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Original Article

Dentistry Section

# A Clinical, Randomised, Double-Blind Study on the Use of Nano-Hydroxyapatite and Arginine During at-Home Tooth Bleaching

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## ABSTRACT

**Introduction:** Home bleaching is a popular cosmetic technique that delivers quick results, reduces chair time, and has a lower risk of side effects compared to office bleaching.

**Aim:** To evaluate the effect of nano-hydroxyapatite (n-HAP) and arginine on Bleach-Sensitive Teeth (BST) and colour change after at-home bleaching treatment across three months of follow-up.

**Materials and Methods:** Sixty subjects were randomly allocated into one of three groups (n=20): 1) CONTROL, treated with 22% carbamide peroxide (CP)+toothpaste without a desensitising agent; 2) NANO, treated with CP +n-HAP; and 3) ARGININE, treated with CP + arginine. An air jet was used to evaluate BST associated with a modified Visual Analog Scale (VAS). A spectrophotometer was used to measure the colour of the maxillary incisors.

**Results:** The Friedman vs Kruskal-Wallis tests showed that the BST reported in the experimental groups was lower when compared with the control group one day after the end of treatment ($p \leq 0.05$). However, no significant difference was observed at 30, 60 or 90 days of evaluation ($p > 0.05$). ANOVA showed no significant difference between groups when comparing mean $\Delta E$ ($p > 0.05$).

**Conclusion:** The subjects treated with n-HAP and arginine presented lower sensitivity when compared to the control group one day after the end of treatment. In addition, there was no impairment of the efficacy of the at-home bleaching treatment over the 90-day evaluation period.

**Keywords:** Clinical trial, Colour, Desensitising agents, Tooth sensitivity

## INTRODUCTION

At-home bleaching can be regarded as a popular cosmetic technique for treating dental discolouration since it provides rapid results, involves reduced chair side time, and has lower risk of side effects compared to in-office bleaching [1,2].

The effectiveness of home bleaching for vital teeth has been proven over the years [3-5]. However, the risks more commonly reported with tooth whitening include increased tooth sensitivity and mild gingival irritation [6,7], which have been reported to affect between 37% and 90% of the patients undergoing at-home bleaching [8-12]. With the aim of minimising the effects of dental sensitivity, recent studies have reported several methods of treating sensitivity during or after tooth bleaching [13-17]. Nevertheless, the literature presents controversial results regarding the efficacy of the various desensitisers available.

A dentifrice containing 8% arginine, calcium carbonate and 1450 ppm fluoride as sodium monofluorophosphate has been clinically proven to provide superior Dentin Hypersensitivity (DH) relief [18-20]. It was shown that a combination of arginine and calcium carbonate, when deposited on exposed dentinal surfaces, is able to physically block and seal open dentinal tubules [21,22]. For this reason, this desensitising agent has been extensively studied to treat DH [23-25]. However, according to the authors' knowledge, just one clinical trial has evaluated the action of arginine on BST [26], and no study has investigated this with regard to at-home bleaching.

More recently, a bioactive nano-Hydroxyapatite (n-HAP) base has been clinically evaluated in the treatment of DH [27-29], although studies have shown controversial results, and the topic has not yet been systematically analysed. However, clinical studies evaluated n-HAP as a treatment for BST and obtained positive results in pain prevention [13,30,31]. The rationale behind the use of n-HAP on DH 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 [29].

The hypothesis presented by Markowitz K is that BST arises as a consequence of peroxide penetrating the tooth structure and causing direct activation of a neuronal receptor and not through the hydrodynamic theory by Brannstrom M [32,33]. In view of this, the best treatment for BST would be to directly reduce the excitability of the intradental nerves. However, several clinical trials have tested obliteration agents in the prevention and treatment of BST, presenting promising results [14-17]. These agents may increase the mineral density of enamel, hindering the diffusion of peroxide to the nerve endings and thus reducing sensitivity.

As already mentioned, the desensitising agents used in this clinical study act by obliterating the dentinal tubules, which could impair dental permeability through hydrogen peroxide diffusion. Therefore, the analysis of colour change has become necessary to assess the efficacy of the bleaching treatment associated with these desensitising agents.

