

RESEARCH

Open Access



Desensitizing toothpastes for dentin sealing and tertiary dentin formation in vitro and in vivo: a comparative analysis

Juhyun Lee^{1†}, Geumbit Hwang^{1†}, Hyeri Gug², Ji-Hyun Lee², Su-Jin Park² and Joo-Cheol Park^{1*}

Abstract

Background: Dentin hypersensitivity is a painful response to external stimuli applied to exposed dentinal tubules. Various toothpastes with active desensitizing ingredients for the relief of dentin hypersensitivity are commercially available. However, data from several studies suggest that the effects of desensitizing toothpastes are unstable and brief. This study aimed to investigate the effect of toothpastes containing CPNE7-derived oligopeptide (CPNE7-DP) and other active desensitizing ingredients in the dentin microleakage, tubule occlusion and tertiary dentin formation.

Methods: Using scanning electron microscopy (SEM), we evaluated the patency of dentinal tubules on the surface of human dentin disks after brushing experiments with the various toothpastes. Dentin was histologically evaluated in a hypersensitivity model of canine teeth, after the exposed dentin area was brushed for 6 weeks. The toothpaste used in group 1 (control) did not contain any desensitizing ingredients; that used in group 2 contained CPNE7-DP; Colgate Sensitive was used in group 3; and Sensodyne Rapid Relief was used in group 4. Finally, we conducted microleakage analysis to investigate the dentin sealing effect. The microleakage analysis data were subjected to one-way ANOVA and post-hoc Tukey tests ($\alpha = 0.05$).

Results: In the SEM images, all four groups of teeth exhibited partial occlusion of the dentinal tubules on the tooth surface. In the in vivo hypersensitivity model, group 2 exhibited a newly formed tertiary dentin, whereas no new hard tissue formation was observed in groups 1, 3, and 4. Microleakage analysis revealed that the volume of dentinal fluid flow was significantly smaller in group 2 than in group 1.

Conclusions: These results indicate that CPNE7-DP is a promising active ingredient with long-term dentin sealing effects.

Keywords: Dentin hypersensitivity, Desensitizing toothpaste, CPNE7-DP, Dentin sealing, Tertiary dentin

Background

Dentin hypersensitivity is a prevalent problem in dental practice and affects approximately 25% of the adult population [1, 2]. It is described as brief but sharp pain that arises from exposed dentin in response to external stimuli and that cannot be attributed to any other form of dental disease or defect [3]. Among the explanations for these painful response, the hydrodynamic theory is generally accepted [4]. According to this theory, the cause of dentin hypersensitivity is the increased fluid movement

[†]Juhyun Lee and Geumbit Hwang contributed equally to this work and share first authorship.

*Correspondence: jcapark@snu.ac.kr

¹ Department of Oral Histology-Developmental Biology & Dental Research Institute, Laboratory for the Study of Regenerative Dental Medicine, School of Dentistry, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea

Full list of author information is available at the end of the article



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

within open dentinal tubules [5]. The painful symptoms of dentin hypersensitivity can be reduced by dentinal tubule occlusion [5, 6].

Desensitizing toothpaste—a dental product used at home—is the first choice for dentin hypersensitivity owing to its convenience, low cost, and noninvasiveness [7, 8]. Various desensitizing toothpastes are commercially available. These toothpastes exert their effect by blocking pulpal nerve responses or occluding dentinal tubules [9]. Toothpastes for blocking pulpal nerve response contain potassium salts; however, the efficacy of potassium salts is controversial [9, 10]. The majority of desensitizing toothpastes work by occluding dentinal tubules and contain several active ingredients, including calcium carbonate, arginine, and strontium acetate [9, 11]. Previous studies have demonstrated that these active ingredients act as desensitizing agents by reducing pain [12–16]. Although tubule occlusion was observed in several studies, it was superficial and not resistant to acid challenges and saliva immersion [17, 18]. Therefore, desensitizing agents with long-term tubule-occluding effects must be developed using appropriate assessment methods.

The copine family comprises ubiquitous calcium-dependent, phospholipid-binding proteins that are highly conserved across several species [19]. One copine, CPNE7, reactivates odontoblasts and promotes the formation of physiological dentin [20] and reacts with calcium ion in dentinal fluid owing to its high calcium ion-binding affinity [21]. In a dentin hypersensitivity model, CPNE7 induced biological dentin sealing, and the effect was permanent rather than transient [22]. Subsequently, Lee et al. synthesized CPNE7-derived oligopeptide (CPNE7-DP), which, as recombinant CPNE7 protein, also induced dentinal tubule occlusion [23].

Therefore, this study aimed to evaluate the effect of CPNE7-DP-containing toothpaste and two commercial desensitizing toothpastes on dentinal tubule occlusion and sealing. Tubule occlusion on the dentin surface was evaluated via scanning electron microscopy (SEM). To investigate the long-term dentin sealing effect in clinical situations, tertiary dentin formation was analyzed in an *in vivo* hypersensitivity model after the teeth were brushed with the toothpastes. Dentin permeability and sealing were measured using a microleakage measuring device.

