Effectiveness of an in-office calcium-phosphate-based desensitizer: A six-month randomized-controlled trial and a SEM study of in-vivo treated teeth

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Abstract

Aim: The aim of this single-centre, triple-blind, randomized controlled clinical trial was to evaluate the effectiveness of an in-office desensitizing agent containing tetracalcium phosphate and dicalcium phosphate anhydrous in providing relief for dentin hypersensitivity vs 5% fluoride varnish during a six-month follow-up period. Occlusion of dentinal tubules after in-vivo treatment was also evaluated via SEM analysis.

Materials and Methods: Seventy-five patients suffering from dentin hypersensitivity (DH) were randomly allocated to a treatment with one of three desensitizing agents: tetracalcium phosphate and dicalcium phosphate anhydrous powder mixed with the liquid solution provided by the manufacturer, or the same powder mixed with saline solution, or 5% fluoride varnish. Air-blast hypersensitivity was assessed after 15, 90, and 180 days, using both Schiff and Visual Analogue (VAS) scales at baseline.
Twenty-five teeth from 5 subjects with exposed dentin were previously planned and chelated with EDTA, then either treated with one of the investigated agents or not treated at all. After two weeks, the teeth were extracted and analysed via SEM.

Results: No significant differences due to treatment factors were found (p = 0,535), while a significant time-related effect (p = 0,000) was observed. All treatments could progressively reduce pain perception at each follow-up time point.
SEM analysis has shown partial or total occlusion of the dentinal tubules in all treatments. No occlusion was seen in nontreated teeth.

Conclusion: The tested treatments could reduce DH, and such effect increases as time passes. DH reduction is still present six months after treatment.

Keywords: Calcium Phosphate, Clinical Trial, Desensitizing Agent, Dentinal Hypersensitivity, Sodium Fluoride, Fluoride Varnish, Scanning Electron Microscope.

Introduction

Dentin Hypersensitivity (DH) is a very common clinical situation among adults, and it can cause considerable discomfort to patients.[1] DH is defined as a "short, sharp pain arising from exposed dentin in response to stimuli typically thermal, evaporative, tactile, osmotic, or chemical and which cannot be ascribed to any other form of dental defect or disease".[2] Reported DH prevalence varies considerably among published studies because different study designs are used to assess DH in different settings.[3] Several cross-sectional studies published in the last few years report a DH prevalence ranging from 20% to 46% in South America, Europe, and Asia,[4-9] while a lower prevalence is reported in the United States.[10] DH seems to be associated with the abrasiveness of toothpaste, gingival recession, and periodontal therapy.[11, 12]

Thus far, the mechanism underlying the onset of DH has not been fully explained, but the most widely accepted hypothesis is the hydrodynamic theory,[13] according to which increased fluid flowing in the open dentin tubules due to osmotic, tactile, chemical, or thermal stimuli causes changes in pressure, resulting in stimulation of pulp nerve endings. The hydrodynamic theory suggests that two factors might be responsible for DH onset: exposed dentin and open dentinal tubules.[14] In some cases of dentin exposure, restorative,[15,16] surgical,[17] or combined[18,19] treatments can be carried out, but if there are no clear indications for surgical/restorative treatment, desensitizing agents able to either occlude the dentinal tubules or to desensitize the pulp nerve are available.[20]

The treatment options for DH are based on the use of both agents capable of occluding the dentinal tubules thanks to their chemical, physical, or photobiomodulative properties and agents capable of inhibiting the nerve activity.[14] Agents used to obtain physical occlusion of dentinal tubules are pumice paste, sodium bicarbonate, hydroxyapatites, bioglasses, glass ionomers, dentin bonding agents, and resins; treatments aimed at obtaining chemical occlusion include fluorides, oxalates, glutaraldehyde-based agents, and calcium compounds; a photobiomodulating effect is obtained with laser therapy; and, finally, potassium nitrates and guanethidine are used to induce nerve desensitization. All these treatments options seem to lead to better outcomes if compared with placebos, but a comparison between treatment groups did not revealed significant differences.[14]

This research, in particular, focuses on the evaluation of a recently introduced calcium-phosphate-based agent named Teethmate Desensitizer (Kuraray Noritake Dental Inc., Tokyo, Japan) (TMD) that belongs to the chemical occlusion group. Its powder-liquid formulation contains tetracalcium phosphate and

dicalcium phosphate anhydrous, which is combined in an aqueous environment generate hydroxyapatite,[21-23] the main component of teeth and bones and, therefore, of special interest as a natural occluding material.[24]

