

A Novel Desensitizer Paste containing Calcium Phosphate: Randomized, Placebo-controlled, Double-blinded and 6 Months Trial

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ABSTRACT

Aim: This study aims to investigate the effect of a calcium phosphate-based desensitizer paste on reduction of dentin hypersensitivity (DH).

Materials and methods: This crossover study was designed as randomized, double-blinded, and placebo-controlled trial. Teethmate AP paste (TAP), containing tetracalcium phosphate (TTCP) and dicalcium phosphate anhydrous (DCPA) dispersed in a glycerol/polyethylene glycol paste, was compared with placebo (PLA), a calcium phosphate-free analog paste. A total of 45 patients with one hypersensitive cervical lesion in each of two contralateral quadrants were allocated to the trial when baseline sensitivity (pretreatment sensitivity score, PRE) on air-blast (AB) stimulation and probe scratching (PS) measured on a visual analog scale (VAS; 0–10) was ≥ 6 . Patients were recalled after 1 day, 1 week, and 1, 3, and 6 months. One-way analysis of variance (ANOVA), Tukey's *post hoc* test, and pairwise comparisons between TAP and PLA were conducted at all time points ($\alpha < 0.05$).

Results: Both treatments reduced DH significantly during the 6-month course. Immediately after treatment (posttreatment sensitivity score, POST), TAP sensitivity on AB was reduced to 63%, after 6 months to 39% of the PRE score, and PS to 60 and 54% respectively. Application of PLA reduced AB sensitivity at POST and 6 months to 79 and 60%, and on PS stimulation to 79 and 67% respectively. At all time points, TAP and PLA were significantly different ($p < 0.05$).

Conclusion: Teethmate AP paste is a biocompatible and effective desensitizing agent when used for the treatment of moderately severe DH.

Clinical significance: Calcium phosphate-based desensitizers are one of the most effective desensitizing agents and are expected to play an important role in the treatment of DH.

Keywords: Calcium phosphate, Clinical trial, Desensitization, Placebo, Teethmate desensitizer.

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INTRODUCTION

The Canadian Advisory Board defined DH as "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."¹ Hypersensitive dentin is mostly diagnosed at the buccal surfaces of teeth, where enamel is missing due to erosion, abrasion, and attrition or at denuded root surfaces in gingival recession.^{2,3} Only when exposed dental tubuli are patent at both ends can hypersensitivity occur. Brännström's hydrodynamic theory^{4,5} suggests that external stimuli, mostly thermal, evaporative, or osmotic, lead to inward or outward fluid shifts in the dentinal tubules triggering pain due to stimulation of A- δ fibers around odontoblasts. Consequently, most treatments of DH rely on total or partial sealing of the orally open tubuli.⁶ None of the many products available in the market with different mechanisms of action, such as poorly soluble salts, protein precipitation agents, coats with polymerizable materials comply fully with the expectations of long-term elimination of dentin sensitivity.⁷ Treatment of hypersensitive dentin by calcium phosphate precipitation on serial application of sodium phosphate and calcium chloride solutions was already published more than 20 years ago.^{8,9} A few years later, Japanese researchers described the occlusion of dentinal tubules using a different calcium phosphate precipitation method, namely, application of an acidic calcium and phosphate-containing solution followed by neutralization with a basic solution.¹⁰

Similarly, an *in vitro* study on reduction of dentin permeability using a slurry of DCPA and calcium hydroxide in sodium fluoride and carboxymethyl cellulose solution

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proved that fluoride-containing hydroxyapatite was precipitated on dentin, partly obturating dentin tubules, and thus reducing the hydraulic conductance of dentin.¹¹ Recently, calcium phosphate-containing desensitizers, a spin-off from calcium phosphate cements,¹² were commercialized as powder-liquid mixture and as a paste compound. These have gained considerable professional interest, not least due to their high biocompatibility.¹³ Main components are TTCP ($\text{Ca}_4[\text{PO}_4]_2\text{O}$) and DCPA (CaHPO_4) that are eventually transformed in aqueous environment to hydroxyapatite (HA: $\text{Ca}_{10}[\text{PO}_4]_6[\text{OH}]_2$)¹² which is the principal mineral in enamel and dentin. Phase transformation by dissolution-precipitation is the basic reaction mechanism. In aqueous environment, TTCP and DCPA dissolve and supply Ca_2^+ and PO_4^{3-} .¹⁴ Since this solution is supersaturated with respect to apatite, the less-soluble compound HA is precipitated.