Methods

Human dentin preparation

The experimental protocol for this study was approved by the Institutional Review Board in Seoul National University Dental Hospital, Seoul, Korea (S-D20140007). The experiments involving extracted human teeth were performed in accordance with the Declaration of

Helsinki. Informed written consent was obtained from each participant prior to the experiments. Five extracted human molars were obtained from Seoul National University Dental Hospital, stored in phosphate-buffered saline (PBS) at 4°C before use, and then sectioned mid-coronally into 1-mm-thick dentin disks. Each disk was sectioned into four fan-shaped pieces by a low-speed diamond wheel saw (Model 650; South Bay Technology Inc., San Clemente, CA, USA) under constant water cooling. The pieces were rinsed with PBS twice for 5 min each and immersed in 0.5-M ethylenediaminetetraacetic acid (EDTA) solution for 5 min to remove inorganic debris. The processed pieces were then washed again with PBS twice for 5 min each. To remove the smear layer and fully open the dentinal tubules, the pieces were etched with 32% phosphoric acid for 5 min and sonicated by an ultrasonic processor (VCX-750; Sonics & Materials, Inc., Newtown, CT, USA) six times for 5 min each. The pieces were washed with 1X PBS three times for 5 min each and then stored in artificial saliva. The artificial saliva consisted of 0.7-mM CaCl₂, 30-mM KCl, 0.2-mM MgCl₂·6H₂O, 4.0-mM NaH₂PO₄, 0.3-mM NaN₃, and 20-mM HEPES buffer [24].

In vitro treatment of human teeth

From the five human teeth, 20 dentin disks were randomly divided into five groups ($n=4$). The disks in the negative control group were kept in artificial saliva and were not brushed at all. The disks in the other four groups were brushed with different toothpastes: group 1 (control), with toothpaste not containing any desensitizing ingredients; group 2, with toothpaste containing CPNE7-DP (HysensBio Co., Ltd., Gwacheon, Korea); group 3, with Colgate Sensitive Complete Protection Toothpaste (Colgate-Palmolive Company, New York, NY, USA); and group 4, with Sensodyne Rapid Relief (GlaxoSmithKline, Brentford, UK). The toothpastes had different active ingredients, which are summarized in Table 1.

Each group was divided into two subgroups characterized by the duration of toothpaste application (2 weeks or 4 weeks); each subgroup comprised two dentin disks. The toothpastes were applied to the disks with microbrushes (M6500-F Micro Applicator; TPC Advanced Technology Inc., City of Industry, CA, USA), and each disk was manually brushed for 1 min twice a day for 2 or 4 weeks. After each brushing session, the disks were washed with distilled water and immersed in artificial saliva until the next brushing session.

Preparation of experimental toothpastes

The toothpastes of Group 1 (Control) and Group 2 (CPNE7-DP-containing toothpaste) were manufactured in the lab, excluding the two commercial toothpastes. The

Table 1 Summary of the experimental groups

Group	Product name	Active ingredient	Company
1	Control (non-desensitizing ingredients)	–	
2	CPNE7-DP-containing toothpaste	CPNE7-DP	HysensBio Co.
3	Colgate Sensitive Complete Protection Toothpaste	Calcium carbonate, arginine	Colgate-Palmolive Company
4	Sensodyne Rapid Relief	Strontium acetate	GlaxoSmithKline

CPNE7-DP CPNE7-derived peptide

toothpaste of Group 2 was the addition of CPNE7-DP to the toothpaste of Group 1, and all other components are the same. CPNE7-DP was synthesized as mentioned in the previous study [23]. For experimental toothpaste production, first, purified water and D-sorbitol solution were mixed. Second, Tricalcium phosphate, aminocaproic acid, allantoin, hydrous silicic acid, sodium PCA solution, hydroxyapatite, CPNE7-DP (Group 2 only), enzyme-treated stevia, and xylitol were added and stirred in a stirrer for about 40 minutes. Third, (concentrated) glycerin and xanthan gum were added and stirred for about 40 minutes. Fourth, (concentrated) Glycerin, Carboxymethyl Cellulose Sodium Salt (CMC) were added and stirred for about 40 minutes. Stirring conditions from steps 2 to 4 were as follows; PADDLE 10-30 rpm, DISPERSE 500-600 rpm, HOMO 2400-3200 rpm. Fifth, sodium cocoylmethyltaurate were added and stirred for about 20 minutes. Finally, the Flavoring agents were added and stirred for about 15 minutes. The stirring conditions for steps 5 and 6 were PADDLE 10-30 rpm, DISPERSE 450-650 rpm. Each step is stirred under reduced pressure conditions (-760 mmHg). The detailed ingredients and contents of toothpaste are recorded in supplementary Table 1.

SEM analysis

The disks brushed with toothpaste were fixed in 0.1 M of cacodylate buffer (pH 7.4) containing 2.5% glutaraldehyde for 30 min and in 0.1 M of cacodylate buffer containing 1% osmium tetroxide for 1 h. The disks were dehydrated in graded acetone and then critical point dried. Each sample was sputter-coated with a thin layer of gold and observed under the scanning electron microscope (S-4700; Hitachi, Ltd., Tokyo, Japan) at an accelerating voltage of 10 kV.