This clinical study evaluated the effects of arginine and n-HAP on sensitivity reduction and colour change after an at-home bleaching treatment during three months of evaluation. The following null hypotheses were tested: H01- no difference in post-treatment sensitivity between the tested groups (control, arginine and nano-hydroxyapatite) in the different evaluation periods (0, 1, 30 and 60 and 90 days after bleaching treatment); and H02- no difference in colour change ($\Delta E$) between the groups tested (control, arginine and nano-hydroxyapatite) in the different evaluation periods (0, 1, 30 and 60 and 90 days after bleaching treatment).

## MATERIALS AND METHODS

**Ethical aspects:** This randomised, double-blind, controlled clinical study followed the Consolidated Standards of Reporting Trials (CONSORT) Statement [34]. The research ethics committee from the Health Sciences Institute of the Federal University of Pará reviewed and approved the study under number code 1.098.632. It was registered with the Brazilian Registry of Clinical Trials website with the following register identification: RBR-6qbztf. All subjects signed terms of free and informed consent before taking part in this study, in full accordance with the World Medical Association Declaration of Helsinki [35].

**Settings and locations:** From pre-established criteria, there were selected 60 volunteers for the study. The clinical trial was performed from August 03, 2015, through November 13, 2015, in the school of dentistry at the Federal University of Para.

**Sample size calculation:** BioEstat software (Mamiraua Civil Society, Tefé, Amazonas, Brazil) was used to calculate the sample size using data from a pilot study conducted with 10 subjects and following the same methodology as this study. A statistical power of 80%, an error α of 5%, and a sample loss prediction at study end of 20% were considered. The resulting sample calculated for this study was 20 subjects per group, totaling 60 patients.

**Selection of subjects:** All participants included in this study were recruited by advertisements attached to notice boards located at the university buildings. The patient's age range was 18 to 26-years-old, and all presented good oral health status and a shade of the anterior teeth A2 or darker. Patients who had undergone a previous bleaching procedure, presented prior tooth sensitivity; patients with caries, enamel hypoplasia, restoration, gingival recession, dentin exposure, visible cracks on enamel, or pulpitis were excluded. Additionally, participants who had undergone endodontic treatment in any of the six upper anterior teeth were excluded. Patients, who were using oral removable orthodontic appliances, were under continuous use of anti-inflammatory or analgesic drugs, had parafunctional habits, habit of smoking, and pregnant or breastfeeding were also excluded [36].

Randomisation was performed by a numerical draw, and 60 subjects were divided into three groups (n=20) according to [Table/Fig-1]. Before starting the study, all subjects received professional prophylaxis with a suspension of pumice and water.

| | Control | Nano | Arginine | p-value |
|---|---|---|---|---|
| **Gender:** | | | | |
| Male n (%) | 9 (45%) | 11 (55%) | 8 (40%) | 0,489* |
| Female n (%) | 11 (55%) | 9 (45%) | 12 (60%) | |
| **Age (years):** | | | | |
| χ(±SD) | 23,45 (±2,26) | 24,30 (±2,39) | 23,55 (±2,41) | 0,619** |
| CI (95%) | 17,50-27,80 | 17,92 – 27,98 | 17,19-27,77 | |
| **Colour:** | | | | |
| **L0** | | | | |
| χ(±SD) | 78,55 (±1,22) | 78,43 (±1,58) | 78,90 (±1,37) | 0,531** |
| CI (95%) | 76,04-82,85 | 75,39 – 82,78 | 76,28-81,12 | |
| **a0** | | | | |
| χ(±SD) | 1,84 (±0,52) | 2,12 (±0,45) | 2,09 (±0,41) | 0,678** |
| CI (95%) | 1,21-2,29 | 1,23 – 2,03 | 1,20-2,99 | |
| **b0** | | | | |
| χ(±SD) | 23,56 (±1,05) | 23,89 (±0,98) | 23,88 (±1,17) | 0,619** |
| CI (95%) | 21,88-26,89 | 21,77-26,52 | 21,82-26,12 | |

**[Table/Fig-1]:** Demographic characteristics according to the experimental groups.
*G test
**ANOVA

Subjects were instructed to not drink liquids or eat food for one hour prior to the exam. The subjects were instructed to chew pieces of orthodontic rubber in order to mechanically stimulate saliva production, which would not be swallowed but excreted into a beaker. The operator then recorded the amount of saliva, discounting any foam that had formed. The salivary flow rate (ml/min) was calculated for each volunteer. Subsequently, salivary pH was measured using a pH meter (510 Benchtop pH Meter, Oakton Instruments, Vernon Hills, Illinois, USA) calibrated in advance according to the manufacturer's instructions. Only subjects who had a salivary flow rate between 1 and 2 mL/min and pH between 6.5 and 7.0 were included in the study.

