Randomized controlled clinical trial on the efficacy of dentin desensitizing agents

博士論文

Randomized controlled clinical trial on the efficacy of dentin desensitizing agents

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ABBREVIATIONS

DH: Dentin Hypersensitivity

AB: Air blast

PS: Probe scratching

VAS: Visual Analog Scale

MSC: MS Coat One F

NAN: Nanoseal

TMD: Teeth Mate Desensitizer

GLU: Gluma Desensitizer PowerGel

HEMA: 2-hydroxyethylmethacrylate

HA: Hydroxyapatite

CaF_2: Calcium Fluoride

Ca_3PO_4: Calcium Phosphate

CPD-100: Calcium Phosphate Dihydrate

PRE: Preoperative

POST: Postoperative

ABSTRACT

Objective: To investigate the effects of four dentin desensitizers on pain reduction in hypersensitive cervical dentin lesions. **Material and methods**: The trial was designed as randomized, controlled, four-arm, single-masked study. Fifty subjects with at least one hypersensitive lesion in each of the four quadrants were allocated. The requested pre-operative pain, determined as response to 2 seconds air-blast (AB) and probe scratching (PS), was ≥ 5 on a VAS scale, 0=no through 10=worst pain. Randomly each subject received each of the four treatments: MS Coat One F (MSC, Sun Medical, Japan), Nanoseal (NAN, Nishin, Japan), Teethmate Desensitizer (TMD, Kuraray Noritake, Japan) and Gluma Desensitizer PowerGel (GLU, HeraeusKulzer, Germany). The investigator assessed blindly the pain response using the two stimuli and recorded the patients' VAS scores before and immediately after application, after 1week, and after 1, 3 and 6 months. Statistical data treatment: ANOVA and post-hoc testing ($p \leq 0.05$). **Results**: Forty-nine subjects completed the trial. Preoperative dentin hypersensitivity (DH) for the groups was not significantly different. All desensitizers reduced DH significantly throughout the 6-months observation. ANOVA revealed significant differences among VAS scores, obtained with the desensitizing agents ($p<0.001$). Ranking by post-hoc testing was: MSC>NAN>TMD>GLU ($p<0.05$). Upon PS NAN and TMD showed slight but significant regain of sensitivity after 6 months. For GLU PS scores immediately after application and after 6 months were not significantly different, whereas recalls after 1w, 1m and 3 m revealed significantly lower scores. **Conclusion**: The calcium phosphate based TMD and GLU proved highly effective in reducing sensitivity.

INTRODUCTION

Dentin hypersensitivity (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 pathology[1]. DH may occur when dentin is exposed to the oral cavity and when dentinal tubules are patent both at the pulpal and the oral surface [2]. Among the several theories put forward to explain how pain is transferred from the exposed dentin surface to the pulp the most widely accepted one is Brännström's hydrodynamic theory [3,4]. According to this theory sensitivity of dentin is the result of stimulus-induced fluid flow in the dentinal tubules and concomitant activation of sensory nerves in the pulp/dentin border area[5]. On this background a reasonable therapy of DH should hamper or exclude fluid flow by tubular obstruction. For this purpose a plethora of agents and products is available on the market to modify the dentin surface or tubules by chemical, mechanical and physical means, such as protein precipitation, plugging of tubular entrances by crystal/salt precipitation, laser treatment and resin sealing [6,7].

Literature reports on prevalence of DH show very large variations ranging from 3 to 98% [8]. This heterogeneity is mainly explained by the selection criteria used for different study samples and especially by the selected diagnostic approaches [9]. DH is always a diagnosis of exclusion. Upon screening dentists must exclude by differential diagnoses clinical symptoms similar to cervical DH, such as cracked tooth syndrome, dental caries, pulpitis, to mention only a few [10,11].

In spite of the numerous agents and regimens suggested for in-office pain relief of DH there is no consensus on the efficacy of different therapeutic approaches [12]. Although *in vitro* assessments of the hydraulic conductance of dentin are frequently reported in the dental literature as a measure to quantify fluid flow inside dentinal tubules following different treatment modalities, such data may at the best be considered rough screening tools of potential clinical usefulness [13-15]. Thus, the ultimate proof of clinical effectiveness remains randomized controlled clinical testing.