In vivo dentin hypersensitivity model with canine teeth

All experiments involving animals followed the protocols approved by the Ethics and Institutional Animal Care and Use Committee of Seoul National University (SNU-180416-2-1 and SNU-171020-5-2). This study also conformed to the Animal Research: Reporting In Vivo

Experiments (ARRIVE) guidelines for preclinical animal studies. Four beagles (aged between 1 and 2 years) were obtained from the Experimental Animal Center of College of Dentistry and Use Committee of Seoul National University and used for the in vivo dentin hypersensitivity model. Each group consisted of 1 beagle dog with 10 premolars (2 maxillary premolars and 3 mandibular premolars on each side). Before the preparation of the cervical area on the buccal side, all the calculus was removed. For disinfection before dentin exposure, the tooth surfaces were swabbed with cotton balls soaked in 0.5% chlorhexidine. To mimic class V cervical lesions in human patients with dentin hypersensitivity, a high-speed handpiece was used to create modified class V – like cavities on the buccal surfaces of the teeth. The depth of the cavities was half the diameter of the high-speed round bur (Carbide Bur FG Round #4, FG4-014; Komet Dental, Lemgo, Germany). The smear layer was removed with 17% EDTA for 2 min. All defects were exposed during the tooth brushing period. All toothpastes were applied using the Bass brushing method, 1.5 min for each quadrant, once daily for 6 weeks. The samples were obtained after vital perfusion with the Karnovsky solution.

Histological analysis

The premolars ($n=5$) were extracted, fixed in 4% paraformaldehyde, decalcified in 30% formic acid, and embedded in paraffin. The samples were coronally divided, perpendicular to the cavity, into 5- μ m-thick sections. The sections were stained with hematoxylin and eosin and observed under an optical microscope (Axiolab 5; ZEISS Microscopy, Jena, Germany).

Microleakage analysis

To evaluate the microleakage of dentinal fluid from the cervical lesions, the apical 3 mm of single roots was eliminated ($n=5$). A high-speed carbide bur (FG#330; SS White Dental, Seoul, Korea) was used to prepare each root end for a 2-mm depth along the root canal, and a 0.9-mm metal tube was inserted into the canal. To insert the metal tubes, we used 37% phosphoric acid (Any-EtchTM; Mediclus Co., Ltd., Cheongju, Korea), adhesive

agent (3M™ Single Bond Universal Adhesive; 3M ESPE, St. Paul, MN, USA), and flowable composite resin (3M™ Filtek™ Supreme Ultra Flowable Restorative; 3M, Alexandria, MN, USA). The whole surfaces of the teeth were coated with nail polish several times, except the defect area. The prepared samples were kept in distilled water until the microleakage test. The microleakage test was conducted as previously described [22]: a machine (nano-Flow; IB Systems, Seoul, Korea) was used to measure the movement of the bubbles (indicating leakage) caused by the flow of distilled water from the tooth apex to the exposed dentin at 70-cm H₂O. All measurements were taken at 40 min after connecting the sample. The 20-min outflow was recorded, excluding the initial 20-min outflow.

Statistical analysis

Statistical analyses were performed using GraphPad Prism software (version 5, GraphPad Software, CA, USA). All values are expressed as the mean ± standard deviation for at least three independent experiments. The normal distribution was confirmed using the Kolmogorov-Smirnov test with Dallal-Wilkinson-Lillie for *p*-value ($\alpha=0.05$). Between-group statistical analyses were performed using the one-way analysis of variance followed by Tukey's multiple comparison test (*p*-value < 0.05). Statistically significant differences between groups were considered at **p* < 0.05, ***p* < 0.01 and ****p* < 0.001.

Results

SEM analysis of dentinal tubule

After the 2- or 4-week protocol of tooth brushing, the surface images of the dentin disks were analyzed via

SEM at 2500x magnification. The negative control disks showed that the smear layer was removed, and dentinal tubules were fully open (Fig. 1A, F); on the contrary, all experimental disks revealed partially occluded dentinal tubules (Fig. 1B–E, G–J). In groups 2 and 3, the disks brushed for 2 weeks exhibited more tubule occlusion than did those in groups 1 and 4 (Fig. 1C, D). Among all experimental groups, the disks brushed for 4 weeks exhibited a slightly heavier deposition on the intertubular dentin and firm occlusion of the dentinal tubules, in comparison with those brushed for 2 weeks. However, we found few other differences in each group between the disks brushed for 2 weeks and those brushed for 4 weeks. These results indicate that toothpastes cause partial occlusion of open dentinal tubules.