Alginate impressions (Jeltrate Dustless, Dentsply, Petrópolis, Rio de Janeiro, Brazil) were obtained from the mandibular and maxillary arches to create models. Custom-made trays were fabricated using 1 mm thick vinyl polyethylene acetate plates (Bio-Art Dental equipment, São Carlos, SP, Brazil) under vacuum. All subjects received oral hygiene kits containing a toothbrush (Bristle Indicator Oral B, São Paulo, SP, Brazil) and toothpaste (Colgate, São Paulo, SP, Brazil) with 1450 ppm fluoride to use three times a day.

Sixty subjects were randomly allocated by numerical draw into three groups (n=20): 1) Control-home bleaching with 22% carbamide peroxide (3M™ ESPE™ OMNI™ WHITE&BRITE™ 22% carbamide peroxide tooth whitening system, Sumaré, SP, Brazil)+a toothpaste without a desensitising agent (Contene–Organic natural, Minas Gerais, Brazil); 2) Nano–22% carbamide peroxide+a desensitising agent containing 20% n-HAP (Nano P®–FGM, Joinville, SC, Brazil); and 3) Arginine–22% carbamide peroxide + a toothpaste containing 8% arginine (Colgate® Sensitive Pro-Argin™, São Bernardo do Campo, SP, Brazil). Subjects from all groups received unlabelled containers with the respective toothpaste. Neither subjects nor the operator had knowledge of the content of the unlabelled containers; only the principal investigator who distributed the materials was aware of the contents.

**At-home bleaching:** The subjects received treatment kits containing the bleaching agent, bleaching tray, group-specific toothpaste and a brush. The toothpaste was provided in packaging without a label. The subjects also received a leaflet with instructions for use according to the manufacturer's recommendations. The 22% carbamide peroxide was inserted into the bleaching tray and applied to the respective dental arches for two hours per day over the course of 10 days.

**Desensitising treatment:** Immediately after the bleaching sessions, all subjects applied toothpaste on the whitened teeth for 5 minutes and then removed the toothpaste with water. In the intervals between bleaching treatment sessions, the subjects brushed their teeth three times per day using approximately 2 cm of toothpaste. This was standardised for all groups.

**Pain sensitivity evaluation:** An air jet was applied with a three-way air-water syringe (DabiAtlanteDental products, RibeirãoPreto, SP, Brazil) for the postoperative sensitivity evaluation. Each subject was asked about postoperative sensitivity. This information was recorded using a Visual Analog Scale (VAS) and expressed according to the following intensities: absent (0); mild (1); moderate (2); or severe (3). Sensitivity was recorded before and 1 day after 10 days of home bleaching treatment and 1, 2, and 3 months thereafter.

**Colour evaluation:** The colour evaluation was performed on each subject's maxillary incisors using the Easy shade Advance 4.0 spectrophotometer (VITA Zahnfabrik, Bad Säckingen, Germany) with the CIE L*a*b*system, where colour change values hues were obtained for each group of teeth using the formula: ΔE={(ΔL)2+(Δa)2+(Δb)2}1/2, where: ΔL*=L*-L*0; Δa*=a*-a*0; eΔb*=b*-b*0. The colour evaluation was performed five times: before the bleaching treatment (serving as baseline); 24 hours after the 10th day; and 1, 2, and 3 months after the last application.

Another vinyl polyethylene acetate tray was prepared for each patient to standardise the colour measurement location on each tooth, according to the protocol described by Bizhang M [37]. The trays were perforated in the central region of the buccal surface of the maxillary central incisors to fit the spectrophotometer tip.