For the present investigation four treatment modalities were selected and compared: sealing of dentin with an oxalate-containing pre-polymerized resin suspension, precipitation of calcium- and silicate phosphate from silicate glass mixed with phosphoric acid, hydroxyapatite precipitation from a calcium phosphate desensitizing agent, and dentinal liquid protein precipitation after topical application of a glutaraldehyde containing desensitizer.

Aim of this randomized, controlled, four-arm, single-blind trial was to investigate the effect of four different treatment approaches on patients' perception of stimulus-provoked pain of hypersensitive cervical dentin over a six-months period. The null hypothesis tested was that the different topical treatments would significantly reduce DH throughout the six-months assessment time.

MATERIALS AND METHODS

The "Guidelines for the design and conduct of clinical trials on dentine hypersensitivity" were adopted and followed during planning and execution of the study [12]. Approval for this clinical investigation was obtained from the ethics committee of the local University Review Board (VokkaligaraSangha Dental College and Hospital, Bangalore, India. Approval: VSDC/EC-16, 11/07/2013). The request to include a placebo or a no-treatment option was not approved by the ethical board. The study was conducted in agreement with the principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2008).

Patients for this study were recruited from the Department of Conservative Dentistry and Endodontics, VokkaligaraSangha Dental College and Hospital, Bangalore, India. Main inclusion criterion was presence of at least one sensitive tooth in each of the four quadrants with a VAS (Visual Analogue Scale) score >5 cm on buccal cervical dentin. Seventy-two patients self-reporting tooth sensitivity were screened for participation in 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 three months. Fifty patients were allocated to the study after obtaining written informed consent. For each patient the kind of treatment of the selected tooth in each quadrant was determined using a randomization table of the four treatment modalities. The list was produced on Research Randomizer Calculator (www.socialpsychology.org/randomizer.htm). If

patients had two or more sensitive teeth in the same quadrant the tooth with the highest VAS score was selected, whereas the other teeth remained untreated at this time. According the study protocol all patients received oral hygiene instructions and a professional dental prophylaxis.

Table I shows the patients demographics and Table II gives the numbers of teeth by location and assigned treatment.One week prior to the treatment the investigator assessed dentin hypersensitivity using a cold air stimulus (two-second air blast from a dental syringe directed perpendicular to the lesion surface at 1 cm distance). Neighboring teeth were shielded with the gloved fingers of the investigator. Immediately after stimulation patients were asked to point on a VAS scale (no pain = 0 and worst pain = 10 cm) to the nearest full centimeter number to describe their pain perception. Five minutes later, the investigator applied a tactile stimulus, running a dental explorer across the cervical area of the assigned teeth in horizontal and vertical direction at a relatively mild force, and the patients were asked again to give their VAS pain score.

The desensitizing agents, shown in Table III together with their composition and mode of application were used. Gluma Desensitizer PowerGel was used as positive control, since this desensitizer proved highly effective in a previous clinical study performed at this institution [17].

Upon start of the trial the investigator determined the VAS scores as baseline (PRE) again as described above. Two calibrated operators performed the treatments according to instructions and the randomization table. Within 10 minutes after the last

treatment the investigator assessed sensitivity as immediate response (POST). Patients were recalled after 1 week, 1, 3 and 6 months for sensitivity screening. At each recall the investigator used blank sheets with patients numbers only to avoid bias relative to previous assessments.

Statistical analysis

The treated teeth were the experimental unit for the statistical analyses. Since the data were normally distributed statistical treatment was performed by parametric univariate ANOVA and Tukey's post hoc test with a significance level set at $p \leq 0.05$ (IBM SPSS Statistics, Version 21.0 for Mac, Chicago, IL, USA).

RESULTS

From the 50 patients enrolled 49 completed the 6-month trial. One subject dropped out after the 1-month recall assessment due to moving to another city. No significant differences were detected regarding the pretreatment mean VAS scores for AB and PS, respectively. The box-and-whisker plots in Figures 1 and 2 illustrate the medians, the interquartile distances and extreme VAS scores for the 4 desensitizing products evaluated by testing stages and kind of stimulus, respectively. Figures 3 and 4 display the mean VAS scores registered after AB and PS stimulation at all time points. The error bars denote the 95% intervals of confidence.PS scores were slightly higher than AB scores. For all materials the BL scores were significantly higher than at any of the

following stages. All desensitizers reduced DH significantly throughout the 6-months observation. ANOVA revealed significant differences among VAS scores for the desensitizing agents both after AB and PS stimulation ($p<0.001$). Product ranking by post-hoc testing was: MSC>NAN>TMD>GLU ($p<0.05$). Upon AB stimulation sensitivity scores at time points POST through 6m were not significantly different for each desensitizing product tested.