Furthermore, due to supersaturation of human saliva with calcium phosphate salts, continuously new HA crystals are precipitated.¹⁵⁻¹⁷ When such phosphate-containing formulations are applied as dentin desensitizers, several *in vitro* studies¹⁸⁻²⁰ have proven their efficacy in partially occluding dentinal tubules. So far, there are only two clinical reports published in international literature that underline the potential of these compounds as reasonably effective desensitizing agents.^{21,22} In a previous study, the paste product (TAP; Kuraray Noritake, Dental Inc., Okayama, Japan) was applied for 30 seconds with a rotating rubber cup at 1,000 rpm according to the primary instructions of the manufacturer and compared with distilled water as placebo, applied with a micro-brush.²² In this study, a possible overlying burnishing effect on dentin, caused by the rubber cup application, might have confounded the effect of the calcium phosphate compound's desensitizing action. In the meantime, the modified final manufacturer instructions claim two consecutive 20-second applications with a rubber cup at 500 rpm.

Therefore, following the final manufacturer application instructions, the aim of the present clinical trial was to evaluate the effect of TAP on reduction of DH in a randomized controlled trial compared with an analog placebo paste devoid of the active TAP ingredients.

The null hypothesis was that there was no difference in sensitivity reduction after TAP and placebo paste application respectively.

MATERIALS AND METHODS

Study Design

This trial was designed as a randomized, placebo-controlled, double-masked, and split-mouth study, to evaluate the effects of TAP paste (Kuraray Noritake, Dental

Inc., Okayama, Japan. Batch #: 140829; expiry: 2016-01) compared with placebo gel (PLA; provided by Kuraray Noritake. Batch #: 3P0001; expiry: 2016-07) on desensitization of noncarious buccal cervical lesions of teeth.

The guidelines for the design and conduct of clinical trials on DH were followed during planning and execution of the study.²² Approval for this clinical investigation was obtained from the Ethics Committee of the local University Review Board (KLE Society's Institute of Dental Sciences; Approval: EC/KLESDC-065, 16/10/2014). The study was conducted in agreement with the principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2008). All patients allocated to this trial signed an informed consent form after receiving thorough verbal and written information regarding possible benefits and risks of the treatments. Patients were informed that one of the compounds to be tested is a placebo.

Materials

The TAP paste is a desensitizer compound for topical application on hypersensitive dentin. The paste components are TTCP, DCPA, and NaF (sodium fluoride) in glycerol and polyethylene glycol and a thickener. Placebo is an analog paste omitting the active components of TAP.

Methods

Patients for this study were recruited from the Department of Conservative Dentistry and Endodontics, KLE Institute of Dental Sciences, Bengaluru, India. The main inclusion criterion was the presence of one hypersensitive tooth with a sensitive buccal cervical dentin site in each of two contralateral quadrants in the upper or lower jaw responding with score ≥ 6 on a 10 cm long VAS.

Two proficient dentists screened 72 patients with exposed dentin due to gingival retraction, self-reporting cervical sensitivity on cold stimuli, and/or mechanical irritation experienced during toothbrushing for eligibility to this trial.

Exclusion criteria were systemic diseases, pulpitis, carious lesions, defective restorations, cracked enamel, active periodontal disease, medication with analgesic drugs, pregnant or lactating women, and professional desensitizing treatment received during the preceding 3 months.

Pretreatment sensitivity scores in response to the following two stimuli were determined from possible candidates. First, DH was assessed using a cold AB stimulus (2-second AB, approximately 40 psi, from a dental syringe directed perpendicular to the lesion surface at 0.5 cm distance) shielding neighboring teeth with cotton rolls.