## STATISTICAL ANALYSIS

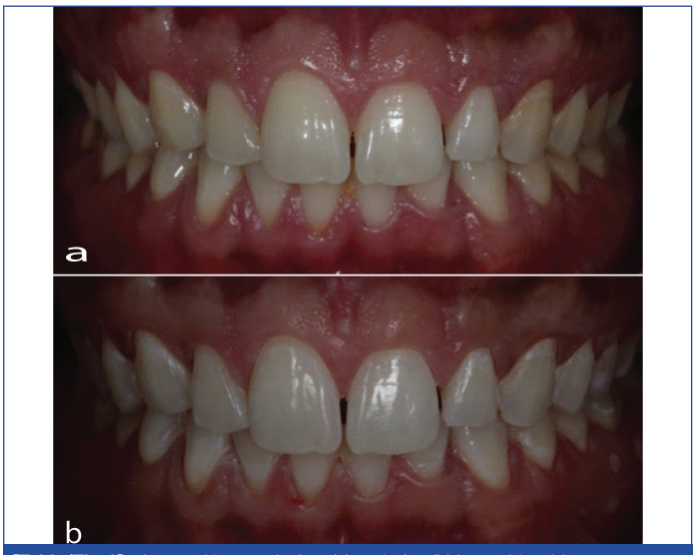
The colour change values (ΔE) for each group of studied teeth and the post-bleaching sensitivity reported by subjects were analysed using the BioEstat program (Mamirauá Civil Society, Tefé, Amazonas, Brazil). The ΔE values obtained for each tooth in each experimental group and at each time point were analysed using analysis of variance (ANOVA). The associations between the intervention group, bleaching session, and sensitivity reported after 24 hours were also tested using ANOVA (Friedman vs Kruskal-Wallis). The significance level adopted for all analyses was 5%.

## RESULTS

The homogeneity of the sample was demonstrated comparing the groups in relation to their demographic characteristics and the initial values of L, a and b used for ΔE, according to [Table/Fig-2,3], illustrate one of the previous clinical cases. and after the bleaching of the house. L * represents the value of 0 (black) to 100 (white) and a * and b * represent the shadow, where a * is the measure along the red-green axis and b * is the measure along the yellow-blue axis. This system was defined by the International Commission on Illumination in 1967 and is referred to as CIELab [38].

| Time | Control | Nano | Arginine |
|---|---|---|---|
| | Md (±IQR) | Md (±IQR) | Md (±IQR) |
| Baseline | 0 (0)$^{Aa}$ | 0 (0)$^{Aa}$ | 0 (0)$^{Aa}$ |
| 1 day | 1 (2)$^{Bb}$ | 0 (0)$^{Aa}$ | 0 (0)$^{Aa}$ |
| 1 month | 0 (0)$^{Aa}$ | 0 (0)$^{Aa}$ | 0 (0)$^{Aa}$ |
| 2 months | 0 (0)$^{Aa}$ | 0 (0)$^{Aa}$ | 0 (0)$^{Aa}$ |
| 3 months | 0 (0)$^{Aa}$ | 0 (0)$^{Aa}$ | 0 (0)$^{Aa}$ |

**[Table/Fig-2]:** Median (Md) and interquartile range (IQR) of the sensitivity reported by the patients at points 1, 30, 60 and 90 days after bleaching according to the experimental method.
Note 1: Different uppercase letters represent inter-group statistical difference for the different tests applied at the same time, p≤0.05.
Note 2: Different lowercase letters represent intra-group statistical difference for the different tests applied at the same time, p≤0.05.




**[Table/Fig-3]:** Intraoral images before (a) and after (b) home bleaching.

[Table/Fig-2] shows the results of the evaluation of sensitivity reported by patients at the five evaluation time points. The Friedman vs Kruskal-Wallis tests showed that the tooth sensitivity associated with the experimental groups was lower when compared with the control group one day after the end of treatment (p=0.033). However, no significant difference was observed 30, 60 or 90 days after the end of treatment (p=0.752). Regarding the intragroup comparison, the sensitivity reported by patients did not differ statistically between baseline and the three month follow-up: Control (p=0.293); Nano (p=0.756); and Arginine (p=0.395).

| Time | Control | Nano | Arginine |
|---|---|---|---|
| | $\bar{\chi}$(±DP) | $\bar{\chi}$(±DP) | $\bar{\chi}$(±DP) |
| 1 day | 5.2 (0.66)$^{Aa}$ | 5.1 (0.52)$^{Aa}$ | 5.0 (0.48)$^{Aa}$ |
| 30 days | 5.0 (0.65)$^{Aa}$ | 5.2 (0.52)$^{Aa}$ | 5.0 (0.52)$^{Aa}$ |
| 60 days | 4.8 (0.55)$^{Ab}$ | 4.7 (0.55)$^{Aa}$ | 4.6 (0.52)$^{Ab}$ |
| 90 days | 4.6 (0.56)$^{Ab}$ | 4.7 (0.53)$^{Aa}$ | 4.5 (0.50)$^{Ab}$ |

**[Table/Fig-4]:** Mean and standard deviation of ΔE values according to the experimental group at different evaluation times (1, 30, 60 and 90 days after treatment).
Note 1: Different upper case letters represent inter-group statistical difference for the different tests applied at the same time, p≤0.05.
Note 2: Different lowercase letters represent intra-group statistical difference for the different tests applied at the same time, p≤0.05.