DISCUSSION

The present clinical trial has proven that the four desensitizing agents tested all reduced sensitivity of cervical hypersensitivity lesions significantly, albeit to different levels. Thus, the null hypothesis tested that the different topical treatments would significantly reduce DH throughout the six-months assessment time has to be accepted.

The most important factor in the etiology of dentin hypersensitivity is exposed dentin as a result of gingival recession associated with exposure of root surfaces and/or as a result of loss of enamel associated with tooth wear or trauma; followed by opening of the dentinal tubules (ie,

loss of cementum or removal of any smear layer). In the present study most of the patients test sites reported sensitivity due to gingival recession.

In agreement with previous reports that females suffer from slightly higher incidence of dentin hypersensitivity, in the present study twice as many females as

men were identified for inclusion and the highest prevalence was in the 31-40 years group [8,9,18]. As reported previously most frequently hypersensitive teeth were premolars [18].

According to the study protocol instead of placebo or a no-treatment option that was not approved by the ethical board, GLU was included as positive control to assess equivalence or superiority of the alternative products investigated [16].

For pain evaluation both evaporative and tactile stimuli were applied (response-based assessment) and pain response was measured on a VAS scale. This rating scale is easily comprehensible and offers in addition the advantage of parametric statistical result evaluation [16].

From the desensitizers tested MS Coat One F (MSC) showed the least reduction in sensitivity, approximately 1.5 VAS sores less than at baseline. MSC contains oxalic acid and a fluoride containing acid polymer. According to the manufacturer calcium oxalate is precipitated upon application to dentin and the acid polymer is claimed to provide a surface sealing film. In a clinical placebo-controlled study with the predecessor product MS Coat (US brand Pain-Free) no difference in pain reduction was found between MS Coat and a placebo formulation throughout three-months evaluation [19].Similarly, in a recently published systematic review of clinical trials of hypersensitivity oxalates were not found to be different from placebo, apart from 3% monohydrogen-monopotassium oxalate [20].

NanoSeal (NAN) is a desensitizing compound recently introduced to the Japanese market. Regarding the composition this product seems to be a spin-off from silicate

cement. It is hypothesized that upon application of the acidic mix to the dentin surface CaF_2, Ca_3PO_4 and phosphosilicate are precipitated into dentinal tubule entrances and on intertubular dentin. Immediately after application and throughout the entire assessment time VAS rating was reduced by almost 3 scores. The slight regain in sensitivity recorded at the six-months recall might indicate that the precipitate is gradually removed by mechanical action and/or erosion in dietary acids.

Teethmate Desensitizer (TMD) is a calcium-phosphate-based material. During more than two decades there has been considerable interest to develop calcium-phosphate compounds for treatment of dentin hypersensitivity [21-25]. Calcium-phosphate compounds are transferred to hydroxyapatite (HA), the main mineral phase in teeth. This means, that such products can be characterized as true biocompatible and biomimetic materials [24]. TMD is the first marketed calcium-phosphate containing desensitizer of this category of biomimetic materials. The present study data proved immediate and long-lasting desensitization with an average reduction of 3 to 4 VAS scores. In recently published *in vitro* evaluations the hydraulic conductance of dentin discs was significantly reduced after application of CPD-100 (experimental version of TMD)[26] and after application of the commercial product TMD [27]. These findings corroborate the present clinical data. An additional advantage of TMD is that the super saturation of saliva with calcium and phosphate might contribute to further HA crystal growth on an existing TMD layer in the long run [23,28].