For almost a century, calcium phosphate-based cements have been used as bone-graft substitutes, and about thirty years ago, they started to be put to the test as desensitizing agents[25–27] thanks to their capability of occluding dentinal tubules. In-vitro tests have provided evidence of TMD's great potential for reducing dentin permeability and its stability properties. These tests have also shown that after EDTA treatment to open the dentinal tubules, the in-vitro application of TMD on human dentin discs induces the formation of a thin layer covering the surface and apparently occluding all the dentinal tubules. After a four-week immersion into an artificial saliva solution, an abundant deposition of newly formed crystallites on the desensitizing layer was observed,[28] leading to a significant reduction in dentin permeability. Moreover, in-vitro treatment with TMD along with a treatment of fluoride varnish seemed to inhibit demineralization in an acid solution.[29] The clinical effectiveness of TMD has also been assessed through some randomized controlled trials.[23,30]

This study was designed as a three-arm, triple-blind, randomized clinical trial aimed at assessing the effectiveness of TMD in treating DH and the stability of its effects over a six-month follow-up period compared to two control regimens. In addition, a scanning electron microscope (SEM) study of in-vivo treated teeth was performed to evaluate TMD's ability to occlude dentinal tubules.

To our knowledge, thus far, SEM evaluations of TMD's action on dentinal surface have been performed exclusively in vitro.

Materials and Methods

This trial is reported according to the CONSORT Statement (Consolidated Standard of Reporting Trials) (http://www.consort-statement.org/). All human trials were approved by the Ethics Committee of Cuneo's Hospital (approval date 12/17/2014). The ethical principles stated in the Declaration of Helsinki for Medical Research were followed.

Clinical Evaluation

Trial design

This study was designed as a three-arm, split-mouth, randomized-controlled, triple-blind clinical trial. Each patient was randomly assigned to a combination of two of the three test treatments: TMD, TMD powder mixed with a sterile saline solution (TMDSS), or 5% sodium fluoride varnish (Profluorid, VOCO GmbH, Cuxhaven, Germany) (NaFV). For each patient, two teeth were randomly assigned to one of the two selected treatments following the split-mouth approach.

Participants

Adult patients complaining of DH who had at least two teeth in two different quadrants (one on the left and one on the right) scoring a value of ≥4 on the visual analogue scale (VAS) after an air blast stimulus (see below) were considered eligible for this study.

Exclusion criteria were:

i. caries or occlusal trauma on the selected teeth,
ii. periodontal surgery performed during the last six months,
iii. desensitizing treatments performed during the last six months,
iv. ongoing orthodontic treatment,
v. use of painkillers during the last 24 hours, and/or
vi. pregnancy/lactation.

Participants were recruited among all consecutive adult patients who presented to our private practice (Cuneo, Italy) between April 2014 and June 2015 complaining of DH. The two most sensitive teeth of two different quadrants were selected for treatment.

Interventions: Three treatments were evaluated in this study: TMD powder mixed with the liquid solution provided by the manufacturer according to his/her instructions, the same TMD powder mixed with a sterile saline solution, or 5% sodium fluoride varnish.

Before treatment, calculus and plaque were carefully removed without using any prophylaxis paste containing desensitizing agents and each tooth was dried with a sterile gauze. Then, after an air blast stimulus, hypersensitivity was subjectively and objectively assessed (room temperature air was directly blown onto the buccal dental cervical surface from a distance of 1 cm for 1 second using dental unit air syringes at 30 psi; the two adjacent teeth were isolated with cotton rolls to avoid interference).[31] The first evaluation was based on the VAS scale, which ranges from 0 (no pain) to 10 (maximum bearable pain). The objective evaluation was based on the Schiff scale: 0 indicates that patients do not respond to air stimulus; 1 indicates that patients respond but do not request stimulus discontinuation; 2 indicates that patients request stimulus discontinuation or, alternatively, move away from the stimulus; 3 indicates that patients consider stimulus to be painful and request discontinuation.[32] Patients were considered to be eligible if two teeth of two different quadrants got a VAS score of ≥ 4.

