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ORIGINAL ARTICLE

Efficiency of desensitizing materials in xerostomic patients with head and neck cancer: a comparative clinical study

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Abstract

Objectives To assess the clinical effectiveness of four desensitizing materials in patients who are xerostomic due to radiotherapy for head and neck cancer (HNC) in comparison to a healthy group with normal salivation.

Methods and materials The study was conducted as a split-mouth randomized clinical trial. Forty HNC patients (group A) and 46 healthy patients (group B) suffering from dentin hypersensitivity (DH) were included. Salivary flow was determined through a scialometric test. Hypersensitivity was assessed with air stimulus and tactile stimulus. The materials used as desensitizing agents were Vertise Flow, Universal Dentin Sealant, Clearfil Protect Bond, and Flor-Opal Varnish. The response was recorded before application of the materials, immediately after, and at 1 week, 4 weeks, and 12 weeks.

Results Salivary flow rates in groups A/B were 0.15/0.53 mL/min (unstimulated) and 0.54/1.27 mL/min (stimulated), respectively. In group A, 100 hypersensitive teeth were included. Application of the desensitizing agents significantly decreased the hypersensitivity immediately and throughout the 4-week follow-up ($p < 0.001$). However, after the 12-week timepoint, a loss of efficacy was detected in all agents ($p = 0.131$). In group B, 116 hypersensitive teeth were included. The materials performed a more stable action, although a loss of effectiveness was detected at 12-week control ($p = 0.297$).

Conclusion The efficiency of the desensitizing agents after the first application was similar in both groups. In the radiated group, this effect lasted for shorter periods than in healthy controls.

Clinical relevance HNC patients with hyposalivation may be a new risk group for DH.

Keywords Dry mouth · Hyposalivation · Dentin hypersensitivity · Radiation therapy · Head and neck cancer

Introduction

Xerostomia describes the subjective symptoms of "dry mouth" frequently deriving from a lack of saliva [1–3]. The disease increases with age, as elderly individuals are more likely to have chronic illnesses and the pharmacological treatments, which are associated with a dry mouth sensation. In addition, xerostomia is the most frequent complication of radiotherapy for the treatment of head and neck cancer (HNC) [4], occurring in up to 80% of patients [2]. This finding is related to the fact that a radiation dose totalling 50–70 Gy is routinely applied during treatment of HNC to destroy malignant cells [5]. Radiation often has to pass through the salivary glands to effectively treat tumours with the consequence of causing irreversible damage to the gland parenchyma with a reduced saliva secretion rate and an alteration in the composition of saliva [6]. The experience of having a dry mouth can have a detrimental effect on patients' quality of life [1, 2]. The reduced salivary flow may severely affect soft and hard oral tissues [7]. First, lubrication of the oral mucosa is reduced, which may cause a dry and burning sensation often associated with difficulty speaking, chewing,

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swallowing, or tasting food and impaired sleep, together with psychological and social disabilities. Second, the antimicrobial activity of saliva and the control of demineralization/remineralization of the teeth are altered. Additionally, reduced salivary bicarbonates, phosphates and urea lower the buffering capacity of saliva [7], and generally, the pH of saliva is reduced from approximately 7.0 to 5.0 [8]. The health-associated microbial population is significantly altered, and a more acidogenic and cariogenic population of *Streptococcus mutans* and *Lactobacillus* spp., in addition to *Candida albicans*, arises [3, 9]. In such a situation, S. *mutans* is particularly aggressive, leading to severe and recurrent caries [10, 11] due to the bacterial ability to attack the vulnerable resin interface between a restoration and the tooth, as well as esterase activities [12, 13]. Xerostomic patients may also experience dental hypersensitivity (DH). This condition is described as a short and sharp sensation of pain associated with tubular dentin exposure as a result of gingival recession, erosion, attrition, abrasion, or abfraction [14, 15]. According to the "hydrodynamic theory," the pain is a result of fluid shifts in the exposed dentinal tubules [16–18]. Therefore, the occlusion of the exposed tubules may reduce the fluid movement inside the dentinal tubules and the clinical symptoms of DH [19]. A large number of different products have been marketed for the treatment of DH [20–22], including various toothpastes or adhesive resins and other resin-based materials [23, 24]. However, generally, the long-term efficacy of these products has been reported to be limited [21]. In healthy patients with normal salivary flow, the reason may be the restrained ability of the products to resist oral environmental stress [20–24]. Such stress is increased in xerostomic patients, who display a more aggressive oral environment for both natural teeth and restorative materials, which makes them a population even more at risk of complications. However, to our knowledge, no study has evaluated the behaviour of desensitizing agents in the acidic oral environment of xerostomic patients after radiation therapy.