Tertiary dentin formation at the dentin–pulp interface

To evaluate long-term dentin sealing effects, we generated an in vivo hypersensitivity model with dogs' teeth. After the exposed dentin area was brushed for 6 weeks, we histologically analyzed the dentin. As presented in Fig. 2, no new mineralized tissue formation was observed in groups 1, 3, and 4. Conversely, group 2 demonstrated newly formed tertiary dentin underneath the tooth defect area; moreover, this newly formed dentin included dentinal tubules. These findings indicate that only the CPNE7-DP-containing toothpaste caused biological tertiary dentin to form, which could result in a long-term dentin sealing effect.

Comparison of permeability and sealing ability

The representative graphs of dentinal fluid flow according to time are presented in Fig. 3. The negative control demonstrated a rapid increase in dentinal fluid flow over time

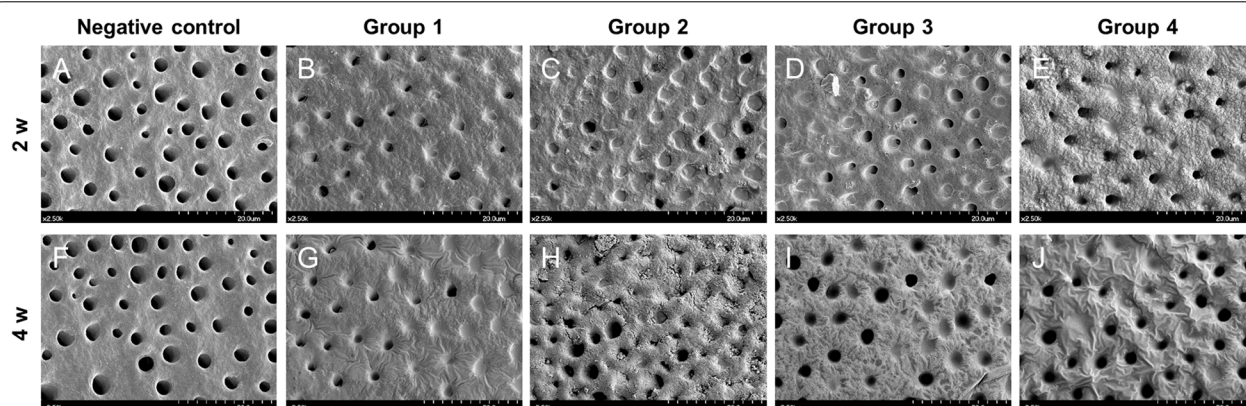


Fig. 1 Scanning electron microscopic images of human dentin disks at 2500x magnification, after brushing for 2 or 4 weeks. The upper row presents the disks after 2 weeks of toothpaste application, and the lower row presents those after 4 weeks of application. In the negative controls (A and F), the dentin surface appeared free of smear layer, and the dentinal tubules were completely open. In the experimental disks (B–E and G–J), partial occlusion of dentinal tubules was observed

