The efficacy of a novel zinc-containing desensitizer CAREDYNE Shield on dentin hypersensitivity: study protocol for a pilot randomized controlled trial

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Study protocol

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Abstract

Background: Dentin hypersensitivity (DH) is a condition characterized by short and sharp pain which will arise in response to tactile, chemical, thermal, evaporative or osmotic stimuli. The painful symptoms cause discomfort to the patients and decrease their quality of life. Recently, a novel zinc-containing desensitizer CAREDYNE Shield is developed. It is a new type of desensitizer which acts as a desensitizer by inducing chemical occlusion of dentinal tubules, and releases zinc ion for root caries prevention. However, the clinical effectiveness of CAREDYNE Shield on DH is still unclear. Therefore, the aim of this study is to evaluate the effectiveness of CAREDYNE Shield on DH by comparing with that of another desensitizer Nanoseal commonly used in Japan.

Methods/Design: This study protocol is a two-arm parallel pilot randomized controlled trial. Forty DH patients will be randomly allocated into 2 groups. Participants in the intervention group will be treated with CAREDYNE Shield; participants in the control group will be treated with Nanoseal. Primary outcome is the reduction of pain intensity in response to air stimuli measured with 5-points verbal response scale from baseline to 4 weeks after the intervention and Fisher's exact test will be used for analysis.

Discussion: CAREDYNE Shield can be casually applied to subgingival areas and proximal surfaces because it reacts with only tooth substance. Moreover, zinc is reported to reduce the demineralization of enamel and dentin and inhibit biofilm formation, plaque growth and dentin collagen degradation. Therefore, CAREDYNE Shield may be expected to become a novel useful desensitizer which act not only as a desensitizer but also as a root caries inhibitor.

Background

Dentin hypersensitivity (DH) is a condition characterized by short and sharp pain which will arise in response to tactile, chemical, thermal, evaporative or osmotic stimuli, and which cannot be ascribed to any other form of dental defect or pathology (2, 3). Recent systematic review reported the range of DH prevalence in various population varied from 1.3% to 92.1%, and an estimate DH prevalence analyzed with the random-effects meta-analysis was 33.5%; the 95% confidence interval was 30.2% to 36.7% (4). The painful symptoms cause discomfort to the patients and decrease their quality of life (5).

Normally, dentin is covered by enamel or cementum and is not affected by direct stimuli; however, once dentin has been exposed and dentinal tubules have been patent to oral environment, the painful symptoms of DH will arise in response to external stimuli. Dentin exposure results from loss of enamel or cementum, and loss of enamel results from erosion, abrasion or abfraction; loss of cementum results from gingival recession associated with improper tooth brushing, periodontal disease or periodontal surgery.

Lots of theories have been suggested to explain the mechanisms of DH; however, the hydrodynamic theory has been widely accepted (6, 7). According to this theory, fluid movement in the patent dentinal tubules occur in response to external stimuli; it stimulates sensory nerve endings located at the dentin-

pulp interface. Thus, the dentinal tubule occlusion which would reduce the fluid movement in the dentinal tubules is one of the ideal DH treatment, and is performed with adhesive systems or desensitizing agents which form insoluble mineral precipitates in the patent dentinal tubules (8).

One of desensitizing agents which form insoluble mineral precipitates in patent dentinal tubules is the fluoroaluminocalciumsilicate-based desensitizer Nanoseal (Nippon Shika Yakuhin, Yamaguchi, Japan). The components are similar to that of silicate cement. Nanoseal acts as a desensitizer by a chemical reaction resulting in insoluble nanoparticles that aggregate on the tooth surface for dentinal tubule occlusion and is suggested to protect root surface from demineralization because of ions such as calcium or fluorine released from Nanoseal (9-11). Thus, Nanoseal may act not only as a desensitizer but also as a root caries inhibitor.

Recently, the fluorozinccalsiumsilicate-based desensitizer CAREDYNE Shield (GC Dental Industrial Corporation, Tokyo, Japan) has been developed. It acts as a desensitizer by inducing chemical occlusion of dentinal tubules and contains a novel functional filler which releases not only ions like calcium or fluorine but also zinc. Zinc is reported to reduce the demineralization of enamel and dentin, and inhibit dentin collagen degradation, plaque growth and biofilm formation (12, 13).

However, the effectiveness of CAREDYNE Shield on DH is still unclear; therefore, the aim of this study is to investigate the effectiveness of CAREDYNE Shield on DH by comparing with that of Nanoseal. PICO question of this study is described in Table 1.