Patients were asked to point on the VAS scale (no pain = 0, worst pain = 10 cm) to the nearest full centimeter number describing their pain perception. A tactile stimulus was applied 5 minutes later, running a sharp dental explorer across the cervical area of the teeth in horizontal and vertical directions at a relatively mild probing force PS, and the patients were asked again to describe the VAS pain score experienced. Finally, 45 patients with one sensitive tooth in each of two quadrants, responding to both stimuli with VAS score ≥ 6 and fulfilling the criteria mentioned earlier, were allocated to the trial (PRE). Treatment of the selected tooth in each of the two quadrants was assigned by a randomization list produced on Research Randomizer Calculator (www.socialpsychology.org/randomizer.htm). Then, the operator cleaned the respective tooth with a wet cotton pellet and applied TAP or PLA using a soft rubber cup filled with the respective paste rotating at 500 rpm twice for 20 seconds each. Excess paste was rinsed off with water. Within 15 minutes after the treatment, the blinded investigator (DM) applied the same stimuli as above and registered the POST on a blank evaluation sheet, indicating the patient's number and the treated teeth only. All patients were recalled to the investigator for blinded sensitivity assessment after 1 day, 1 week, and 1, 3, and 6 months.

Sample size estimation was based on findings from a previous study²¹ that showed a minimum significant difference of 1 in VAS. With a total of 45 patients entering this crossover repeated measures, the probability is 80% that the study will detect a treatment difference at a two-sided 0.05 significance level if the true difference in VAS scores between the treatments is 0.5, assuming that within-patient standard deviation of the response is 0.7. Statistical data were analyzed by one-way ANOVA,

followed by Tukey's multiple comparisons and two-tailed paired t-test. The level of statistical significance was set as $\alpha \leq 0.05$ (IBM Statistical Package for the Social Sciences Statistics, version 21 for Macintosh).

RESULTS

All 45 patients allocated (30 females, 15 males) completed the 6-month trial. No adverse reactions were reported.

Table 1 summarizes the number of patients treated by age group and gender. Average age of the patients was 35.5, with a range of 27 to 45 years. From the 90 teeth treated, 14 were canines, 70 premolars, and 6 were molars.

Graph 1 shows the mean sensitivity scores and standard deviations on AB stimulation after application of TAP and PLA respectively, at baseline (PRE) and at the five recall time points.

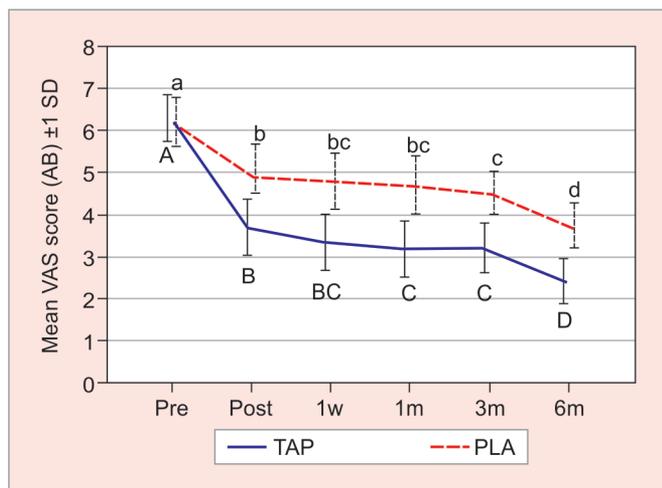
Immediate reduction from baseline sensitivity (POST) was 37% for TAP and 21% for PLA, and at the final 6-month recall, it was 61 and 40% respectively. Apart from the PRE pain scores, at all other time points, the scores for TAP and PLA were significantly different ($p < 0.05$).

According to one-way ANOVA ($p < 0.001$) and Tukey's *post hoc* test, the different upper- and lower-case letters in the graph denote time points that are significantly different ($p < 0.05$).