The positive control Gluma Desensitizer PowerGel (GLU) proved highly

effective with VAS score reductions of more than 4 scores relative to baseline. These results confirm findings of previous clinical studies, including a recent trial conducted at this research unit [17,29,30].Using confocal laser scanning microscopy, scanning and transmission electron microscopy Schüpbach et al. [31] visualized intrinsically blocked dentinal tubules to a depth of 200 μm inside the tubules following application of Gluma desensitizer. In a spectroscopic investigation the reaction mechanism between glutaraldehyde and 2-hydroxethylmethacrylate (HEMA) was described as a two-step reaction. First glutaraldehyde reacts with serum albumin inducing precipitation that mediates in a second step polymerization of HEMA [32].

Generally, evaluation of treatment options for dentin hypersensitivity is a difficult task, since both placebo effects and natural desensitization over time may confound or overlap the clinical results due to apposition of peritubular and secondary dentin. Dentin hypersensitivity studies are pain studies. Therefore, it has to be taken into account that pain is associated with psychological and emotional effects that may affect patients' pain response. The split-mouth study design selected for this trial seems to be the most appropriate model for this kind of studies, where the patients act as their own control [33].

CONCLUSIONS

After the six-month follow-up of four treatment modalities for cervical dentin hypersensitivity it can be concluded that all desensitizing agents tested reduced

sensitivity significantly initially and over time. The highest reductions in sensitivity were obtained with the positive control GLU and the calcium-phosphate based product TMD.

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Figure legends

Fig. 1 Box-and-whisker plots of VAS scores after air blast stimulation by desensitizing products and testing stages.

PRE = VAS before treatment.

POST = VAS immediately after treatment.

Fig. 2 Box-and-whisker plots of VAS scores after probe scratching stimulation by desensitizing products and testing stages.

PRE = VAS before treatment.

POST = VAS immediately after treatment.

Fig. 3 Means of VAS sensitivity scores for air-blast stimulation (AB) by treatment and testing times. The error bars denote the 95% intervals of confidence (CI). PRE = VAS before treatment. POST = VAS immediately after treatment. Different lower-case letters next to the product abbreviations show that desensitizer effects on sensitivity reduction were significantly different according to Tukey's post-hoc test.

Fig. 4 Means of VAS sensitivity scores for probe-scratch stimulation (PS) by treatment and testing times. The error bars denote the 95% intervals of confidence (CI). PRE = VAS before treatment. POST = VAS immediately after treatment. Different lower-case letters next to the product abbreviations show that desensitizer effects on sensitivity reduction were significantly different according to Tukey's post-hoc test.

Table I Materials tested, composition, mechanism of action, application

Material	Manufacturer	Batch/Exp.	Composition	Mechanism	Application
Gluma Desensitizer PowerGel (GLU)	HeraeusKulzer, Hanau, Germany	031538/03-2015	Glutaraldehyde, hydroxyethyl-methacrylate (HEMA), pyrogenic silica, water, dye	Blocks tubules by precipitation of protein in dentin fluid	Clean, rinse, application 60s dwell, rinse, air-dry
MS Coat One F (MSC)	Sun Medical Co., Shiga, Japan	GG2/02-2016	Polymethyl-methacrylate, polystyrene sulphonic acid copolymer, oxalic acid, fluoride, water	Reacts with tooth structure and forms precipitate that blocks dentin tubules	Clean, dispense liquid and apply/rub with applicator for 30 s, air-blast for 5-10 s, rinse
NanoSeal (NAN)	Nippon ShikaYakuhin Co., Ltd. Shimonoseki, Japan	A2E1/02-2015	A) F-Ca-Al-Si glass in aqueous dispersion B) H_3PO_4 aqueous solution	Reacts with tooth structure and forms precipitate that blocks dentin tubules	Clean, rinse, mix A & B, apply to dentin for 20s, rinse with water
Teethmate Desensitizer (TMD)	Kuraray Noritake Dental Inc. Okayama, Japan	011131/10-2015	Powder:Tetra-calcium phosphate, Dicalcium phosphate anhydrous. Liquid: Water, preservative	Powder-liquid mix reacts to form hydroxy-apatite. Sealing of dentin	Clean, rinse, dispense and mix powder and liquid (15 s), apply with applicator, rub for 30 s, rinse

Table II Numbers of teeth treated by age groups and gender

	Age groups of patients (in years)			
	<21	21-30	31-40	41-50
Female	1	9	23	1
Male	-	3	11	2
Total	1	12	34	3