Table 1. PICO question

Criteria	Description
P (Participants)	non-carious human permanent teeth with DH
I (Intervention)	DH treatment with CAREDYNE Shield
C (Control)	DH treatment with Nanoseal
O (Outcome)	the reduction of pain level in response to air stimuli

DH: dentin hypersensitivity

Methods

Trial design

This study protocol is a two-arm parallel pilot randomized controlled trial, and it was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and Consolidated Standards of Reporting Trials (CONSORT) guidelines (14, 15). A SPIRIT checklist is attached in Additional file 1.

Participant timeline

To describe the time schedule of enrolment, intervention and assessment, a SPIRIT figure and a CONSORT flow chart are mentioned in Table 2 and Figure 1.

Table 2. SPIRIT figure

	Enrolment	Post-allocation
Timepoint	0	4 weeks (range: 3-5 weeks)
Enrolment:		
- Eligibility screen	X	
- Informed consent	X	
- Allocation	X	
Intervention:		
- CAREDYNE Shield	X	
- Nanoseal	X	
Clinical assessment:		
- Air blow	X	X
- Inspection	X	X
- Palpation	X	X

Study setting

All procedure of this study will be performed in Department of Periodontology and Endodontology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Sample size

There are no previous clinical studies which investigate the effectiveness of CAREDYNE Shield on DH; therefore, at least 15 participants will be required in each group to perform a sample size calculation in a subsequent study (16). With a 20% dropout rate, a total of 40 participants will be recruited in this study.

Eligibility screen

When DH complaints are presented from patients in Nagasaki University Hospital, eligibility criteria described in Table 3 are verified by the dentist in charge of the patient.

Table 3. eligibility criteria

Inclusion criteria
Outpatients
Participants who presented with DH complaint
Participants who agreed to attend this study after informed consent
Exclusion criteria
Participants who have allergy to desensitizing materials used in this study
Participants who are pregnant or lactating
Participants taken DH treatment within the last 6 months
Participants with systemic disease that mislead the results of this study
Participants who presented with pain complaints that mislead the results of this study
DH teeth with restoration that mislead the results of this study
DH teeth with caries or advanced periodontal disease
DH teeth taken periodontal surgery or orthodontic treatment within the last 3 months

DH: dentin hypersensitivity

Informed consent

After eligibility screen, the potential participants who met eligibility criteria will be taken informed consent with the informed consent form attached in Additional file 2. Then, they will be enrolled in this study by an examiner who will be blinded to the allocation. Signed informed consent form is mandatory for enrollment.

Randomized allocation

After enrollment, baseline assessments will be performed by the examiner who enrolled the participant in this study. Then, randomized allocation will be performed in a 1:1 ration by the dentist in charge of the patient with opaque sealed envelopes which prepared before participant recruitment and on which “Nanoseal” or “CAREDYNE Shield” is printed. Participants allocated in the intervention group will be treated with CAREDYNE Shield; meanwhile, participants allocated in the control group will be treated with Nanoseal. The information of desensitizers used in this study is described in Table 4.

Table 4. Desensitizers used in this study.

Material	Manufacturer	Composition
CAREDYNE Shield	GC Dental Industrial Corporation, Tokyo, Japan	Solution A: Fluorozinccalciumsilicate glass Solution B: 10-15% phosphoric acid
Nanoseal	Nippon Shika Yakuhin Co., Ltd., Shimonoseki, Japan	Solution A: Fluoroaluminocalciumsilicate glass Solution B: 10% phosphoric acid

Allocation concealment

After the allocation, the operator who performed allocation will record operator's name, baseline date and type of teeth to be treated in the allocation list. The list will not contain the allocated group name to conceal allocation and participant's name and ID number to protect personal information. Allocation information will be recorded in the electric carte which other research staffs cannot check without any browsing history.

Blinding of participants

Participants will be blinded during this study and disclosure of allocation to participants will be performed in the case described as follows: (1) participant requests to stop or change allocated intervention, (2) worsening disease or new disease occurs, (3) continuing this study is judged to be inappropriate for the participant and (4) this study is terminated.

Intervention

After randomized allocation, the participants in the intervention group will be treated with CAREDYNE Shield and the participants in the control group will be treated with Nanoseal by the operator who performed allocation. Prior to the application of CAREDYNE Shield or Nanoseal, dental prophylaxis and water rinse will be performed to remove plaque deposits; the areas to be treated will be isolated with cotton rolls and dried with cotton pellets; two equal proportions of solution A and solution B will be mixed with micro-brush and applied to the dentin surface for 20 seconds; then, rinsed with water. 4 weeks after the treatment, clinical assessments will be performed by the examiner who enrolled the participant in this study.

