test group).

Group 2: 6% hydrogen peroxide (HP) (control group).

All subjects received supragingival scaling at least 1 week, but not longer than 1 month, prior to the bleaching procedures. Extrinsic stains were removed for more accurate assessment of baseline colour.

An operator not involved in the research protocol performed the randomization. Details of the allocated group were recorded on cards contained in sequentially numbered sealed envelopes that were blindly assigned after completion of all baseline assessments.

All subjects were visited for tooth sensitivity at baseline, at 24 h, after 7 and 14 days. All subjects were visited for tooth

Table 1. Baseline characteristics of the subjects (mean ± SD)

	Group 1: 6% hydrogen peroxide and 2% n-Ha (n = 30)	Group 2: 6% hydrogen peroxide (n = 30)	P
Age	27 ± 9.7	29 ± 10.5	>0.05
Sex (F:M)	16:14	17:13	>0.05
Shade	9.05 ± 1.35	9.75 ± 1.55	>0.05

No statistically significant difference was found between groups regarding mean baseline tooth shade, age and sex.

Table 2. Details of the material used in the study

Group	Product	Ingredients
Group 1: 6% hydrogen peroxide and 2% nano-hydroxyapatite (test group)	PrevDent® (Baroniestraat, Amsterdam, The Netherlands)	6% hydrogen peroxide and 2% nano-hydroxyapatite
Group 2: 6% hydrogen peroxide (control group)	PrevDent® (Baroniestraat, Amsterdam, The Netherlands)	6% hydrogen peroxide

shade values at the beginning of the treatment period (baseline) after 7 and 14 days and after 9 months (end of the follow-up) after bleaching.

The evaluations of the patients were carried out by two trained and calibrated dentists who were blinded to the treatment modality. 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 assessed an interexaminer reproducibility κ scores of 0.89.

Tooth sensitivity evaluation

During the visits, six teeth per patient were assessed using the most common and validated stimuli tests: tactile test and air blast test.

The teeth were isolated with cotton rolls and stimuli were applied to each tooth. Stimuli tests were performed according to a standard methodology (18, 19), 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 (20).

Visual analogue scale

Subjects were instructed on how to use a visual analogue scale (VAS) and asked to complete a training exercise at the screening visit. At baseline and immediately after any time point (24 h, 7 and 14 days), 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 dentine hypersensitivity.

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

1 Subject does not respond to stimulus (–no significant discomfort, or awareness of stimulus).

2 Subject responds to stimulus but does not request discontinuation of stimulus (discomfort but no severe pain).

3 Subject responds to stimulus and requests discontinuation or moves from stimulus (pain during application of stimulus).

4 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 (21).

Tooth shade grade

The examiners who were blinded to the treatment modality measured the tooth shade of the study teeth at the beginning of the treatment period (baseline) after 7 and 14 days and after 9 months (end of the follow-up) after bleaching. Tooth colour shade was evaluated using an established and standardized scale Vitapan Classic shade guide (Vita Zahnfabrik). Colour measurements were performed under standardized conditions and lighting.

Throughout the 270 days of the study, the subjects were asked to brush their teeth with a non-whitening dentifrice at least twice a day in order to standardize their oral hygiene.

The tabs of the shade were arranged from B1 to C4 from the lightest to the darkest shade. The mean score for the six anterior teeth (test teeth) was then calculated, and each subject received a single shade value.

Bleaching treatment

The bleaching material was used according to the manufacturer's instructions. Isolation of gingiva and soft tissue was obtained with cheek retractor, face bib, cotton rolls and masking cream (Fig. 1). In Group 1, 6% HP and 2% n-HA were mixed to obtain a foam that was left on the teeth for 10 min (Fig. 2). After 10 min, the foam was removed without rinsing



Fig. 1. Isolation of gingiva and soft tissue was obtained with cheek retractor, face bib and cotton rolls.



Fig. 2. 6% HP and 2% n-HA were mixed to obtain a foam that was left on the teeth for 10 min.



Fig. 3. Application of a serum of 2% n-HA on the teeth for 3 min.

and a new layer of foam was applied on the teeth for 10 more min. The procedure was repeated six times to have a total time of foam application of 60 min. Then, a serum of 2% n-Hap only was left on the teeth for 3 min (Fig. 3). After that, rinsing was allowed.

In Group 2, 6% HP was applied for 10 min on the teeth, then removed and applied again for a total of 6 times in order to have a total time of HP application of 60 min.

Statistical analysis

The normality distribution of all scores was assessed using the Kolmogorov–Smirnov test. All data presented normal distribution criteria. Differences across the two groups for all parameters at baseline and at each time point (24 h, 7, 14 days and 9 months) were assessed using ANOVA tests and Tukey tests which were carried out using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA). Statistical significance was set at with a level of $P < 0.05\%$.

Results

Sixty volunteers were enrolled in this study, and all subjects completed the bleaching procedures and participated at the follow-up appointments as well. None of the patients required the use of pain relievers. Baseline characteristics of the subjects are reported in Table 1. There was no statistically significant difference between groups regarding mean baseline tooth shade, age and sex. (Table 1).