Table III Distribution of teeth by location and treatment (n = 50)

	Maxillary				Mandibular			
	MSC	NAN	TMD	GLU	MSC	NAN	TMD	GLU
Laterals	3	1	-	-	-	-	1	2
Canines	20	10	-	-	1	2	3	8
Premolars	24	33	2	2	1	2	36	34
Molars	1	2	-	-	-	-	8	4

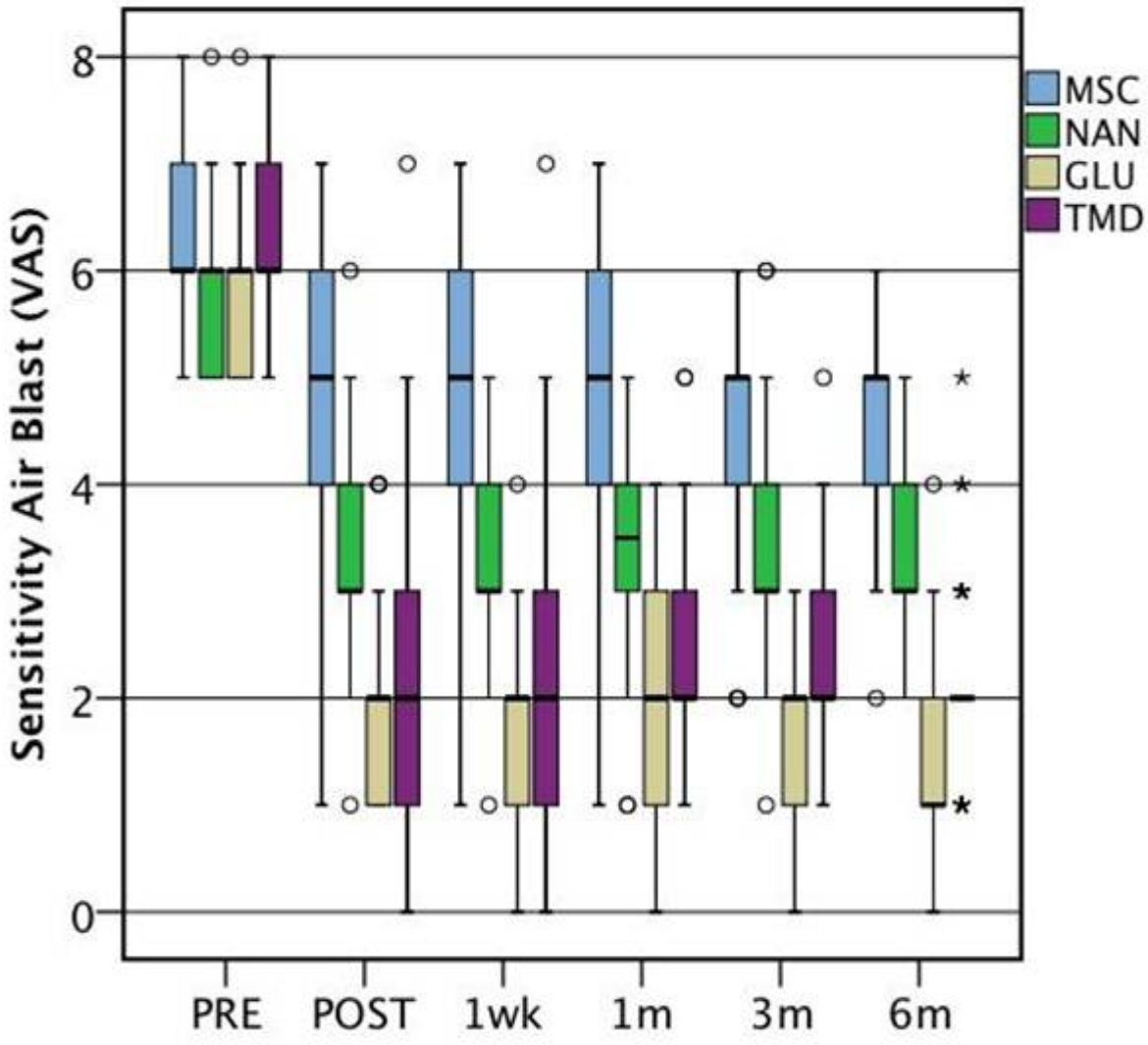

Figure 1. Box-and-whisker plots of VAS scores after air blast stimulation by desensitizing products and testing stages.