Patients were then randomly allocated to one of the three treatment groups: 1) TMD vs TMDSS, 2) TMD vs NaFV, or 3) TMDSS vs NaFV. For each patient, the two selected teeth were then randomly assigned to their specific treatment.

Agents were given to the treating clinician in a double small bowl to prevent him or her from identifying the product.

After drying the tooth with gauze, the selected product was applied with a brush for 30 seconds as recommended by producer, and then the tooth was prevented from getting wet by placing cotton rolls for five minutes. This last decision was made arbitrarily by authors to avoid an early washout of the material.

Outcomes

The first outcome taken into consideration was the residual DH, respectively, at fifteen days, then three months, and then six months after treatment. The assessment, carried out by resorting to the same procedure used during the initial evaluation, was performed at several follow-up time points by a blind investigator.

The second outcome taken into consideration was the adverse events reported at each follow-up point and possibly due to the desensitizing treatment.

Randomization and blinding

A computer-generated random list of 81 patients was created to decide whether to treat them with either TMD and TMDSS, TMD and NaFV, or TMDSS and NaFV on the basis of a split-mouth experimental design. Only one investigator, not involved in either the clinical evaluation or treatment, was aware of the sequence and allowed to access the file. The randomized codes were put into sequentially sealed envelopes that were opened after the initial DH evaluation. To determine which treatment to administer to the right and to the left teeth, a further couple of envelopes were prepared for each patient, containing the letters A and B, and then sealed. An independent assistant was then asked to write "right" and "left" on the envelopes. The two selected agents were prepared and put into small bowls labelled with the letters A and B. Only the investigator allowed to access the file was aware of the link between the desensitizing agent and the letter. The envelopes were opened by a treating clinician blinded to the process before administering the agent, and the link between the letter and the mouth side were disclosed to the non-blinded investigator.

Sample-Size Calculation

The sample-size calculation was performed with a power of 0.90, an effect size of 0.15 and α=0.05, using the GPower software (GPower 3.1). The ideal number of observations per group was increased to take into account the multilevel analysis[33] with an attrition rate for the follow-up drop out of 7.4%. Thus, the number of patients in each group ranged from 48 to 52.

Statistical Analysis

Data for both investigated variables (VAS and Schiff scores) initially failed to reach normal distribution criteria using Shaphiro-Wilk test ($p<0.05$). Thus, they were transformed to $\log_e$ (VAS+1) and $\log_e$ (SCHIFF+1), and 5% of outliers were excluded from the analysis (Graph Pad Prism 6.0). Four time points were settled as follows: t0 (immediately after treatment), t1 (14 days on), t2 (three months on) and t3 (six months on). Observations at the different time points were considered level 1, treatments (teeth) were considered level 2, and patients were considered level 3. The changes in teeth hypersensitivity induced by the three different treatments (TMD, TMDSS, NaFV) were initially evaluated for each outcome, using a random coefficients regression model (SPSS, version 22). Since the variance of random effects was equal to zero in both analysis, only fixed effects were taken into account. Thus, a repeated measure MANOVA using a GLM (General Linear Model) procedure and pairwise comparison with Tuckey test were performed (SPSS, version 22).

Sem Evaluation

Five patients with at least four non-decayed/non-restored teeth scheduled for extraction and with vestibular gingival recession were selected. Two weeks before extraction, the whole vestibular root surface was planned with Gracey curettes under local anaesthesia and pre-treated with 24% EDTA paste to open the dentinal tubules. Then each surface was either randomly treated with one of the investigated agents or not treated at all. Twenty teeth were pre-treated: among these, five were not treated at all, and fifteen were treated in equal proportions respectively with either TMD, TMDSS, or NaFVa.

Patients were instructed not to vary their oral-hygiene habits until tooth extraction.

Two weeks after the experimental treatment, the teeth were extracted, and particular attention was taken not to come into contact with the treated surface. Then, the treated surfaces were observed at high magnification (up to 10000×) by means of a LEO 1450VP scanning electron microscope (SEM) equipped with software for image acquisition and analysis. Prior to SEM observations, the teeth were subjected to a preliminary cleaning operation aimed at removing the surface impurities by means of an MDM 3.5RS ultrasonic machine (by dipping the samples in deionized and demineralized water).

