

The effect of a novel crystallised bioactive glass-ceramic powder on dentine hypersensitivity: a long-term clinical study

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SUMMARY The aim of this comparative clinical study was to evaluate a novel bioactive glass-ceramic (Biosilicate[®] 1–20 µm particles) to treat dentine hypersensitivity (DH). Volunteers ($n = 120$ patients/230 teeth) received the following treatments: G1-Sensodyne[®], G2-SensiKill[®], G3-Biosilicate[®] incorporated in a 1% water-free-gel and G4-Biosilicate[®] mixed with distilled water at 1:10 ratio. G1 and G3 were applied at home, daily for 30 days; G2 and G4 were applied once a week by a dentist (four applications). A visual analogue scale (VAS) was employed to evaluate pain for each quadrant in one sensitive tooth at baseline, weekly during treatment and during a 6-month follow-up period. Dentine hypersensitivity values (G1/ $n = 52$), (G2/ $n = 62$),

(G3/ $n = 59$) and (G4/ $n = 59$) were analysed with Kruskal–Wallis/Dunn tests. All the products were efficient in reducing DH after 4 weeks. Among the four materials tested, G4 demonstrated the best clinical performance and provided the fastest treatment to reduce DH pain. Distilled water proved to be an adequate vehicle to disperse Biosilicate[®]. Low DH scores were maintained during the 6-month follow-up period. The hypothesis that the novel bioactive glass-ceramic may be an efficient treatment for DH was confirmed.

KEYWORDS: biomaterial, clinical study, dentine hypersensitivity

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Introduction

Biomaterials such as bioactive glasses and glass-ceramics have been demonstrated to be effective in bone regeneration (1) and have been proposed to treat dentine hypersensitivity (DH) (2–5). According to the literature, DH is an oral condition that can affect from 1.3% (6) to 98% (7) of the adult world population, depending on the type of population studied and the methods used to evaluate the prevalence of DH (8) and is characterised by a short, sharp pain in response to thermal, evaporative, tactile, chemical or osmotic stimuli, which cannot be ascribed to any form of dental pathology (9–11). Dentine hypersensitivity has been reported to correlate with the exposure of open dentinal tubules to the oral environment (12). From the

published literature, neural stimulus blockers, anti-inflammatory drugs, tubule occluding agents, tubule sealants, remineralising agents and laser therapy have been used to treat sensitive teeth. Most of these desensitising agents are available either as over-the-counter or in-office treatments; the clinical efficacy of these products, however, is quite variable (9).

The current challenge in the treatment of DH is the development of methods and materials for the alleviation of pain. In this context, multidisciplinary research projects have focused on the development of innovative materials and treatment protocols which, in principle, could offer both immediate and long-lasting relief to patients with DH (8, 11).

The similarity between bone, dentine and enamel led to the hypothesis that bioactive glasses and

glass-ceramics could be efficient in providing permanent or more durable occlusion of dentinal tubules, through *in-situ* deposition of hydroxy carbonate apatite (HCA). Evidence has been previously demonstrated that a bond is formed between bioglass particles and human dentine (13). Chemical analyses demonstrated that ions from a bioactive glass migrate into the dentine, and micro-diffractometry indicated the presence of apatite at the interface. According to Efflandt *et al.* (14), bonding appears to be as a result of an affinity of collagen for glass (14). The applicability of bioactive glasses in treating DH has been evaluated, for instance, by *in vitro* studies mixing the bioactive materials into dentifrices or melting the particles with Nd:YAP laser (2–4) in an attempt to provide novel methods or products to occlude dentinal tubules.