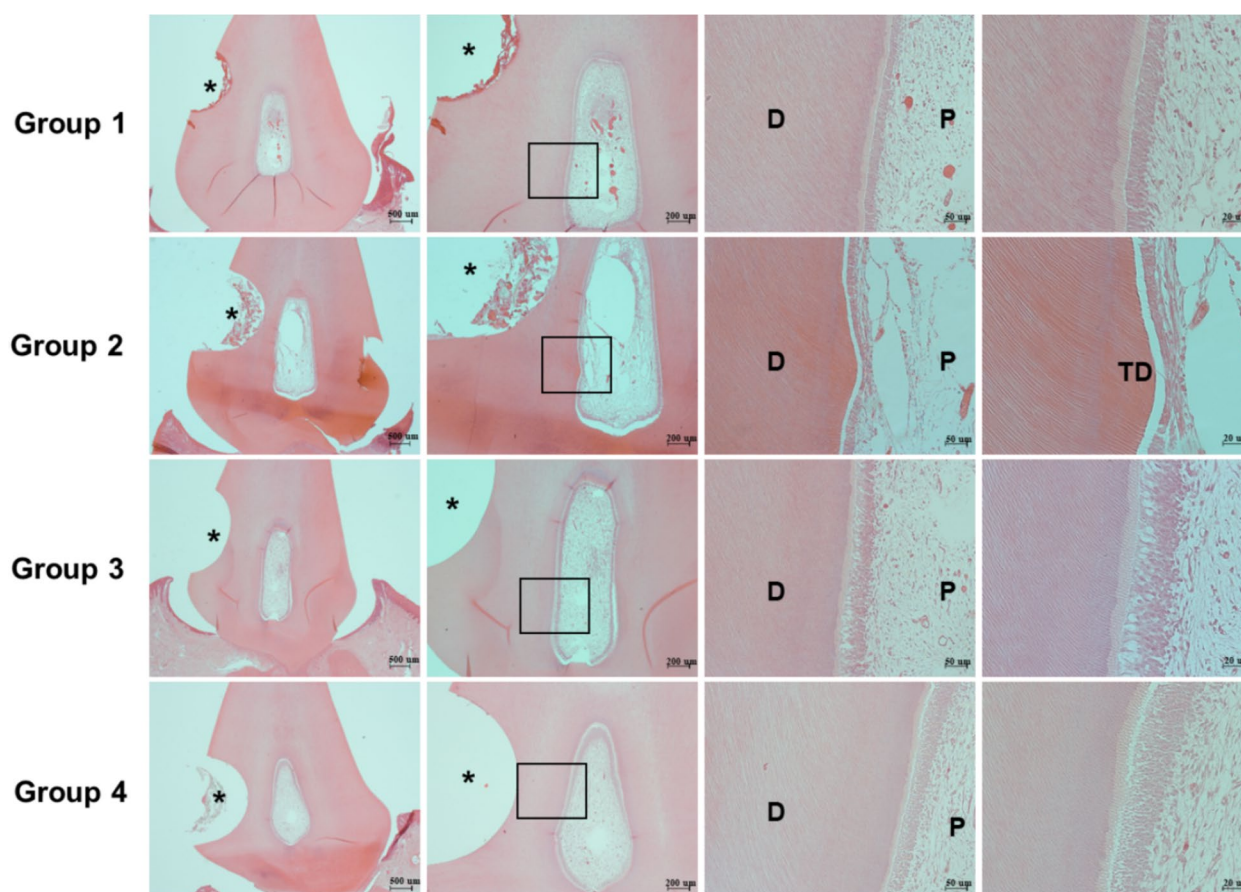


Fig. 2 Histologic analysis after application of various toothpastes in the dentin hypersensitivity model with canine teeth. The toothpastes were applied using the Bass method to all groups of teeth, once daily for 6 weeks. In groups 1, 3, and 4, no histologic changes were observed in the dentin–pulp interface. In contrast, group 2 showed newly formed tertiary dentin. Boxed areas are shown at higher magnification. The asterisk indicates the defect area; D represents dentin; P represents pulp; TD represents newly formed tertiary dentin

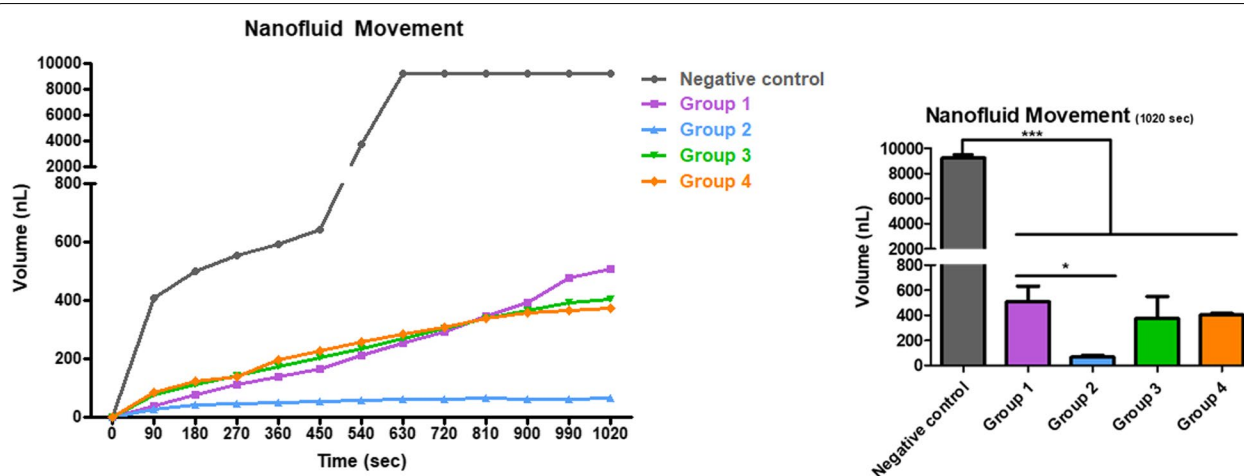


Fig. 3 Representative graphs of dentinal fluid flow after application of various toothpastes. This flow progressively increased in groups 1, 3, and 4; that of group 2 was significantly lower than that of the group 1. (* $p < 0.05$ and *** $p < 0.001$)

because the dentinal tubules were fully open. In groups 1, 3, and 4, the dentinal fluid flow progressively increased because the dentinal tubules were partially occluded. Subsequently, a statistical analysis was performed using the volume of the dentinal fluid flow at 1020 sec. In comparison to the negative control, all groups presented noticeably reduced dentinal fluid flow. The volume of dentinal fluid flow was significantly smaller in group 2 than in group 1, although the dentinal tubules were only partially blocked, according to the SEM images of the dentin surface. On the other hand, the volume of dentinal fluid flow in group 3 and 4 did not differ significantly compared to that of group 1. These results indicate that the CPNE7-DP-containing toothpaste had a better dentin sealing effect than did the toothpaste of group 1.

Discussion

Exposure of dentin caused by gingival recession or tooth abrasion is a major cause of dentin hypersensitivity [25]. When various stimuli (e.g., thermal, tactile, and osmotic) come into contact with exposed dentin, the fluid movement in the dentinal tubules stimulates the pulp nerve and causes a brief but sharp pain [3, 4]. Various desensitizing toothpastes have been developed for the relief of this pain, which can be reduced by dentinal tubule occlusion. Most desensitizing toothpastes contain active ingredients, such as calcium carbonate, arginine, and strontium acetate [9, 26]. The desensitizing effect of these toothpastes has been proven in previous studies; however, the durability of the effect is controversial, inasmuch as it is unstable in the presence of saliva or acid [27, 28].