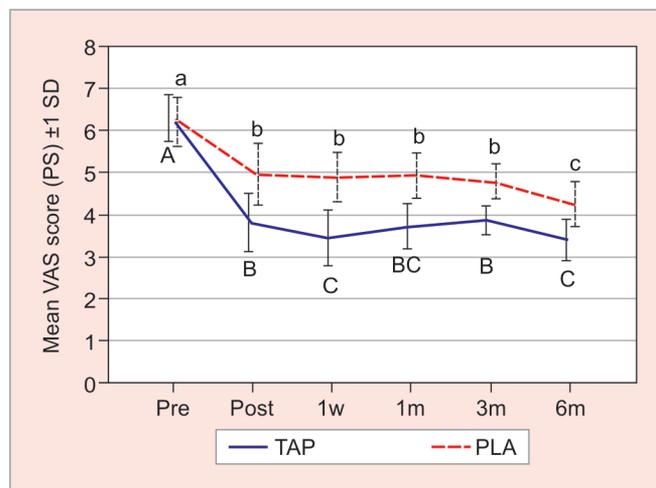
Similarly, Graph 2 displays the mean VAS scores recorded on PS. Percentage decrease in scores from PRE

Table 1: Number of patients treated by age group (in years) and gender

Gender	21-30	31-40	41-50
Female	2	23	5
Male	4	10	1
Total	6	33	6



Graph 1: Visual analog scale pain scores and standard deviations after stimulation with AB. Different lower and upper case letters denote significantly different time point groups for TAP and PLA respectively ($p < 0.05$). PRE groups were not significantly different, whereas all other group comparisons between TAP and PLA were different ($p < 0.05$)



Graph 2: Visual analog scale pain scores and standard deviations after stimulation with PS. Different lower and upper case letters denote significantly different time point groups for TAP and PLA respectively ($p < 0.05$). PRE groups were not significantly different, whereas all other group comparisons between TAP and PLA were different ($p < 0.05$)



sensitivity at POST and 6 months were 40 and 46% for TAP, and 21 and 33% for PLA. When separately analyzed with one-way ANOVA ($p < 0.001$) and Tukey's tests (upper- and lower-case letters) both treatments resulted in moderate reductions in sensitivity between POST and at 6-month recalls.

At all recalls, TAP scores were significantly smaller than PLA scores ($p < 0.05$).

DISCUSSION

The null hypothesis that there was no difference in sensitivity reduction after TAP and PLA paste application must be rejected.

During the course of the study, TAP resulted in significantly lower pain scores than PLA at all time points. When compared with the data of a previous clinical trial, where TAP was applied with a rotating rubber cup once for 30 seconds and placebo which was distilled water was applied to the sensitive lesions for 30 seconds with a soaked microbrush, both showed striking similarity with the current results.^{22,23} The same operators and investigators as in this trial performed the previous trial at the same institution. Therefore, it may be concluded that the different modes of rubber cup application have a minor effect, if any, on desensitization obtained with TAP throughout the 6 months observation period.

Furthermore, comparison of the results obtained after placebo application, 30 seconds application of distilled water with a soaked microbrush, or twice 20 seconds application of the placebo paste in a rotating rubber cup was very similar.

After 6 months, the sensitivity on AB stimulation was reduced to 61% in the present and 54% in the previous trial. Thus, application of the paste with a rubber cup has apparently no major confounding effect on sensitivity that might hypothetically be caused by burnishing of the exposed dentin surface.