Zanotto *et al.* (15) developed a crystalline powder of bioactive quaternary P_2O_5 - Na_2O - CaO - SiO_2 glass-ceramic (Biosilicate®*). The first *in vitro* results demonstrated that this novel material significantly increases osteogenesis in cell culture experiments (16). A subsequent *in vivo* study (17) demonstrated that filling extracted tooth sockets with these bioactive glass-ceramic particles preserves alveolar bone ridge height and allows osseointegration of Ti implants. A further *in vitro* study demonstrated the potential of micron-sized (1–20 μm) particles of Biosilicate® with regard to induce dentinal tubule occlusion (5). Observations from this study indicated that an HCA-bonded layer was deposited on the dentine surface. Scanning electron microscopy (SEM) photographs demonstrated a definite pattern of dentinal tubule occlusion for Biosilicate® mixed with distilled water and applied on dentine discs. After 24 h of reaction in artificial saliva, the dentinal tubules could no longer be observed, which indicated that a possibly mineralised layer had formed on the dentinal surface. Fourier transform infrared (FTIR) spectroscopy was performed after 2 min, 30 min and 12 h of reaction. An HCA peak clearly appeared on the dentine surfaces after 30 min, promoted by Biosilicate®.

Following the positive *in vitro* results with micron-sized particles of Biosilicate®, the present clinical investigation was designed. Importantly, the crystalline character of Biosilicate® offers a great advantage over all other types of bioglasses because crystallisation significantly changes the fracture characteristics of

glass, yielding less sharp and less abrasive particles, which could then be safely added to dentifrices or gels to treat DH.

Therefore, the aim of this clinical study was to observe whether Biosilicate® could be an effective desensitising agent for the treatment of DH. To study this novel material, a null hypothesis was assumed that the experimental Biosilicate® would be as effective as some commercial brand products for the treatment of DH. Thus, to test this hypothesis, we evaluated comparatively four parameters: (i) the efficacy of Biosilicate® in reducing DH pain; (ii) the time needed for the initial action of Biosilicate® on DH pain; (iii) the long-term duration of the effect of treatment; and (iv) two types of vehicle (distilled water or gel) for clinical and in-home application of Biosilicate®.

Materials and methods

Pre-study period: subject selection, calibration and study design

Subject selection. The research protocol was approved by the Ethics Committee of the Faculty of Dentistry, University of São Paulo, Ribeirão Preto (process number: 2003.1.654.58.7). All patients were fully informed on the nature of the study and signed a Term of Acceptance defined by the Ethics Committee. Volunteers complaining of cervical DH were recruited for the clinical study. The volunteers were examined and selected in accordance with a detailed clinical diagnosis of DH (oral health questionnaire, radiographic examinations and clinical examination). The exclusion criteria were as follows: previous desensitising therapy used in the last 6 months; therapeutic drug history (chronic use); pregnancy; orthodontic appliance; and crowned, extensively restored or abutment teeth. Only one tooth with a DH diagnosis per quadrant was selected for each patient, yielding a maximum of four teeth per volunteer. A sensitive tooth was selected if the examiners received a positive response of pain when a stimulus (tactile, evaporative and cold) was applied to the cervical region and no dental pathology was observed.

Calibration. In the subject selection period, all volunteers were trained to use a visual analogue scale of pain (VAS). After DH diagnosis had been confirmed for a patient, different kinds of stimuli were applied to

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Table 1. Study groups' product information and proposed mechanism of action

Product – group	Product availability	Composition	Proposed mechanism of action
G1-Dentifrice Sensodyne® – Glaxo Smithkline	Over-the-counter	Potassium nitrate at 5%, 1·187 ppm of active fluoride (MFP).	Depolarising effect on neural conduction of pain.
G2-Sensi Kill® – DFL	In-office	Solution 1: phosphate dipotassium, sodium fluoride, methylparaben and distilled water. Solution 2: calcium chloride, sodium benzoate and distilled water.	Calcium phosphate deposition on the dentinal surface and into dentinal tubules – tubule occlusion.
G3-Biosilicate® gel – Vitrovita	Over-the-counter	Fully crystallised bioactive glass ceramic of the quaternary P ₂ O ₅ –Na ₂ O–CaO–SiO ₂ .	HCA layer formation on dentinal surface and into dentinal tubules – tubule occlusion.
G4-Biosilicate® powder – Vitrovita	In-office	Fully crystallised bioactive glass ceramic of the quaternary P ₂ O ₅ –Na ₂ O–CaO–SiO ₂ .	HCA layer formation on dentinal surface and into dentinal tubules – tubule occlusion.