In this study, we compared the dentin sealing effect of CPNE7-DP-containing toothpaste and two commercially available toothpastes and investigated permanent changes, such as tertiary dentin formation. In the SEM analysis, tubule occlusion was observed in all experimental groups but not in the negative control group; however, not all open dentinal tubules were completely occluded. In addition, we observed a little difference in the tubule occlusion between disks brushed for 2 weeks and those brushed for 4 weeks. Because the SEM images depicted only the tooth surface, SEM may be insufficient for the evaluation of the entire dentin sealing effect. We also measured the dentinal fluid flow by microleakage analysis. The dentinal fluid flow was decreased in groups 1, 3, and 4 in comparison with the negative control, but it was still present. This finding may be attributable to the partial occlusion of dentinal tubules observed in the SEM image, suggesting that the pain is partially reduced but still exists. In group 2, in which the CPNE7-DP-containing toothpaste was used, the dentinal fluid flow was significantly decreased in comparison with group 1 as well as the negative control. Of more importance is that

we observed newly formed tertiary dentin with tubular structure in group 2 of the dogs' teeth but no such change in the other groups.

CPNE7-DP, a synthetic oligopeptide derived from CPNE7 protein, was studied in previous research. Lee et al. demonstrated that CPNE7-DP was noncytotoxic, induced odontoblast differentiation *in vitro*, and induced regeneration of tubular dentin in models with shallow and deep cavities. In addition, they confirmed that peritubular dentin formation was induced by the CPNE7-DP treatment in the model of beagle tooth defects to promote dentinal tubule occlusion, and the volume of the dentinal fluid flow was significantly reduced [23]. These findings—less dentinal fluid flow and newly formed tertiary dentin—were essentially in agreement with the results in group 2 of this study. Therefore, we suggest that the use of toothpaste containing CPNE7-DP can cause permanent changes, such as tertiary dentin formation, which would result in long-term dentin sealing effects.

In the toothpaste used in group 3, calcium carbonate and arginine were active ingredients. The combination of these two substances forms a positive complex with the negatively charged dentin surface, which facilitates tubular occlusion [29]. Other studies have demonstrated that ions of strontium acetate, the active ingredient of the toothpaste used in group 4, were exchanged with calcium ions, which caused the formation of strontium crystals within dentinal tubules; thus, strontium can cause occlusion of dentinal tubules [30–32]. Therefore, we speculate that partial tubule occlusion occurred in groups 3 and 4 as a result of the action of these active ingredients. Several reports have demonstrated that the combination of arginine and calcium carbonate is more effective than strontium acetate in the treatment of dentin hypersensitivity [33–35]. Similarly, we found that microleakage volume was smaller in group 3 than in group 4. In addition, calcium carbonate is able to induce *in vitro* cell differentiation of human dental pulp stem cells into odontoblasts [36], and strontium at specific doses could influence proliferation, odontogenic differentiation, and mineralization of human dental pulp stem cells *in vitro* via the calcium-sensing receptor [37]. Nevertheless, in this study, hard tissue formation was not observed in groups 3 and 4, in which toothpaste containing calcium carbonate and strontium acetate, respectively, was used.

Our results indicate that CPNE7-DP-containing toothpaste can induce tertiary dentin formation to promote a sustained dentin sealing effect and act as a successful desensitizer. In addition, the effect was evaluated in both *in vitro* and *in vivo* assessments. This method of analysis is useful for precise evaluation and understanding of therapeutic agents for dentin hypersensitivity. A limitation of this study is that we did not evaluate the stability

of CPNE7-DP-containing toothpaste in a dietary acid challenge, and this should be evaluated in future studies.

Altogether, our findings have important implications for the use of CPNE7-DP as a novel biological active ingredient in the treatment of dentin hypersensitivity. Ultimately, treatment with CPNE7-DP-containing toothpaste for dentin hypersensitivity may offer a new and fundamental way with a low risk of recurrence and little microleakage. Furthermore, CPNE7-DP has the potential for being used widely in combination with dental materials in clinical practice.

Conclusions

This study demonstrated that CPNE7-DP-containing toothpaste induced not only a reduction in dental fluid flow but also the biological formation of tertiary dentin. The formation of tertiary dentin was not observed with the use of toothpastes containing calcium carbonate, arginine, or strontium acetate. Thus, CPNE7-DP-containing toothpaste could be a promising agent with long-term dentin sealing effects that could help relieve dentin hypersensitivity.

Abbreviations

CPNE7-DP: CPNE7-derived oligopeptide; SEM: Scanning electron microscopy; EDTA: Ethylenediaminetetraacetic acid; PBS: Phosphate-buffered saline.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12903-022-02558-8>.