Results

Of the 133 patients complaining of DH assessed for eligibility, 81 were recruited. Seventy-five of the initial 81 completed the study. The number of teeth treated in each group was 50 for TMD, 52 for TMDSS, and 48 for NaFV (Fig. 1). The mean age of the patients was 43.3 years (DS 12.1, from 25 to 79 years), and only 15 were males (20%).

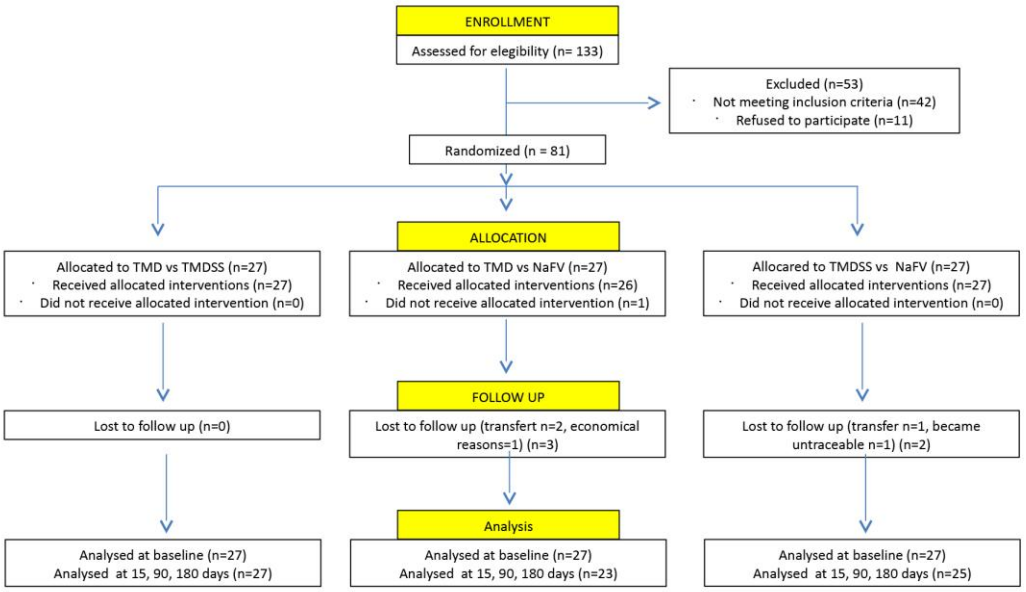

Fig. 1: CONSORT flow diagram of the patients

Adverse events

No adverse reactions to the components of the products were observed during the study, either subjective or objective.

DH parameters

Repeated measure MANOVA

The multivariate test carried out by the GLM procedure highlighted a significant effect of the time factor (p = 0,000) and a nonsignificant effect of the treatment factor (p = 0,535) **(Table 1)**. Interaction was not significant either (p = 0,080).

Table 1: Multivariate test to evaluate the effect of factors (treatment and time) and their interaction through Wilk's lambda. The results were considered significant for p<0.05

Effect	Wilk's Lambda	F	Significant
Between subjects (Treatment)	0,979	0,786	0,535
Within subjects (Time)	0,403	35,012	0,000
Treatment-Time interaction	0,875	1,640	0,080

The univariate test highlighted a significant effect of the time factor in both VAS and Schiff scale **(Table 2)**. Since variance was not homogeneous in the three groups of data for both the VAS and Schiff scale, the Huynh-Feldt correction was used to assess the effect of the time" factor (VAS: F = 70,741; p = 0,000; Schiff: F = 77, 744; p = 0,000).

Table 2: Univariate test to evaluate the effect of time for VasT and ShiffT scale. The results were considered significant for p<0.05

Effect	Scale		F	Significant
Time	VasT	Huynh – Feldt	70,741	0,000
	SchiffT	Huynh – Feldt	77,744	0,000