HCA, hydroxy carbonate apatite.

choose the two most severe stimuli, as recommended (10). The selected sample responded with higher levels of pain for a blast of air (45%), dental explorers (30%) and cold water (25%). However, no exact confidence values of DH pain were found between the two examiners and the two test stimuli (Kappa value = 0·6). Regarding this issue, we did not consider these patients as inconsistent responders nor the dentists as inconsistent examiners; we attributed this situation to the dynamic behaviour of the DH pain. Therefore, the study collected data with only one calibrated examiner and one test stimulus. To calibrate the examiner regarding the application of the products, some of the non-selected patients were invited to participate in the calibration training. Those patients who were diagnosed with caries, fractured restorations or other dental causes were provided treatment in the Dental School.

Study design. A total of 142 patients were randomised to the four groups of desensitising agents (Table 1).

This investigation was designed to be a long-term, clinical, simple randomised and double-blinded (at group 3) study and was conducted following the 'Guidelines for the design and conduct of clinical trials on dentine hypersensitivity' (10).

Clinical assessment procedures and application of the products

Two days after the calibration day, all selected volunteers were invited for the 'day zero' of the study when the baseline scores were measured. A response-based method was chosen to assess the pain caused by DH.

The stimulus was a blast of air from a triple syringe (3 cm from the tooth surface), applied to the cervical region of the selected teeth for 3 s. The subject response was quantified using a VAS, in which the patient places a mark on a 0–10 labelled scale (0 referred to 'no pain' and 10 to 'intolerable pain'). On day zero and subsequent visits, all the selected volunteers were clinically examined in accordance with the American Dental Association (ADA) guidelines on Clinical Trial Protocols (Council on Scientific Affairs, 2007) to observe any potential side effects of the products. This examination procedure observed several areas separately: the mucous membranes of the tongue, the hard and the soft palate, the gingiva, the muco-buccal folds, the inner surfaces of the cheeks and the sublingual space areas. Normal appearance was recorded as positive or negative. In addition, all volunteers received a new toothbrush (Johnson & Johnson Reach® – Comfort clean, soft bristles[†]) – at the beginning of the study, at 3 months (patients were required to return their old toothbrush to receive a replacement toothbrush) – and printed instructions regarding the study protocol. The products were applied in accordance with the protocol:

G1: The patients were instructed to brush their teeth with the desensitising dentifrice according to normal oral hygiene, two times per day (at morning and night) for 30 days.

G2: The dentist, using a micro-applicator, rubbed solution 1 on the cervical region of the selected teeth

[†]Johnson & Johnson Reach®, São José dos Campos, SP, Brazil.

for 5 s and kept the area moistened with the solution for 30 s. With another micro-applicator, solution 2 was rubbed on the same region for 2 s and the area was kept moistened for 10 s, in accordance with the manufacturer's instructions (18). The application was made weekly, for a total of four times.

G3: The patients were instructed to put one drop of the gel on a washed and dried indicator fingertip and to massage the cervical region of the identified teeth for about 30 s, after regular oral hygiene, two times per day (at morning and night) for 30 days. Instructions were given not to eat, drink or wash prior to 1 h after application.

G4: The dentist, using a micro-applicator, applied on the cervical region of the selected teeth for 5 s a solution that was composed of Biosilicate[®]: distilled water in a ratio of 1:10. A tube of 1.5 mL was used to hold about 0.15 mg of Biosilicate[®] powder, which was mixed with 1.35 mL of distilled water immediately before the application. The application was made weekly, for a total of four times.

This protocol allowed a total of four applications for G2 and G4 and 60 applications for G1 and G3. To observe possible changes in DH in a short period of time, the pain score was assessed weekly during the 30 days of the use of the products. For G2 and G4, assessments were made 20 min after each application and for G1 and G3 after each 7 days of home use. The study protocol was only interrupted in two situations: (i) if no regression of VAS values was observed in 30 days. In such cases, the subject would be retired from the study sample and other treatment options would be employed for pain relief; (ii) if the volunteers decided to leave the study at any time during the study for any reason. VAS scores were recorded after finishing the treatment (maximum of 30 days or four applications) for 6 months, once per month, for a total of 6 months.