After bleaching, both treatments demonstrated significant improvements in tooth shade ($P < 0.05$) within each group (Table 3) (Fig. 4a, b). At the 9-month recall, tooth shade remained significantly lighter than at baseline in each group ($P < 0.05$) (Table 3). However, a relapse of the tooth shade was observed compared with the 7 and 14 days post-bleaching results ($P < 0.05$) (Table 3). Colour change evaluation resulted in no difference between the two groups (Table 3).

6% HP with n-HA produced significantly lower sensitivity ($P < 0.05$) than the bleaching product without n-HA for the time point evaluation at 24 h. (Table 4). No significant difference in dental sensitivity was reported at the other time points (7 and 14 days post-bleaching) between and within the two groups.

The evaporative (cold air) sensitivity data are summarized in Table 4. Mean values ranged from 0.52 (baseline) to 0.98 (24 h), 0.65 (7 days) and 0.57 (14 days) for Group 1 (HP 6% + n-HA 2%). There was no statistical difference within Group 1 at any time point. For Group 2 (HP 6%), mean values ranged from 0.57 (baseline) to 1.85 (24 h), 0.72 (7 days) and 0.71 (14 days). Significant higher values of cold air sensitivity ($P < 0.05$) were found within Group 2 at 24 h. Significant difference ($P < 0.05$) was found between Group 1 and Group 2 at 24 h, with Group 2 showing higher values of cold air sensitivity.

The tactile test sensitivity data are summarized in Table 4. Mean values ranged from 0.44 (baseline) to 0.92 (24 h), 0.51

Table 3. Tooth shade values (mean \pm SD)

Groups	Baseline (mean \pm SD)	7 days (mean \pm SD)	14 days (mean \pm SD)	9 months (mean \pm SD)
6% HP and 2% n-Hap (Group 1)	9.05 \pm 1.35 (A)	5.25 \pm 2.05 (B)	5.17 \pm 2.15 (B)	6.97 \pm 3.05 (C)
6% HP (Group 2)	9.75 \pm 1.55 (A)	5.54 \pm 1.90 (B)	5.23 \pm 1.97 (B)	6.89 \pm 2.88 (C)

Different letters indicate statistically significant differences ($P < 0.05$).

No statistically significant differences were found (ANOVA) between the two groups in terms of tooth shade values at any time points.

However, significant difference was found in terms of tooth shade values ($P < 0.05$) within each group between baseline and the other time points.

(7 days) and 0.53 (14 days) for Group 1 (HP 6% + n-HA 2%). There was no statistical difference within Group 1 at any time point. For Group 2 (HP 6%), mean values ranged from 0.53 (baseline) to 1.53 (24 h), 0.64 (7 days) and 0.55 (14 days). Significant higher values of tactile sensitivity ($P < 0.05$) were found within Group 2 at 24 h. Significant difference ($P < 0.05$)

was found between Group 1 and Group 2 at 24 h with Group 2 showing higher values of tactile sensitivity.

Subjective evaluation

Mean VAS scores at baseline, 24 h, 7 and 14 days for each treatment group are summarized in Table 5. The VAS score was significantly higher ($P < 0.05$) in Group 2 at 24 h when compared to the other time point assessments in both Group 1 and Group 2. On the other hand, no significant difference in tooth sensitivity was reported at any other time points.

Discussion

The aim of this clinical trial was to address practitioner concerns regarding the efficacy, longevity and degree of hypersensitivity of bleached teeth after in-office vital bleaching with low concentration of hydrogen peroxide with or without n-HA.

The results showed a significant improvement in tooth shade for both groups at all time points when compared to baseline. However, a relapse of the tooth shade was observed compared with the immediate post-bleaching results in both groups.

A significant reduction in dentin hypersensitivity for the test group at air blast test, tactile tests and subjective evaluation (VAS) was recorded at 24 h post-bleaching when compared to the control group. After 9 months of follow-up, no adverse events were reported by participants.

To obtain the greatest effectiveness of whitening, the highest concentration of bleaching gel should be applied for the longest contact time with the tooth structure (22). However, this method would result in undesirable side effects such as dentin hypersensitivity (23, 24). Both the American Dental Association and the new European regulations allow the use of bleaching agents only with low concentration of hydrogen peroxide.

In an attempt to combine efficacy and safety, the tested bleaching agent has a 6% concentration of hydrogen peroxide



Fig. 4. (a) Before treatment with 6% HP and 2% n-HA. (b) After treatment with 6% HP and 2% n-HA.