PRE = VAS before treatment.

POST = VAS immediately after treatment.

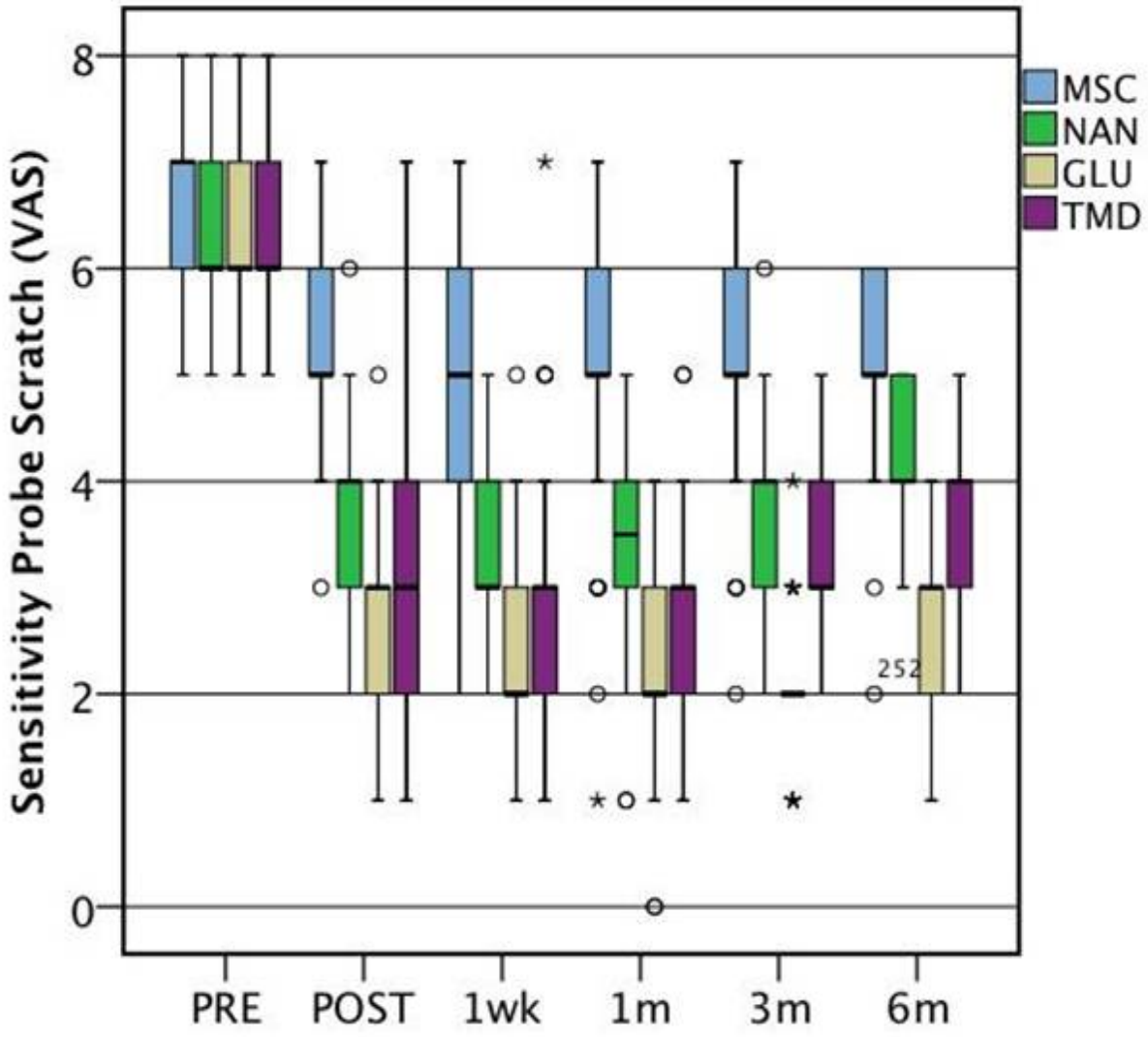

Figure 2. Box-and-whisker plots of VAS scores after probe scratching stimulation by desensitizing products and testing stages.