Statistical methods

The tooth was considered the unit of study, as pain is directly correlated with it. As the recorded VAS scores were not evenly distributed (not a normal distribution) within the study population, we employed the Kruskal–Wallis test and the Dunn test ($\alpha = 0.05$) using Prism 5.0 software, under Windows XP System[‡]. Only the data

from volunteers completing the 6-month study were analysed.

Results

A total of 120 patients complied with the protocol and completed the 6-month clinical study. A total of 232 teeth were evaluated: 52, 62, 59 and 59 in G1, G2, G3, and G4, respectively. A total of four, five, five and eight patients were excluded from G1, G2, G3 and G4, respectively, because they withdrew from the study. Withdrawal was considered to have occurred after one appointment had been scheduled but not attended. It is important to note that these excluded patients were all contacted. No complaint about the study protocol was received and patients informed the investigators that their pain had diminished. No patient was eliminated purely because of non-regression of DH. No soft tissue changes were observed during the study.

Figure 1 summarises the mean DH values for all groups at different periods of time. The results can be observed from three different perspectives: values from the total period (W0–M6), values obtained from the micro-period of weeks (W0–W4) during which the products were being applied and values obtained during the 6-month follow-up period (M1–M6).

Baseline (W0) DH values did not differ among the four groups ($P > 0.05$), which is evidence that the random distribution of the selected patients among groups was effective. Analysing data from the total study duration (W0–M6), we observed that all products were statistically effective in reducing DH. Considering the global diminution of pain over the course of the total period, Biosilicate[®] mixed with distilled water (G4) displayed the greatest effect, followed by Sensi Kill^{®§} (G2), Sensodyne^{®¶} (G1) and Biosilicate[®] dispersed in gel (G3). Pain assessments during product usage (W0–W4) were useful in analysing the rapidity of each formulation in reducing DH. Figure 1 also shows the statistical significance of the pain diminution during this period of the study. The interpretation of this data leads us to the following conclusion: G1, G3 (including placebo users) and G4 showed the steepest fall in pain values between W0 and W1 measurements. G2 was not able to reduce pain in the first application but was able to reduce pain at W2, W3 and W4 measurements. This

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[‡]Graphpad Software, San Diego, CA, USA.