During this study, other any dental treatment to DH teeth are prohibited, and all intervention procedure will be recorded by the operator in electronic chart to improve adherence to intervention protocols. Discontinuing intervention will be performed in the case described as follows: (1) participant requests to stop or change allocated intervention, (2) worsening disease or new disease occurs, or (3) continuing this study is judged to be inappropriate.

Primary outcome

Primary outcome is the reduction of pain intensity in response to air stimuli measured with 5-points verbal response scale from baseline to 4 weeks after the intervention. To evaluate the pain level, air blast will be applied with a three-way dental syringe after the isolation of the DH teeth with cotton rolls; then, participants will be asked verbally to rate the level of pain intensity with 5-points verbal rating scale (VRS; a numerical scale from 0 to 4 summarized in Table 5).

Table 5. Verbal Rating Scale

Score	Level of pain intensity
0	no pain
1	mild pain
2	moderate pain
3	severe pain
4	extremely intense pain

Secondary outcome

Secondary outcomes are the change of gingival condition near the treated area measured with the gingival index (GI) and the change of oral hygiene status at the treated dentin surface measured with the plaque index (PI) from baseline to 4 weeks after the intervention (17, 18). GI and PI will be evaluated with inspection and palpation.

Data collection

Outcome assessment will be performed at baseline and 4 weeks after the intervention by the examiner who enrolled the participant in this study. Calibration was performed to promote data quality. Examiner's name, date of assessment, type of teeth and the acquired outcomes will be recorded in the assessment form and it will be given to the lead principal investigator (PI).

Data management

Double data entry will be performed by two research staffs independently. To protect confidentiality, the correspondence table of the anonymizing code and participant's names will be prepared, and all documents containing personal information obtained in this study will be kept strictly in lockable filing cabinets in the office for more than 5 years after this study; then, discarded through a shredder.

Statistical design

The primary outcome will be analyzed with Fisher's exact test and the analysis will be conducted according to the intention-to-treat principle. Participants who discontinue or deviate from intervention protocols or with any missing data will be excluded. Any additional analyses will not be performed.

Access to data

PI will have access to the final study data and make the final decision to terminate this study. Other research staffs will not access to any data acquired in this study.

Monitoring

Monitoring will be performed by one of our research staffs according to the standard operating procedures and the results will be given to PI within 2 weeks after monitoring. When adverse events or

other unintended effects of the intervention happen, PI will perform appropriate treatments to the participant, report to the Nagasaki University Hospital Clinical Research Ethics Committee (REC) and share this information with the research staffs. Data monitoring committee is not necessary because the DH treatment with Nanoseal or CAREDYNE Shield is general practice and low-invasive intervention procedure.

Potential benefits and harms

This study will contribute to the future clinical improvements. Meanwhile, atopic dermatitis is the potential side effect of the intervention.

Discussion

It is recommended that at least 2 different stimuli, especially tactile, cold or air stimuli, should be used for the clinical assessment of DH because DH may be different for different stimuli (3). However, only air stimuli will be evaluated in this study because this study will be performed for sample size calculation which is based on the primary outcome; the reduction of pain intensity in response to air stimuli. Tactile stimuli will be evaluated as secondary outcome in a future large-scale study. Meanwhile, GI and PI will be used as secondary outcome in this study. If the reduction of GI or PI is observed, the effectiveness of CAREDYNE Shield for the reduction of GI or PI will be investigated in future clinical study.

Desensitizers like CAREDYNE Shield and Nanoseal which induce chemical occlusion of dentinal tubules are biocompatible and react with only tooth substance; thus, it can be casually applied to subgingival areas and proximal surfaces. Moreover, for several decades, lots of *in vitro* studies have been performed to investigate the function of zinc and reported that zinc reduces the demineralization of enamel and dentin, inhibits dentin collagen degradation, plaque growth and biofilm formation (1, 19-22). Thus, CAREDYNE Shield which releases zinc ion may be expected to become a novel useful desensitizer which acts not only as a desensitizer but also as a root caries inhibitor.

Declarations

Ethics approval and consent to participate

This study protocol has been approved by the Nagasaki University Hospital Clinical Research Ethics Committee (authorization number: 19102101) prior to participant recruitment, and registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR; No. UMIN000038072) on 21st September 2019. Informed consent will be obtained from all study participants. The modified study protocol will not be performed without REC approval. The results of this study will be disseminated to public via open access publication.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

TM has received Nanoseal and CAREDYNE Shield from GC for this study, and authors have not received any financial support. The competing interests will be managed by Conflict of Interest Committee of Nagasaki University Hospital.

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Not applicable

Authors' contributions

TM is a main author of this manuscript and responsible for this study. All authors revised the manuscript and approved the final version of the manuscript.