Application of TAP with a rotating rubber cup is, however, considered reasonable since the TTCP and DCPA particles dispersed in the carrier paste should be pushed or pressed into the open dentinal tubules for initial partial obturation. Then, as soon as the glycerol/polyethylene glycol paste is rinsed off, the two calcium orthophosphate species are exposed to an aqueous environment, dentinal liquid from the one and saliva from the other aspect. Calcium and phosphate ions are dissolved, leading to oversaturation relative to less-soluble calcium phosphates, metastable intermediate precursor phases, and hydroxyapatite that are precipitated at nucleation sites, either neighboring apatite crystals from solid dentin or other inorganic and organic molecules.^{12,24,25} The driving force for these reactions is the relative solubilities of the reactants and the resulting crystal products. Precipitation

of precursor or apatite crystals decreases the concentration of Ca_2^+ and PO_4^{3-} , thus continuously dissolving the starting components TTCP and DCPA, unless the less-soluble phase is directly precipitated on and possibly overgrowing the primary calcium phosphate species.¹⁴ This reaction presumably leads to further obturation of the tubular entrances, a decrease in tubular liquid shifts on stimulation, and thus decreasing sensitivity by time as demonstrated in this study. It was not surprising that even placebo application resulted in significant decrease of sensitivity, as has been shown in previous investigations.^{22,23,26,27}

Pain is a subjective phenomenon depending on emotional components. Natural remineralization processes from saliva in the mouth may also be responsible for spontaneous regression of the symptomatology. The balanced crossover design with repeated measures selected for this study seems to be the most appropriate model because each individual subject serves as his or her own control. Thus, the influence of confounding covariates is much reduced. Pain studies use changes in numerical value of VAS scores or score changes in percentage between pre and post medication as measures of success. It is, however, difficult to define at which percentage score reduction a treatment should be considered successful. It seems to be preferable to acknowledge the patient's perception as the deciding criterion for success. None among the 45 subjects in the present study asked for an alternative treatment, as warranted according to the patient consent form, if the patient requests. It should be kept in mind that the patients allocated to this trial were aware that one of the pastes administered was placebo. This might indicate that the subject's threshold for treatment acceptability is around 40% or even less in pain reduction relative to the moderate VAS pain score of around 6 at PRE, achieved with the placebo treatment.

In summary, it is concluded that topical treatment of moderate cervical dentin sensitivity with the calcium phosphate containing TAP paste is effective, meeting the patients' expectations and satisfaction. In particular, the high biocompatibility of this desensitizing agent and the suggested biomimetic mineralization process of exposed dentin are valuable features.

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REFERENCES

1. Canadian Advisory Board on Dentin Hypersensitivity. Consensus-based recommendations for the diagnosis and management of dentin hypersensitivity. *J Can Dent Assoc* 2003 Apr;69(4):221-226.