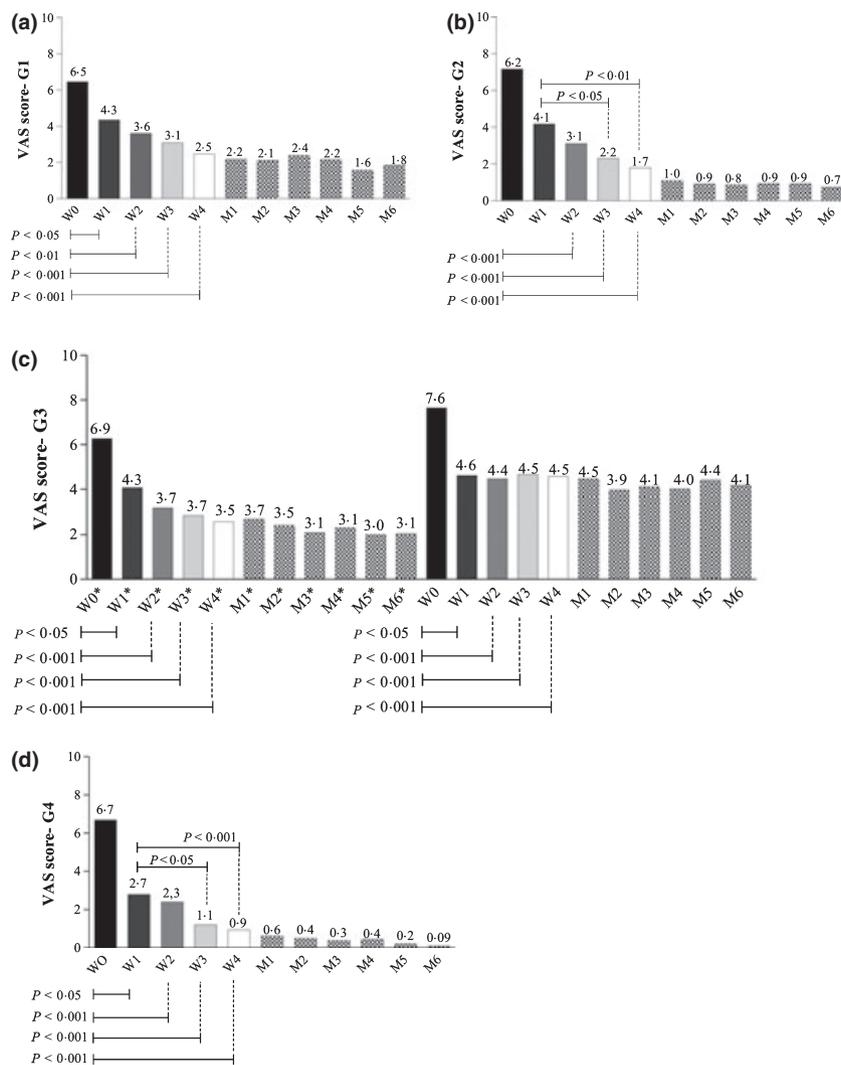


Fig. 1. Graphic illustration of dentine hypersensitivity (DH) values from the assessments, presented separately for each group. On the x axis, W0 refers to the baseline. W1, 2, 3 and 4 refer to the sequence of weeks, and M 1, 2, 3, 4, 5 and 6 refer to months. On the y axis, the 1–10 values of DH pain. In (a) the results for G1; (b) for G2; (c) for the double-blind evaluation at G3 where letters W or M plus an asterisk (*) refer to patients that used gel with Biosilicate®, and the letters W or M without an asterisk refer to patients that used the same gel without Biosilicate® particles, (d) for G4. The mean values of DH pain along the 6 months are presented over each column. The statistical significance of the comparison of DH values in the first month of the study is presented in the graphic.

trend was not observed for G1 or G3. G4 effectively decreased pain throughout the W2, W3 and W4 assessments.

Comparison between the pain values for this period revealed a significant difference among the products. For instance, G4 showed lower DH pain values than G3 at W3 [$P < 0.05$] and W4 [$P < 0.01$]. Considering that G3 and G4 showed similar baseline pain values, the difference between the pain scores at W3 and W4 demonstrates the superior performance of G4 in reducing DH.

The observation of pain values during the follow-up period (M1–M6) was interpreted as the durability of treatment success. The pain values observed at M1 (the first measurement after the end of treatment) did not differ significantly from that observed at M2, M3, M4,

M5 and M6 for any of the products, which meant that all products presented reasonable durability. Figure 1 additionally illustrates the profile of DH pain throughout the total period of the study for each group.

For G3, no statistical difference ($P > 0.05$) in the diminution of pain was observed for patients that used the water-free gel with Biosilicate® when compared to those who used the water-free gel without Biosilicate®. These results indicate that the volunteers that used only the water-free gel for 1 week also experienced a moderate reduction in DH.

Discussion

In vitro studies evaluating innovative applications for bioactive glass-ceramics in the field of dentistry are

important for evaluating potential desensitising agents. Previously reported studies have reported the effectiveness of various desensitising agents in the treatment of hypersensitive teeth as well as the effectiveness of bioactive glasses on the remineralisation of both enamel and dentine (2, 4, 5, 13, 14, 19, 20). It is important to note that while *in vitro* studies may provide information regarding any proof of principle or concept, one cannot extrapolate these laboratory results into the clinical environment, hence the requirement for undertaking clinical investigation of these products. Following a positive *in vitro* study, it is essential to determine whether a potentially effective desensitising product in the clinical environment; however, clinical studies evaluating DH are much more complex and demanding than *in vitro* studies. The most difficult aspects of such a study include obtaining a well-defined and consistent sample size population that adheres to the inclusion and exclusion criteria, as well as maintaining volunteer compliance throughout the duration of the study.