PRE = VAS before treatment.

POST = VAS immediately after treatment.

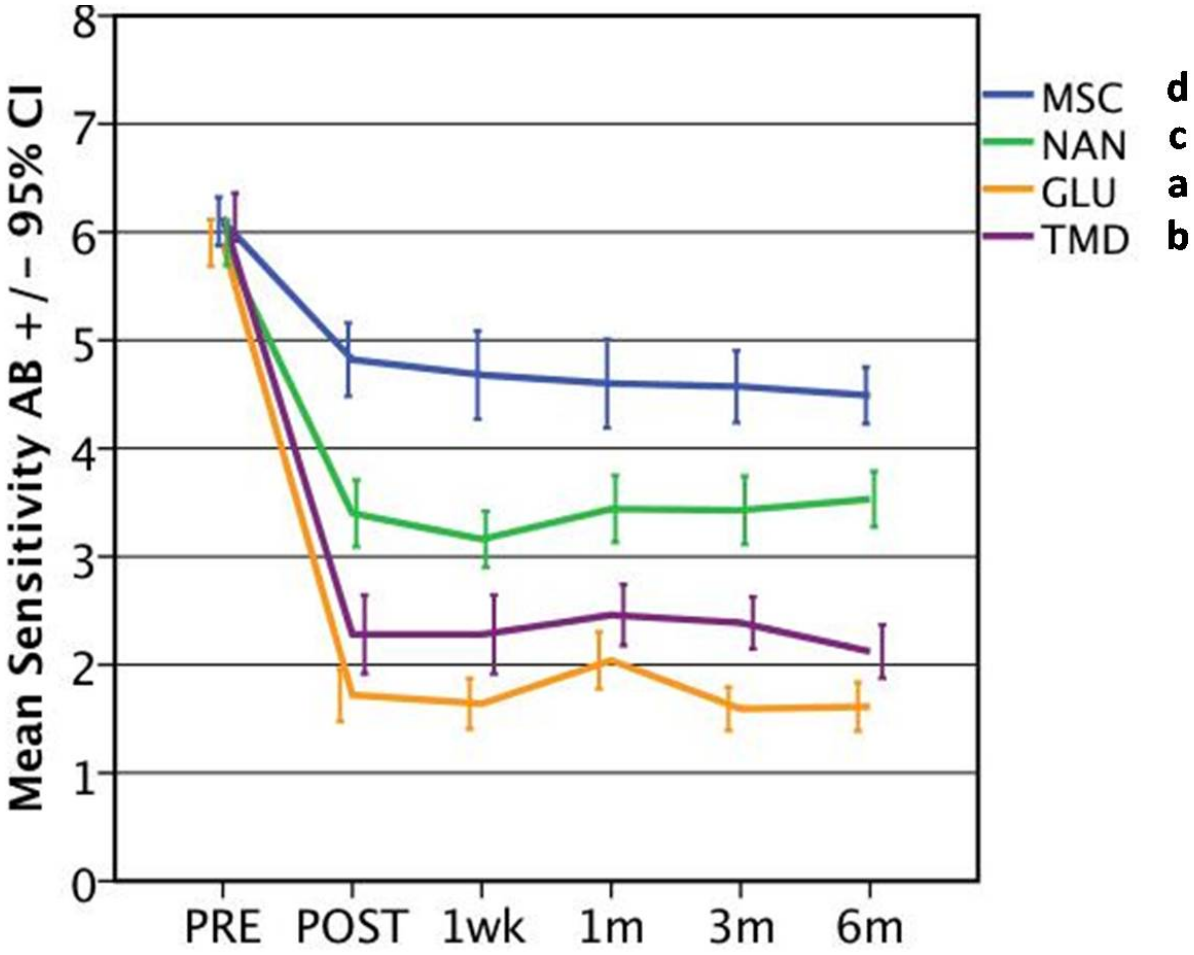

Figure 3. Means of VAS sensitivity scores for air-blast stimulation (AB) by treatment and testing times. The error bars denote the 95% intervals of confidence (CI). PRE=VAS before treatment. POST=VAS immediately after treatment. Different lower-case letters next to the product abbreviations show that desensitizer effects on sensitivity reduction were significantly different according to Tukey's post-hoc test.