Additional file 1: Supplementary Table 1. Ingredient and content of experimental toothpastes.

Additional file 2: Supplementary Table 2. Raw data of microleakage analysis.

Acknowledgements

Not applicable.

Authors' contributions

JL contributed to the acquisition of data and wrote the initial framework. GH was a major contributor in writing the manuscript and interpreted the data. HRG and JHL contributed to the acquisition and analysis of data. SJP contributed to the analysis of data. JCP contributed to the study design and supervision of field work project coordination. All authors read and approved the final manuscript.

Funding

This study was supported by the Basic Science Research Program implemented by the Ministry of Science and ICT of South Korea and the National Research Foundation (Grant No. NRF- 2018R1A5A2024418) and a Korea Medical Device Development Fund grant (Project Number: 9991007198, KMDF_PR_20200901_0068-2021-02) funded by the Korean government (the Ministry of Science and ICT; the Ministry of Trade, Industry and Energy; the Ministry of Health & Welfare; and the Ministry of Food and Drug Safety).

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

The experimental protocol with extracted human teeth was approved by the Institutional Review Board of Seoul National University Dental Hospital (S-D20140007). The experiments involving extracted human teeth were performed in accordance with the Declaration of Helsinki. Informed written consent was obtained from each participant prior to the experiments. We confirm that all methods involving animals were performed in accordance with the relevant guideline and regulations below. This study conformed to the Animal Research: Reporting In Vivo Experiments (ARRIVE) guidelines for preclinical animal studies. All experiments involving animals followed the protocols approved by the Ethics and Institutional Animal Care and Use Committee of Seoul National University (SNU-180416-2-1 and SNU-171020-5-2).

Consent for publication

Not applicable.

Competing interests

HRG, JHL, and SJP are employed by HysensBio Co., Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Author details

¹Department of Oral Histology-Developmental Biology & Dental Research Institute, Laboratory for the Study of Regenerative Dental Medicine, School of Dentistry, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea. ²HysensBio, Co., Ltd., 10 Dwitgol-ro, Gwacheon-si, Gyeonggi-do, Republic of Korea.

Received: 16 February 2022 Accepted: 3 November 2022

Published online: 11 November 2022

References

1. Splieth CH, Tachou A. Epidemiology of dentin hypersensitivity. *Clin Oral Investig*. 2013;17(Suppl 1):S3–8.
2. Favaro Zeola L, Soares PV, Cunha-Cruz J. Prevalence of dentin hypersensitivity: systematic review and meta-analysis. *J Dent*. 2019;81:1–6.
3. 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;24(11):808–13.
4. Pashley DH, Galloway SE. The effects of oxalate treatment on the smear layer of ground surfaces of human dentine. *Arch Oral Biol*. 1985;30(10):731–7.
5. Brannstrom M. The hydrodynamic theory of dentinal pain: sensation in preparations, caries, and the dentinal crack syndrome. *J Endod*. 1986;12(10):453–7.
6. Pashley DH. Dentin permeability, dentin sensitivity, and treatment through tubule occlusion. *J Endod*. 1986;12(10):465–74.
7. Arnold WH, Groger C, Bizhang M, Naumova EA. Dentin abrasivity of various desensitizing toothpastes. *Head Face Med*. 2016;12:16.
8. Cunha-Cruz J, Wataha JC, Zhou L, Manning W, Trantow M, Bettendorf MM, et al. Treating dentin hypersensitivity: therapeutic choices made by dentists of the northwest PRECEDENT network. *J Am Dent Assoc*. 2010;141(9):1097–105.
9. Addy M, West NX. The role of toothpaste in the aetiology and treatment of dentine hypersensitivity. *Monogr Oral Sci*. 2013;23:75–87.
10. Sharma S, Shetty NJ, Upoor A. Evaluation of the clinical efficacy of potassium nitrate desensitizing mouthwash and a toothpaste in the treatment of dentinal hypersensitivity. *J Clin Exp Dent*. 2012;4(1):e28–33.
11. Miglani S, Aggarwal V, Ahuja B. Dentin hypersensitivity: recent trends in management. *J Conserv Dent*. 2010;13(4):218–24.
12. Gedalia I, Brayer L, Kalter N, Richter M, Stabholz A. The effect of fluoride and strontium application on dentin: in vivo and in vitro studies. *J Periodontol*. 1978;49(5):269–72.