Clinical studies have evaluated different types of treatments and products for DH. For example, the efficacy of low-level gallium–aluminium–arsenide laser and sodium fluoride varnish in DH treatment has been evaluated (21). The study was performed with 12 patients, yielding a total of 60 teeth. Pain was assessed immediately after the first application, then with 15- and 30-day follow-ups. The authors concluded that both treatments were effective in decreasing DH. Another clinical study evaluating products that may relieve DH during the first 5 days of treatment assessed the efficacy of a bioadhesive gel containing 5% or 10% potassium nitrate on 45 patients immediately and at 2, 4, 7 and 14 days after gel application. The results demonstrated efficacy of the 10% potassium nitrate gel at 48–96 h after the initiation of treatment (22). An additional clinical study compared five products with regard to their efficacy in DH treatment. The authors tested one fluoride varnish, two dentine adhesives, one desensitiser with benzalkonium chloride, 2-hydroxyethylmethacrylate (HEMA) plus fluoride and HEMA plus glutardialdehyde. The 3-month study, performed with 277 sensitive teeth (52 subjects), was considered by the authors to be a long-term evaluation. Measurements of pain (with VAS) were assessed immediately after treatment and at 10 days and 3 months into the follow-up period. All products were statistically efficient in reducing DH at all evaluation periods. However, after 3 months, the DH values increased. The authors attrib-

uted the short duration of DH alleviation following treatment with fluoride varnish to a lack of bonding between dentine and the product. They hypothesised that for polymeric films (adhesives), thin film wear (caused by mastication and tooth brushing procedures) and the exposure of pre-acid-treated dentinal tubules could contribute to renewed pain (23).

The studies cited above indicate that, currently, the materials and methods used to treat DH could be improved to obtain an easy, fast, non-invasive, durable treatment to relieve the pain caused by exposed dentinal tubules. This is the current challenge in the area of DH. Thus, micron-sized particulate bioactive materials, able to induce the formation of HCA, applied in the simplest possible way, could potentially represent a satisfactory option for the treatment of DH (as well as for the regeneration of dentine and enamel). Another important point is the antimicrobial activity of the bioactive glasses of the $\text{SiO}_2\text{-Na}_2\text{O-CaO-P}_2\text{O}_5$ when suspended in aqueous solutions *via* the release of their ionic compounds over time (24, 25). Hypothetically, a pH rise effect and/or an antimicrobial effect could affect microorganisms that have entered inside the dentinal tubules and the subsequent DH caused by this aggressive stimulus. The first question raised in this study, whether Biosilicate[®] could be used to decrease DH pain, was answered by the results demonstrating a considerable decrease in DH pain when Biosilicate[®] was used.

Corroborating these results, clinical studies with calcium sodium phosphosilicate also showed that bioactive glasses (or glass-ceramics) may be effective materials to treat DH when incorporated into oral health products. A dentifrice containing calcium sodium phosphosilicate (Novamin^{®**}) was compared to placebo and a commercially available strontium chloride dentifrice to determine the efficacy of each formulation in treating DH. The dentifrice containing calcium sodium phosphosilicate was more effective in reducing DH than the SrCl_2 formulation or the placebo (26). A clinical study with 50 periodontal patients evaluated a product based on calcium sodium phosphosilicate (Novamin[®] Tooth Root Conditioner) in the course of the periodontal treatment. The results demonstrated that there was a significant decrease in DH when the product was applied along with the periodontal therapy (27). Another clinical study evaluated three dentifrices containing 5% potassium nitrate;

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0.4% stannous fluoride and 7.5% calcium sodium phosphosilicate on DH, and the results demonstrated that the product containing the bioactive calcium sodium phosphosilicate reduced DH faster than the other dentifrices in the study (28). A 4-week clinical study with 20 volunteers evaluated a dentifrice containing 7.5% calcium sodium phosphosilicate on DH and demonstrated a 90% reduction in DH at week 4 (29).