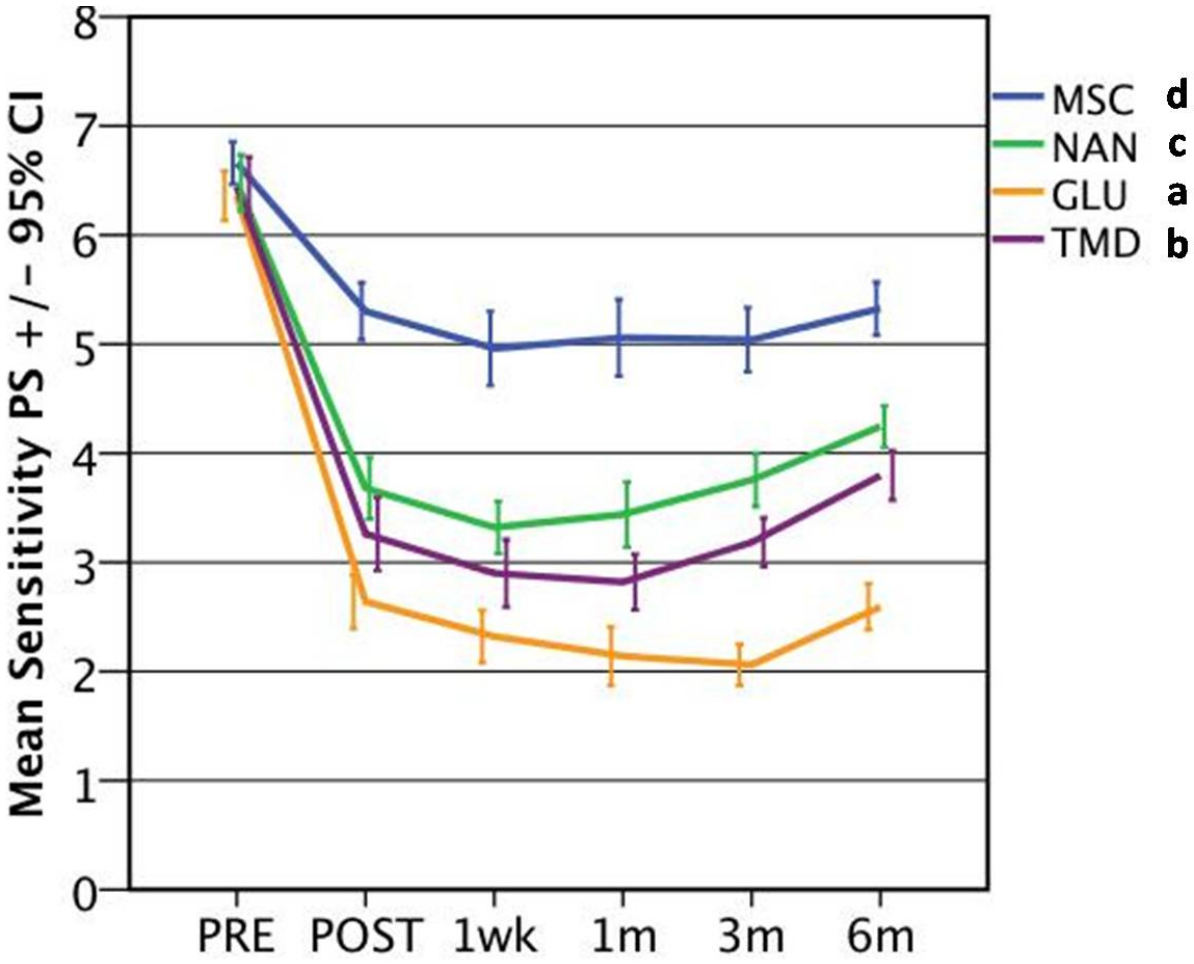

Figure 4. Means of VAS sensitivity scores for probe-scratch stimulation (PS) by treatment and testing times. The error bars denote the 95% intervals of confidence (CI). PRE=VAS before treatment. POST=VAS immediately after treatment. Different lower-case letters next to the product abbreviations show that desensitizer effects on sensitivity reduction were significantly different according to Tukey's post-hoc test.