13. Pearce NX, Addy M, Newcombe RG. Dentine hypersensitivity: a clinical trial to compare 2 strontium desensitizing toothpastes with a conventional fluoride toothpaste. *J Periodontol*. 1994;65(2):113–9.
14. Silverman G, Berman E, Hanna CB, Salvato A, Fratarcangelo P, Bartizek RD, et al. Assessing the efficacy of three dentifrices in the treatment of dentinal hypersensitivity. *J Am Dent Assoc*. 1996;127(2):191–201.
15. Docimo R, Montesani L, Maturo P, Costacurta M, Bartolino M, DeVizio W, et al. Comparing the efficacy in reducing dentin hypersensitivity of a new toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride to a commercial sensitive toothpaste containing 2% potassium ion: an eight-week clinical study in Rome, Italy. *J Clin Dent*. 2009;20(1):17–22.
16. Fu Y, Li X, Que K, Wang M, Hu D, Mateo LR, et al. Instant dentin hypersensitivity relief of a new desensitizing dentifrice containing 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride: a 3-day clinical study in Chengdu, China. *Am J Dent*. 2010;23 Spec No A:20A–7A.
17. Arnold WH, Prange M, Naumova EA. Effectiveness of various toothpastes on dentine tubule occlusion. *J Dent*. 2015;43(4):440–9.
18. Gandolfi MG, Silvia F, H PD, Gasparotto G, Carlo P. Calcium silicate coating derived from Portland cement as treatment for hypersensitive dentine. *J Dent*. 2008;36(8):565–78.
19. Tomsig JL, Creutz CE. Copines: a ubiquitous family of Ca(2+)-dependent phospholipid-binding proteins. *Cell Mol Life Sci*. 2002;59(9):1467–77.
20. Park YH, Son C, Seo YM, Lee YS, Har A, Park JC. CPNE7-induced autophagy restores the physiological function of mature Odontoblasts. *Front Cell Dev Biol*. 2021;9:655498.
21. Choung HW, Lee DS, Lee JH, Shon WJ, Lee JH, Ku Y, et al. Tertiary dentin formation after indirect pulp capping using protein CPNE7. *J Dent Res*. 2016;95(8):906–12.
22. Park SH, Lee YS, Lee DS, Park JC, Kim R, Shon WJ. CPNE7 induces biological dentin sealing in a dentin hypersensitivity model. *J Dent Res*. 2019;98(11):1239–44.
23. Lee YS, Park YH, Lee DS, Seo YM, Lee JH, Park JH, et al. Tubular dentin regeneration using a CPNE7-derived functional peptide. *Materials (Basel)*. 2020;13(20).
24. Pashley DH, Tay FR, Yiu C, Hashimoto M, Breschi L, Carvalho RM, et al. Collagen degradation by host-derived enzymes during aging. *J Dent Res*. 2004;83(3):216–21.
25. Addy M, West N. Etiology, mechanisms, and management of dentine hypersensitivity. *Curr Opin Periodontol*. 1994:71–7.
26. Hu ML, Zheng G, Zhang YD, Yan X, Li XC, Lin H. Effect of desensitizing toothpastes on dentine hypersensitivity: a systematic review and meta-analysis. *J Dent*. 2018;75:12–21.
27. Wang Z, Ma X, Jiang T, Wang Y, Feng Y, Li R. The dentin tubule occlusion effects of desensitizing agents and the stability against acids and brushing challenges. *Am J Dent*. 2015;28(3):128–32.
28. Joao-Souza SH, Machado AC, Lopes RM, Zezell DM, Scaramucci T, Aranha ACC. Effectiveness and acid/tooth brushing resistance of in-office desensitizing treatments—a hydraulic conductance study. *Arch Oral Biol*. 2018;96:130–6.
29. SensiStat KI. A new saliva-based composition for simple and effective treatment of dentinal sensitivity pain. *Dent Today*. 2002;21(12):42–7.
30. Kun L. Biophysical study of dental tissues under the effect of a local strontium application. *SSO Schweiz Monatsschr Zahnheilkd*. 1976;86(7):661–76.
31. Mishima H, Sakae T, Kozawa Y. Scanning electron microscopy and energy dispersive spectroscopy analysis of calciotraumatic lines in rat labial dentin after acute exposure to strontium chloride. *Scanning Microsc*. 1995;9(3):797–803.
32. Olley RC, Moazzez R, Bartlett D. Effects of dentifrices on subsurface dentin tubule occlusion: an in situ study. *Int J Prosthodont*. 2015;28(2):181–7.
33. Clark D, Levin L. Non-surgical management of tooth hypersensitivity. *Int Dent J*. 2016;66(5):249–56.
34. Magno MB, Nascimento GC, Da Penha NK, Pessoa OF, Loretto SC, Maia LC. Difference in effectiveness between strontium acetate and arginine-based toothpastes to relieve dentin hypersensitivity. A systematic review. *Am J Dent*. 2015;28(1):40–4.
35. Docimo R, Perugia C, Bartolino M, Maturo P, Montesani L, Zhang YP, et al. Comparative evaluation of the efficacy of three commercially available toothpastes on dentin hypersensitivity reduction: an eight-week clinical study. *J Clin Dent*. 2011;22(4):121–7.
36. Hirayama S, Komine C, Takahashi C, Matsui S, Matsushima K. Effects of calcium carbonate on Odontoblast differentiation and calcification ability of human dental pulp cells. *J Oral Tissue Eng*. 2013;11(2):123–34.
37. Huang M, Hill RG, Rawlinson SC. Strontium (Sr) elicits odontogenic differentiation of human dental pulp stem cells (hDPSCs): a therapeutic role for Sr in dentine repair? *Acta Biomater*. 2016;38:201–11.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