The second question raised in this study was how much time is needed for the initial action of Biosilicate® on DH. It is well established that the duration of the study must be dependent on the type of agent. For example, if the product is thought to be effective at reducing DH, then four to 8 weeks may be necessary. However, if the product is designed to eliminate DH for a specific period, it will be necessary to extend the results from immediately after application with a follow-up test, approximating the period thought to be the duration of effectiveness (10). This 6-month study tested the products for two characteristics: the effectiveness in reducing DH and the durability of the effect. Based on the results of a previous *in vitro* study (5), a rapid decrease in DH was expected, as SEM experiments demonstrated a considerable dentinal tubule occlusion by Biosilicate®. The authors have also observed FTIR formation of HCA after 30 min exposure to dentinal surfaces. Nevertheless, the uniform and rapid adsorption of proteins or cells on the surface of the bioactive glasses *in vivo* may act to protect the surface from further direct interaction with the aqueous media, slowing down the transformation reactions as previously demonstrated (30). The expectation generated by the *in vitro* study was confirmed by clinical results that showed a significant and fast decrease in pain, especially in patients treated with Biosilicate® mixed with distilled water. Notably, a sharp fall in DH pain values was observed for the in-office products (G2 and G4) during the first 30 days. The difference in pain reduction observed between G2 and G4 at W1 may be because of the micron-sized character of the bioactive material, while the other in-office product was comprised of two solutions. The solid character of the micron-sized particles helped to initiate the obliteration action engendered by mechanical fixation and by formation of a difficult-to-remove solid barrier. Considering the size range of the particles (1–20 µm) and the SEM results from the *in vitro* study (5), we can assume that some particles were inserted into the

dentinal tubules, at a depth ranging from 2 to 6 µm, while other particles stayed positioned at the entrance of the open dentinal tubules. Initiation of the reaction likely reduced the dimensions of the particles in the bioactive material, facilitating insertion into the dentinal tubules and rendering the obliteration more effective. Regarding the initial events on the Biosilicate® surface, one needs to consider that in G4, which presented the best results, the bioactive material was mixed with distilled water immediately before application and the solution was gently dispensed with a micro-applicator. It is possible that the method of preparation (immediately pre-dissolution and dynamic application) may have helped to reduce the deposition of proteins from saliva on the surface of the material, and as a result, the initial stages of the reaction were not slowed down. Another point was the superficial area of reaction provided by fine Biosilicate® powder – the more finely divided the solid is, the faster the reaction. As a result, it is possible that the rapid formation of the HCA layer occluded the dentine tubules. This might in some way explain that there was a reduction in the pain response to the air blast stimulus from a triple air syringe when applied 20 min after the initial mixing of the bioactive material and distilled water.

The third question of this study, vehicles proposed to disperse Biosilicate®, indicated that the bioactive material used to treat subjects in G3 was not as effective as that applied to subjects in G4. Most likely, the percentage of particles incorporated into the gel (1% wt) was not sufficient to obtain the same level of activity as elicited by a mixture containing bioactive material and distilled water at a 1:10 ratio. Despite this difference in the percentage of particles suspended in the G3 and G4 vehicles, we expected that, *in vivo*, the daily application of the water-free gel would induce dentinal tubule occlusion and DH remission in G3, as had been observed for G4. However, this expected reaction did not take place. A potential reason for the significantly weakened effect of the bioactive particles in G3 was the composition of the water-free gel. In this study to obtain a water-free formulation, the gel was produced with Carbopol®^{††} as a thickener and glycerine as a humectant. Carbopol® is a well-known polymer of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol, which is produced from primary polymer particles that are about 0.2–6.0 µm in diameter.

^{††}Garden Quimica, Guarulhos, SP, Brazil.

Because of its cross-linked structure, Carbopol® is often used in controlled drug delivery (31). The total amount of Biosilicate® particles may not have managed to escape from the cross-linked structure of the gel. Alternatively, the glycerine may have formed a coating over the bioactive particles, making the reaction with saliva and the mineral surface of the teeth more difficult. Surprisingly, we did not observe significant differences between patients in G3 treated with placebo and those who received the experimental treatment. The potential therapeutic power of a placebo (11) is recognised and could be a justification for why both gels (with and without Biosilicate®) were reasonably effective in reducing DH pain after 1 week of home use. Other possibilities include the gel particles playing a role in mechanical, reversible dentinal tubule occlusion and as well as patient behaviour during the study (Hawthorne effect), which may act to decrease DH.