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Trial registration:

UMIN Clinical Trials Registry (UMIN-CTR), UMIN000038072. Registered on 21st September 2019.

Trial status

This study (the protocol version number is version 1.4.0.; approved on 22 October 2019) is ongoing. The recruitment of participants began in December 2019 and it will be continued until November 2020.(1)

Abbreviations

CONSORT: Consolidated Standards of Reporting Trials; DH: Dentin Hypersensitivity; PI: Principal Investigator; RCT: Randomized Clinical Trial; REC: Research Ethics Committee; SPIRIT: The Standard Protocol Items: Recommendations for Interventional Trials; UMIN-CTR: The University Hospital Medical Information Network-Clinical Trials Registry.

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Figures

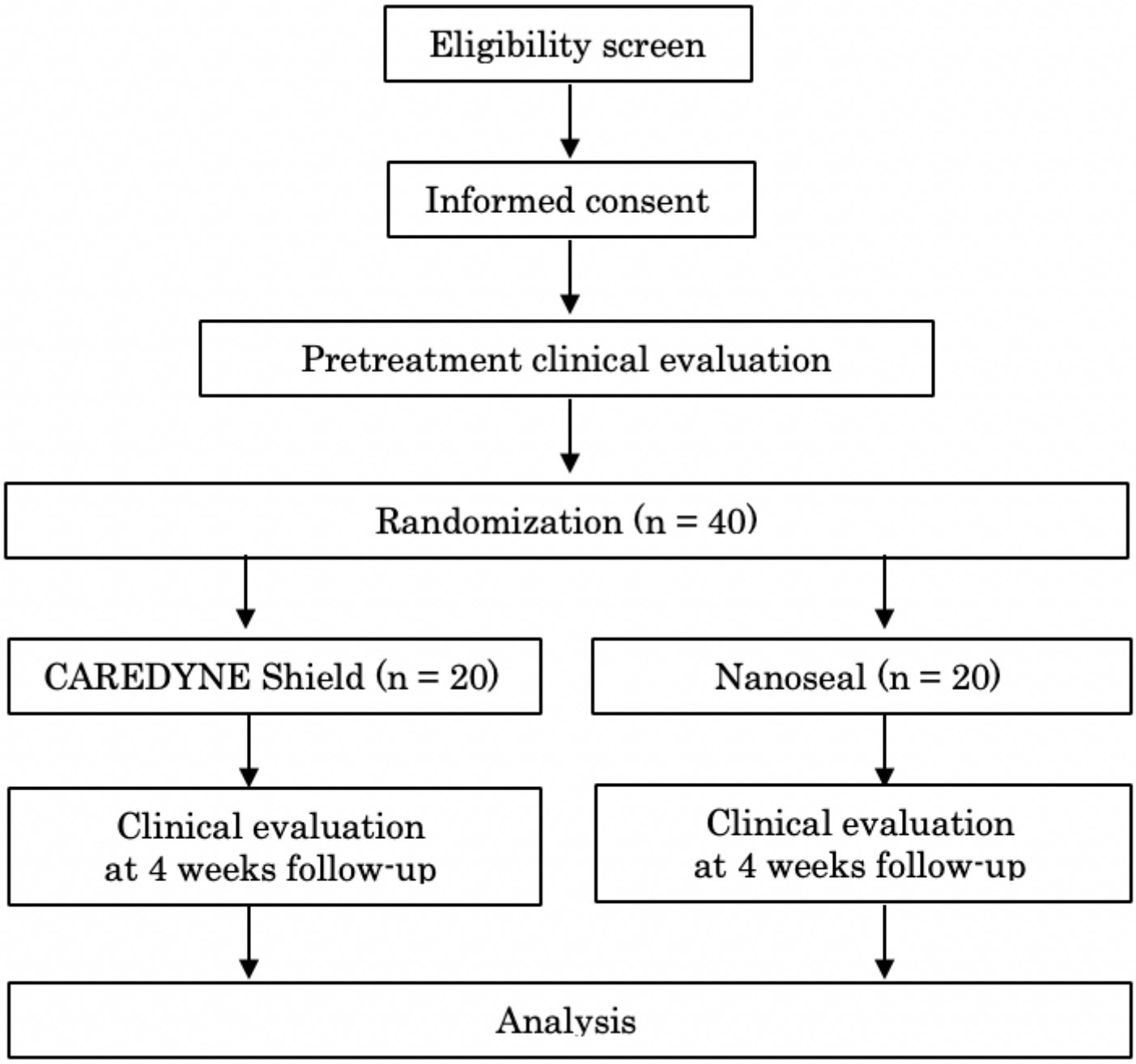

Figure 1

CONSORT flow chart