The pairwise comparison of the effects of the time factor in both scales (Tables 3 & 4) showed that the treatments could progressively reduce pain perception at each follow-up time point. In particular, analysis of the VAS scale estimated marginal means; there was a significant pain reduction at t1 (14%, p = 0,0251), t2 (19%; p = 0,0013) and t3 (35%, p<0,0001) vs t0 in the TMD group. In the same way, also for the TMDSS group and for the NaFV treatment, there was a significant reduction at t1 (13%, p = 0,0501; 17%, p = 0,0035, respectively), t2 (22%, p<0,0001; 25%, p<0,0001), and t3 (32% , p<0,0001; 33%, p<0,0001). For the SCHIFF scale, results were slightly different. For the TMD group, there was a small pain reduction at t1 (15%, p = 0,070) and t2 (15%, p = 0,0860), but

only at t3 (43%, p<0,0001) reached the significance. For the TMDSS group and the NaFV treatment, there was a significant pain reduction only at t2 (34%, p<0,0001; 25%, p<0,0001, respectively) and t3 (47%, p<0,0001; 33%, p<0,0001, respectively), while at t1 it was not significant (9%, p = 0,4778; 6%, p = 0,8209, respectively). The changes over time are evident in Fig. 2.

Table 3: Pairwise comparison of "time" factor in VAS scale, Tuckey t test. The results were considered significant for p<0.05

Measure	Treatment	Time point comparison	Mean difference	p	CI 95% inferior limit	CI 95% superior limit
VAS scale	TMD	t0 vs t1	0,2929	0,0251	0,0259	0,5599
		t0 vs t2	0,3834	0,0013	0,1164	0,6504
		t0 vs t3	0,7305	<0,0001	0,4635	0,9975
		t1 vs t2	0,0905	0,8188	-0,1765	0,3575
		t1 vs t3	0,4376	0,0002	0,1706	0,7046
		t2 vs t3	0,3471	0,048	0,0801	0,6141
VAS scale	TMDSS	t0 vs t1	0,2565	0,0501	-0,0001	0,5131
		t0 vs t2	0,4505	<0,0001	0,1939	0,7071
		t0 vs t3	0,6558	<0,0001	0,3992	0,9124
		t1 vs t2	0,1940	0,2092	-0,0626	0,4506
		t1 vs t3	0,3993	0,0004	0,1427	0,6559
		t2 vs t3	0,2053	0,1670	-0,0513	0,4619
VAS scale	NaFV	t0 vs t1	0,3492	0,0035	0,0876	0,6108
		t0 vs t2	0,4983	<0,0001	0,2367	0,7599
		t0 vs t3	0,6573	<0,0001	0,3957	0,9189
		t1 vs t2	0,1491	0,4575	-0,1125	0,4107
		t1 vs t3	0,3081	0,0134	0,0465	0,5697
		t2 vs t3	0,1590	0,3992	-0,1026	0,4206

Table 4: Pairwise comparison of "time" factor in SCHIFF scale, Tuckey t test. The results were considered significant for p<0.05

Measure	Treatment	Time point comparison	Mean difference	p	CI 95% inferior limit	CI 95% superior limit
SCHIFF scale	TMD	t0 vs t1	0,1776	0,0700	-0,0095	0,3627
		t0 vs t2	0,1705	0,0860	-0,0156	0,3566
		t0 vs t3	0,4864	<0,0001	0,3003	0,6725
		t1 vs t2	-0,0061	0,9998	-0,1922	0,1800
		t1 vs t3	0,3098	0,0001	0,1237	0,4959
		t2 vs t3	0,3159	<0,0001	0,1298	0,5020
SCHIFF scale	TMDSS	t0 vs t1	0,1030	0,4478	-0,0758	0,2818
		t0 vs t2	0,3845	<0,0001	0,2057	0,5633
		t0 vs t3	0,5291	<0,0001	0,3503	0,7079
		t1 vs t2	0,2815	0,0003	0,1027	0,4603
		t1 vs t3	0,4261	<0,0001	0,2473	0,6049
		t2 vs t3	0,1446	0,1597	-0,0342	0,3234
SCHIFF scale	NaFV	t0 vs t1	0,0615	0,8209	-0,1209	0,2439
		t0 vs t2	-0,6570	<0,0001	-0,8394	-0,4746
		t0 vs t3	0,4876	<0,0001	0,3052	0,6700
		t1 vs t2	-0,7185	<0,0001	-0,9009	-0,5361
		t1 vs t3	0,4261	<0,0001	0,2437	0,6085
		t2 vs t3	1,145	<0,0001	0,9622	1,327