The fourth aspect of the study was the clinical durability of the treatments. We expected that Biosilicate® could provide long-term DH alleviation, as bonded HCA will probably be formed inside the dentinal tubules, triggered by the micron-sized bioactive material reaction. This would result in permanent and hypothetically difficult-to-remove obliteration, as a recent study (32) evaluating the biomechanical behaviour of the tissue formed in tibial consolidation demonstrated higher mechanical resistance when Biosilicate® was employed to fill bone defects. Our expectations of the Biosilicate product were confirmed as the product demonstrated (reduced pain response) to be effective both during the study and subsequent follow-up period. Furthermore, all treatments during the M1–M6 periods were shown to have maintained the reduced pain scores as demonstrated at the end of the treatment phase. Similar results were observed in another long-term clinical study that compared products to treat DH with different modes of action (33). In our study, these results generate three direct questions: (i) do neural stimulus blockers, such as potassium nitrate, continue to act for 5 months; (ii) why was DH diminished and maintained at lower levels in patients that used only placebo; and (iii) is this reduction in DH pain permanent? To answer these questions, it is important to consider that in some situations, the products used in oral health treatment are only one part of the solution. For instance, physiological responses, such as reparative dentine, and patient behaviour have an important role in DH relief, especially in long-term alleviation. Also, another point to be considered in

clinical studies is the phenomenon denominated regression-to-the mean (34), often observed when volunteers are presenting extreme pain at the beginning of the study. In these situations is quite difficult to estimate how much the pain regression is as a result of the treatments or the natural course of the condition.

Regarding patient behaviour, all volunteers selected in this investigation were seeking treatment of DH and were motivated to change their 'DH-affected' condition, despite the inclusion and exclusion criteria. The impact of some situations, such as acid diets, incorrect tooth brushing, systemic disorders (35) and psychological disorders (36), on the exposure of open dentinal tubules to the oral environment is well defined (8). However, in most cases, the patients were not aware of this problem. The study protocol deliberately did not establish any education with regard to oral health, although all the selected volunteers received a new toothbrush, which was proven to be effective at the first visit and at the third month – to receive a new toothbrush, the patient needed to return the old one. Patients were also asked about their oral health habits during this first visit. The reader should also be aware that the entire study was performed at the Dental School, where the volunteers were naturally exposed to an environment with available oral health information. Thus, we need to suppose that, in clinical studies, the behaviour of the volunteers is an uncontrolled bias. This assumption may therefore lead us to suggest that the effectiveness and durability of the treatment of DH may depend to some extent on the patient's ability to maintain good oral health practices in matters of diet and tooth brushing habits.

Taken *in toto*, the results from this clinical study suggest that micron-sized particles of Biosilicate® could be an effective desensitising agent for the treatment of DH. This bioactive material demonstrated the best results when mixed with distilled water, reducing DH pain in a short period of time and maintaining this effect over the 6-month follow-up period. Additionally, this clinical study demonstrated that it is important to provide DH patients with desensitising agents that are able to treat DH pain in an easy and non-invasive manner. The mode of action of a DH product therefore should both rapid in nature and effective in producing an occlusive seal within the diameter of the dentine tubules. Ideally, patients should be provided with post-treatment information that will maintain the durability of the DH product.

Further *in vitro* studies are needed to investigate the bonding characteristic of the mineralised structure formed by the reaction between a crystalline bioactive material and dentine and enamel surfaces and the effect of acid attack to these surfaces. Ideally, changes in dentine permeability using an *in vitro* fluid flow system (e.g. Pashley model) should also be incorporated in studies to provide supporting evidence of tubular occlusion from SEM data. Other clinical studies comparing Biosilicate[®] with glass and partially crystallised bioactive materials, in various vehicles used for oral health products, should also be carried out.

Conclusions

The results from this study indicate that micron-sized particles from Biosilicate[®] may provide an immediate, effective and long-lasting treatment for DH sufferers.

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