2. Absi EG, Addy M, Adams D. Dentine hypersensitivity. A study of the patency of dentinal tubules in sensitive and non-sensitive cervical dentine. *J Clin Periodontol* 1987 May;14(5):280-284.
3. Addy M, Pearce N. Aetiological, predisposing and environmental factors in dentine hypersensitivity. *Arch Oral Biol* 1994;39(Suppl):33S-38S.
4. Brännström, M. A hydrodynamic mechanism in the transmission of pain produced stimuli through the dentin. In: Anderson DJ, editor. *Sensory mechanisms in dentin*. Oxford: Pergamon Press; 1963. pp. 73-79.
5. Brännström M, Lindén LA, Aström A. The hydrodynamics of the dental tubule and of pulp fluid. A discussion of its significance in relation to dentinal sensitivity. *Caries Res* 1967;1(4):310-317.
6. Porto IC, Andrade AK, Montes MA. Diagnosis and treatment of dentinal hypersensitivity. *J Oral Sci* 2009 Sep;51(3):323-332.
7. Cunha-Cruz J, Wataha JC, Zhou L, Manning W, Trantow M, Bettendorf MM, Heaton LJ, Berg J. Treating dentin hypersensitivity: therapeutic choices made by dentists of the northwest PRECEDENT network. *J Am Dent Assoc* 2010 Sep;141(9):1097-1105.
8. Imai Y, Akimoto T. New method of treatment for dentin hypersensitivity by precipitation of calcium phosphate *in situ*. *Dent Mater J* 1990 Dec;9(2):167-172.
9. Imai Y, Ikemura R. Bond strength of resin to dentin treated with calcium phosphate desensitizer. *Clin Mater* 1993;12(2):107-111.
10. Ishikawa K, Suge T, Yoshiyama M, Kawasaki A, Asaoka K, Ebisu S. Occlusion of dentinal tubules with calcium phosphate using acidic calcium phosphate solution followed by neutralization. *J Dent Res* 1994 Jun;73(6):1197-1204.
11. Cherng AM, Takagi S, Chow L. Reduction in dentin permeability using a slurry containing dicalcium phosphate and calcium hydroxide. *J Biomed Mater Res B Appl Biomater* 2006 Aug;78(2):291-295.
12. Chow LC. Next generation calcium phosphate-based biomaterials. *Dent Mater J* 2009 Jan;28(1):1-10.
13. Dorozhkin SV. Calcium orthophosphates in dentistry. *J Mater Sci Mater Med* 2013 Jun;24(6):1335-1363.
14. Ishikawa K. Bone substitute fabrication based on dissolution-precipitation reactions. *Materials* 2010 Feb;3(2):1138-1155.
15. Ishikawa K, Eanes ED, Tung MS. The effect of super saturation on apatite crystal formation in aqueous solutions at physiologic pH and temperature. *J Dent Res* 1994 Aug;73(8):1462-1469.
16. Suge T, Ishikawa K, Kawasaki A, Yoshiyama M, Asaoka K, Ebisu S. Duration of dentinal tubule occlusion formed by calcium phosphate precipitation method: *in vitro* evaluation using synthetic saliva. *J Dent Res* 1995 Oct;74(10):1709-1714.
17. Larsen MJ, Pearce EI. Saturation of human saliva with respect to calcium salts. *Arch Oral Biol* 2003 Apr;48(4):317-322.
18. Endo H, Kawamoto R, Takahashi F, Takenaka H, Yoshida F, Nojiri K, Takamizawa T, Miyazaki M. Evaluation of a calcium phosphate desensitizer using an ultrasonic device. *Dent Mater J* 2013 Jun;32(3):456-461.
19. Thanatvarakorn O, Nakashima S, Sadr A, Prasansuttiporn T, Thitthaweerat S, Tagami J. Effect of a calcium-phosphate based desensitizer on dentin surface characteristics. *Dent Mater J* 2013 Aug;32(4):615-621.
20. Thanatvarakorn O, Nakashima S, Sadr A, Prasansuttiporn T, Ikeda M, Tagami J. *In vitro* evaluation of dentinal hydraulic conductance and tubule sealing by a novel calcium-phosphate desensitizer. *J Biomed Mater Res B Appl Biomater* 2013 Feb;101(2):303-309.
21. Mehta D, Gowda VS, Santosh A, Finger WJ, Sasaki K. Randomized controlled clinical trial on the efficacy of dentin desensitizing agents. *Acta Odontol Scand* 2014 Nov;72(8):936-941.
22. Mehta D, Gowda V, Finger WJ, Sasaki K. Randomized, placebo-controlled study of the efficacy of a calcium phosphate containing paste on dentin hypersensitivity. *Dent Mater* 2015 Nov;31(11):1298-1303.
23. Holland GR, Narhi MN, Addy M, Gangarosa L, Orchardson R. Guidelines for the design and conduct of clinical trials on dentine hypersensitivity. *J Clin Periodontol* 1997 Nov;24(11):808-813.
24. Wang LJ, Nancollas GH. Calcium orthophosphates: crystallization and dissolution. *Chem Rev* 2008 Nov;108(11):4628-4669.
25. Wang LJ, Lu JW, Xu FS, Zhang FS. Dynamics of crystallization and dissolution of calcium orthophosphates at the near-molecular level. *Chin Sci Bull* 2011 Mar;56(8):713-721.
26. Addy M, West NX, Barlow A, Smith S. Dentine hypersensitivity: is there both stimulus and placebo responses in clinical trials? *Int J Dent Hyg* 2007 Feb;5(1):53-59.
27. Kienle GS, Kiene H. The powerful placebo effect: fact or fiction? *J Clin Epidemiol* 1997 Dec;50(12):1311-1318.