ANOVA showed no significant differences between groups when comparing mean ΔE at each follow-up time: 10 days (p=0.885), 1 month (p=0.792), 2 months (p=0.264), and 3 months (p=0.423). In the intragroup comparison, no group showed a significant decrease in the value of ΔE after 3 months of follow-up: Control (p=0.092); Nano (p=0.186); Arginine (p=0.409) [Table/Fig-4].

## DISCUSSION

The most popular method of tooth bleaching is the home bleaching system, wherein the patient wears a custom-made bleaching tray containing carbamide peroxide. A systematic review [6] demonstrated that neither the risk/intensity of tooth sensitivity nor the effectiveness of the bleaching treatment was influenced by the choice of at-home or in-office bleaching techniques. Tooth sensitivity is a very common side effect for both bleaching approaches [8-12,39-41] and several desensitising treatments have been made available [13-17].

In this clinical trial, post-treatment sensitivity was recorded for the Control group during the air blast test and subjective evaluation (VAS) at one day post-bleaching when compared to others groups; for this reason, H01 was rejected. The subjects in the NANO group reported no pain at the different evaluation periods. These results are in line with several previous clinical trials [30-32] and can be justified by the mechanism of action of n-HAP.

Numerous reports have shown that n-HAP holds the potential to act as a Ca2+ and PO43– reservoir to maintain the supersaturated state for tooth mineralisation [42-45]. These studies highlighted the capability of n-HAP for dentinal tubule occlusion, as well as its capacity to facilitate crystal deposition and growth on demineralised teeth. According to the manufacturer, the Nano-P® product contains 9000 ppm of sodium fluoride, which contributes to the reduction of demineralisation [46] and enhances desensitisation [47,48]. Additionally, the presence of 5% potassium nitrate in the formulation favors the modification or blocking of the pulpal nerve response by potassium ions, reducing intra-dental nervous excitability by increasing the concentration of potassium ions in the extracellular environment, which in turn causes depolarisation of the pulp nerves, thus interrupting the transmission of pain stimuli [13].

The volunteers in the Arginine group also reported absence of pain in the different evaluation periods. This absence can be attributed to the fact that the product used in this study contains calcium and arginine in its formulation. Arginine is an amino acid found naturally in saliva and when combined with calcium carbonate, has the potential to obliterate open dentinal tubules. This combination renders the tooth surface resistant to acid and thermal attacks, thereby reducing intratubular fluid movement [49]. A systematic review conducted by Sharif MO et al., indicated a potential role for arginine-containing toothpaste in managing

dentin hypersensitivity but unrelated to dental bleaching [50]. However, the results of this study were in accordance with a previously performed clinical trial by Thiesen CH et al., [26]. Furthermore, there was no significant manifestation of sensitivity after 1 month, 2 months or 3 months of follow-up in either group. It is likely that this is related to the action time and dental stimulus of the carbamide peroxide.

It can be expected that the use of desensitising agents would influence bleaching gel diffusion because of their mechanism of action. Previous in vitro studies have shown that the use of desensitising agents has reduced dental permeability [51,52]. However, the results of this study show that bleaching at home is an effective procedure even when desensitization agents were topically applied after each bleaching gel application, considering that both the control group and the experimental groups had whiter teeth at the end of treatment. Because it has a very small molecule, hydrogen peroxide can penetrate the interstitial spaces between the enamel pores [26,39]. This probably explains the similar bleaching results obtained for the different groups. Therefore, H02 was accepted.

## LIMITATION

One of the possible limitations of this study is related to the duration of bleaching treatment; perhaps a more intense painful stimulus may be occasioned by a longer bleaching time. Further longitudinal studies should be developed for the assessment of sensitivity and colour using a long-lasting home bleaching treatment to keep the enamel colour clear.

## CONCLUSION

According to the methodology used in this clinical study, the subjects treated with n-HAP and arginine presented lower sensitivity when compared to the control group one day after the end of treatment. In addition, there was no impairment of the efficacy of the at-home bleaching treatment over the 90-day evaluation period.

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