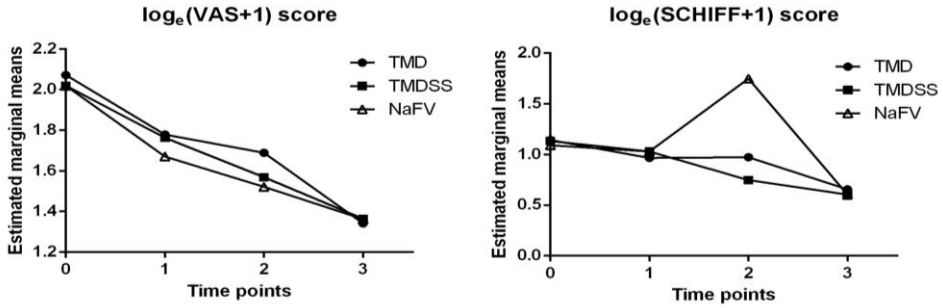

Fig. 2: Log transformed VAS scale (log$_e$(VAS+1); panel A) and SCHIFF scale (log$_e$(SCHIFF+1); panel B) estimated marginal mean values at different time points

SEM images

The SEM images showed similar patterns of tubules occlusion for TMD and TMDSS, but showed a quite different pattern for NaFV. In the first two treatments, dentinal tubules appeared to be only partially occluded, there was a difference in the percentage of occluded tubules among the different specimens, and occluding material was detected inside the tubules (Fig. 3) or their diameter seemed to be smaller (Fig. 3). On the other hand, the treatment with NaFV led to a massive occlusion of tubules that were no longer visible and, in this case, the occluding material seemed to adhere to the outside of the dentinal surface (Fig. 3). Such a massive occlusion was visible in all the NaFV specimens, but in only two TMDSS (Fig. 3) specimens and in no TMD specimen. Almost all untreated specimens showed open dentinal tubules (Fig. 3).

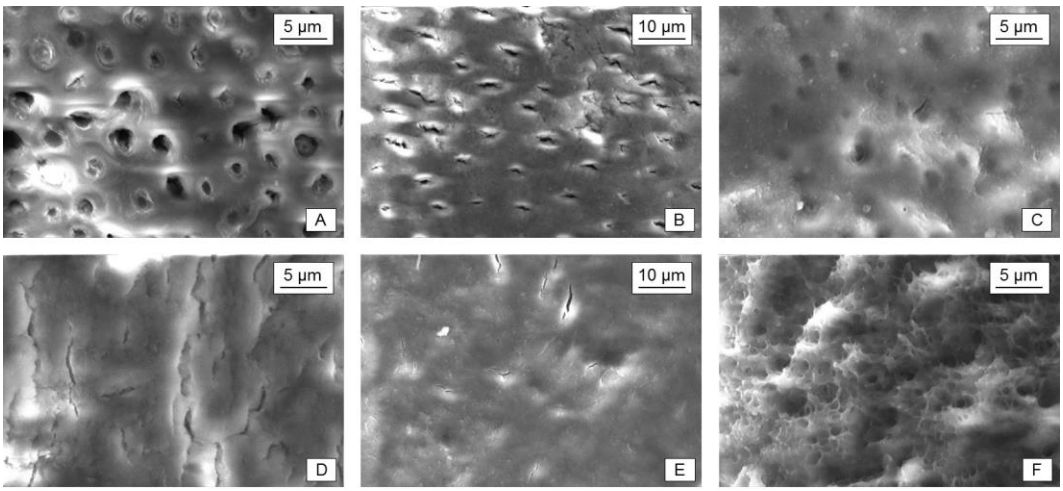

Fig. 3: SEM findings in the experimental groups: A: TMD, original magnification 10000x, Occluding matherial is visible inside dentinal tubules; B: TMD, original magnification 5000x, is visible a reduction of the diameter of dentinal tubules; C: TMDSS original magnification 10000x, is visible a reduction of the diameter of dentinal tubules; D: NaFVa original magnification 10000x, a "massive" superficial occlusion is visible; E: TMDSS original magnification 5000x, a "massive" superficial occlusion is visible; F: Untreated specimen original magnification 5000x, all dentinal tubules seem open.