Table 4. Mean air blast scores and mean tactile scores at baseline, 24 h, 7 and 14 days for each treatment group

Assessment/treatment	Air blast sensitivity			Tactile sensitivity		
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD
Baseline						
Group 1 HP 6%+n-HAP 2%	30	0.52 a	0.38	30	0.44 a	0.37
Group 2 HP 6%	30	0.57 a	0.45	30	0.53 a	0.49
24 h						
Group 1 HP 6%+n-HAP 2%	30	0.98 a	0.76	30	0.92 a	0.45
Group 2 HP 6%	30	1.85 b	0.58	30	1.53 b	0.73
7 days						
Group 1 HP 6%+n-HAP 2%	30	0.65 a	0.32	30	0.51 a	0.43
Group 2 HP 6%	30	0.72 a	0.46	30	0.64 a	0.39
14 days						
Group 1 HP 6%+ n-HAP 2%	30	0.57 a	0.42	30	0.53 a	0.42
Group 2 HP 6%	30	0.71 a	0.26	30	0.55 a	0.47

Different letters indicate statistically significant differences ($P < 0.05$).

Significant difference was found ($P < 0.05$) within Group 2 at 24 h both at air blast and at tactile tests.

Table 5. Mean VAS scores at baseline, 24 h, 7 and 14 days for each treatment group

	Group 1: 6% HP and 2% n-HAP			Group 2: 6% HP		
	Range	Mean	SD	Range	Mean	SD
Baseline	22–41	28.55 a	12.56	19–43	29.77 a	11.76
24 h	25–44	32.93 a	10.94	35–65	49.12 b	12.34
7 days	21–47	30.45 a	11.24	25–45	32.25 a	11.05
14 days	24–39	26.08 a	10.35	20–45	30.55 a	12.45

Different letters indicate statistically significant differences ($P < 0.05$). Significant difference was found ($P < 0.05$) within Group 2 at 24 h.

mixed with 2% concentration of n-HA. The identification of efficacious method to treat tooth sensitivity related to bleaching procedures is an important topic because this condition even if it is temporary and reversible is reported by the majority of patients that undergo a bleaching treatment (6, 25).

Recent studies reported the desensitizing effect of n-HA contained in dentifrices (11, 26, 27). Nano-hydroxyapatite particles seem to be capable of determining the progressive closure of the tubular openings of the dentine (28–30).

Indeed, 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 desensitising toothpastes recently introduced into the market place, which have been formulated specifically for their dentine tubule occluding abilities to reduce the pain of dentine hypersensitivity (31).

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.

Three time points following treatment were recorded, after 24 h, 7 and 14 days. Dentin hypersensitivity was significantly higher at 24 h in Group 2 with all the stimuli tests when compared to Group 1, which proves the clinical efficacy in reducing dentin hypersensitivity at 24 h of hydrogen peroxide with n-Ha treatment. Hydroxyapatite nanoparticles mixed in hydrogen peroxide may therefore improve the biocompatibility of the final product, preventing post-operative sensitivity and increasing the safety of the bleaching process.

In fact, it has been shown that hydrogen peroxide penetrates the dental hard tissues through enamel defects and subsurface pores (32). This penetration gives rise to different levels of bleaching sensitivity, causing reversible pulpitis and consequent teeth thermal sensitivity. Hydroxyapatite nanoparticles mitigate this effect closing or reducing open dentinal tubules.

The brushing frequency was reported to significantly correlate with hypersensitivity (33). To avoid any confounder, oral self-care was standardized as each participant was instructed to brush twice daily using a non-whitening dentifrice and to avoid any desensitizing agents.

Different methods are available to determine the tooth shade change. Spectrophotometers, colorimeters and analogue shade guides are all useful tools for tooth colour measurement.

Instrumental tooth colour measurements are more reproducible (34).

However, recent investigations and the daily clinical practice are still based on established individual shades such as tabs ranked in the order of lightest to darkest.

Therefore, in the present clinical trial, tooth colour examinations were performed using the VITA shade guide because it is still a commonly used method for shade assessment (35, 36).

The results of the present investigation are in accordance with several studies showing that low concentration of hydrogen peroxide is an effective bleaching agent (34–37).

6% hydrogen peroxide improved tooth shade at all time points when compared to baseline. However, a relapse of the tooth shade at 9 months was observed compared with the immediate post-bleaching results (24, 38). Colour regression has been associated with the remineralization process of the hard tissues (39).

Within the limits of the present study, 6% HP produced satisfactory bleaching results with or without 2% n-HA. Both groups had a similar rebound effect at 9 months. 6% HP with 2% n-HA resulted in significant lower tooth sensitivity at 24 h post-treatment.

Clinical relevance

Scientific rationale for the study

Tooth sensitivity is a frequent minor complication of tooth bleaching. This study aimed to compare the effect of 6% hydrogen peroxide bleaching agent with or without 2% nano-hydroxyapatite on tooth sensitivity and colour change.

Principal findings

Significantly lower tooth sensitivity was observed with the use of 6% hydrogen peroxide mixed with 2% nano-hydroxyapatite. No differences in colour change and rebound rate were found between the two groups.

Practical implication

This study suggests that the use of a bleaching agent mixed with nano-hydroxyapatite is a valid method to prevent

post-operative sensitivity. Low concentrations of hydrogen peroxide should be the first choice in the interest of patient safety.

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