Discussion

There are no gold-standard treatments for DH. Even if the desensitizing agents commonly used in office seem to be effective and , in general, seem to have better outcomes than the placebo,[14,34] several studies aimed at evaluating different therapeutic options found no significant differences among the available treatments,[35-39] and it is all the more curious that, despite the fact that patients felt less discomfort after treatment, different studies did not reveal any statistically significant differences among test treatments and the placebo[37,40-42] or even alternative therapies such as hypnosis.[43] This means that treating DH has a strong placebo effect that may disguise the effectiveness of the investigated desensitizer.[40,42] The shorter the follow-up period, the more influent the placebo effect. So far, only a few randomized-controlled trials have evaluated the effectiveness of

desensitizing agents over six and/or nine months.[20,23,30,44-47] This is why in this study, we evaluated the effectiveness of a calcium-phosphate desensitizer, prepared either according to the producer's instructions or mixed with a sterile saline solution, and of sodium fluoride varnish over a six-month period at different time points: before treatment at baseline and at 15 days, 90 days, and 180 days after treatment. A further relevant aspect to be taken into account is that 75 patients were recruited and treated in this trial, which makes it more significant, considering that only one of the 40 randomized trials considered in a recent systematic review[14] involved more than 70 patients,[42] and several studies took into consideration more than two teeth for each patient. In our opinion, such an approach could affect the results of the measurements because of the multiple, repeated painful stimuli exerted on teeth very close to each other. To avoid such a source of bias, only two teeth were selected for each patient, one on the right and one on the left side of the mouth. Furthermore, the split-mouth design allowed us to obtain two samples with the identical distribution of potential effect modifiers and confounders, so these aspects were not considered in the statistical analysis.

Thus far, no single method of measuring DH can be regarded as the ideal standard,[24] and this is the reason why, in this study, two assessment methods were used, namely the VAS scale, a purely subjective pain rating scale that is widely accepted and verified in pain evaluation,[48,49] and the Shiff scale, which gives a more objective evaluation of experimentally induced pain based on the observation of the patients' behaviour by the investigator. The VAS scale alone is beyond doubt the most used in clinical trials on DH,[14] but a combination of both scales has already been used in similar studies.[12]

Even if the use of more than one type of stimulus has been advocated for studies aimed at evaluating desensitizing agents,[24] in this study, a single stimulus was used. Even if tactile evaluation could be more accurate when controlled force is used,[12] the assessment based on air stimulus is more realistic, as it mainly relies on the patient's perception of pain.[50] Furthermore, Chabanski et al. found no difference in the ability of tactile and evaporative stimuli to induce DH.[51] However, the use of a single type of experimental stimulus might be reasonably considered as a possible source of bias in this study.

A recent systematic review on DH treatment[14] highlighted that the most effective treatment options for DH have achieved significantly better outcomes than placebos. Based on this finding, no negative control was performed in this study. Instead, a positive control with sodium fluoride varnish was performed.[52] Sodium-fluoride has proven effective in treating DH in all formulations: liquid solution,[41] gel, bio-adhesive gel,[36,44] varnish,[20,35,37,53,54] paste,[55] and when administered via iontophoresis.[56] Based on these data and on the fact that it belongs to the same class of desensitizer agents (the ones leading to chemical occlusion), we chose sodium fluoride varnish as a positive control.

In our study, no differences were found among the three tested desensitizing agents at any time point. Furthermore, all three treatments could progressively reduce the patient's discomfort at each follow-up time point, and the changes in hypersensitivity, measured according both VAS and Shiff scale, were similar among treatments. We can, therefore, conclude that TMD, prepared according to manufacturer's instructions, TMD mixed with a physiological solution, and NaFVa are all effective in treating DH and that their effectiveness lasts, and even improves, over six months. Some authors reported stable results three months after treatment.[53] Nevertheless, such data contradicts previous findings that highlight the reduced effects of the desensitizing agents as time goes by.[20,30,43,57] Our findings could suggest that the investigated agents cause durable changes in the composition of the dentin surface, which lead to precipitation of crystallites, as shown by in-vitro studies, resulting in a stable occlusion of tubules over time. Our observations via SEM confirmed this hypothesis over two weeks. Once again, it must be emphasized that the previous studies were performed exclusively in vitro, whereas our work involves teeth that were previously treated, left exposed to the actual environment of the oral cavity for two weeks and finally extracted and examined. Compared to studies performed exclusively in vitro, such an in-vivo experimental design provides a much more realistic way to evaluate the actual occlusion of tubules two weeks after treatment.

According to the findings of this study, the effectiveness of the TMD powder is just the same, irrespective of whether it is mixed with the liquid solution provided by the manufacturer or with a sterile physiological solution. We believe that the clinical practice may benefit from such information.

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