Therefore, the aim of the present study was to clinically assess the efficacy of four different resin-based materials for treating DH in a group of xerostomic patients with HNC for up to 12 weeks after application and to compare these data with those from a group of healthy, normally salivating patients.

The null hypotheses were as follows:

- There would be no significant difference between xerostomic and healthy, normally salivating patients.
- There would be no significant differences in DH reduction among the desensitizing agents immediately after application and at 1 week, 4 weeks, and 12 weeks after application.

Materials and methods

Study design and ethical aspects

Figure 1 a and b summarize the study methods.

This study was designed as an interventional, split-mouth, randomized, prospective, single-centre clinical trial. The research was ethically conducted in accordance with the Declaration of Helsinki. The protocol and informed consent forms were approved by the Ethics Committee at the University of Sassari (no. 1000/CE). The study followed CONSORT guidelines and was registered at the US National Institutes of Health (ClinicalTrials.gov) # NCT02766127. All patients were carefully informed about the study's purpose, risks and benefits. Informed consent was obtained from all subjects prior to the study. The subjects received written instructions and were extensively trained for all procedures.

Study population

A total of 112 patients visited the Department of Radiology of the University of Sassari from 06/2014 to 12/2016 for radiotherapy due to HNC. Of these patients, 74 patients were subjected to a regime of dental follow-ups that consisted of a dental check-up and, if needed, dental treatment before, during, and after radiotherapy.

Between 3 and 8 months after the radiation exposure, 42 patients began to complain of DH and were selected for the study, which was part of an ongoing program for evaluating desensitizing agents at the Dental Clinic of the University of Sassari, Italy.

The study inclusion criteria were as follows:

- Generally good health besides the HNC conditions
- A clinical reduction in salivary flow
- The presence of two or three teeth that were hypersensitive to stimulation with a blast of air

These patients were assigned to group A of this study. A group of 46 healthy, normal-salivary patients complaining of DH served as a control (group B).

The study inclusion criteria were as follows:

- Two or three teeth that were hypersensitive in each dental arch
- Sensitive teeth showing abrasion, erosion, or recession with the exposure of the cervical dentin
- Normal salivary flow rate

The study exclusion criteria were as follows:

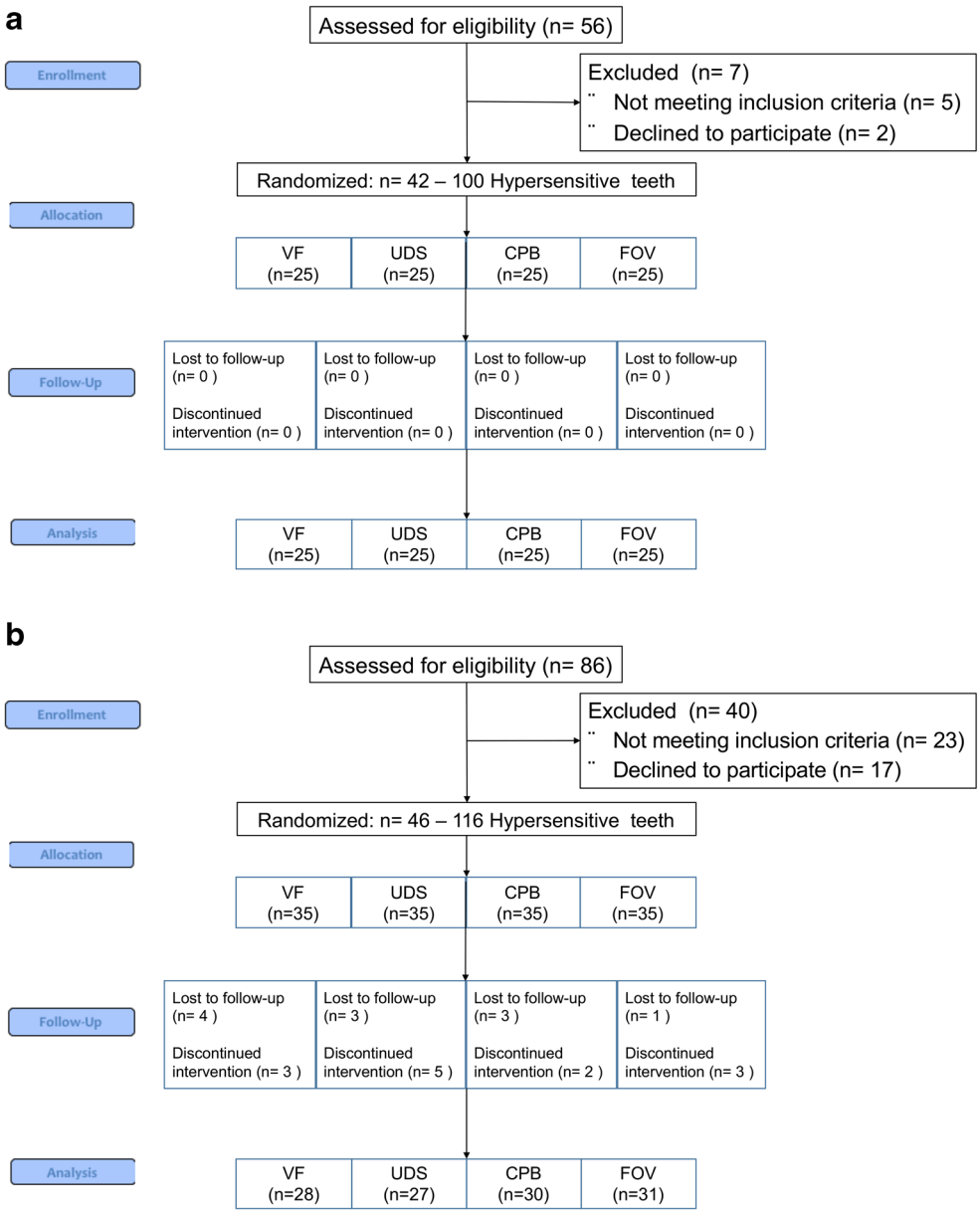

Fig. 1 **a**, **b** Summary of the study methods

- Teeth with subjective or objective evidence of carious lesions, pulpitis, restorations, premature contact, cracked enamel, active periapical infection, or negative sensitivity of the tooth to cold
- Teeth that had received periodontal surgery or root planing up to 6 months prior to the investigation
- Patients who had received professional desensitizing therapy during the previous 3 months
- Patients who had used a desensitizing toothpaste in the last 6 weeks

Patients were also excluded if they were under significant medication that could have interfered with pain perception (e.g., antidepressants, anti-inflammatory drugs, sedatives and muscle relaxants). During the trial period, no patient reported having taken this type of medication.

Sialometric assessment

Recordings of salivary flow rates in both groups were performed in the absence of acute sialadenitis according to the method described by Sreebny [25]. Saliva was collected in a standardized manner. Patients were instructed not to eat, drink, or smoke for 90 min before the sialometric assessment. All measurements were performed at a fixed time of the day, between 10 am and 1 pm, to minimize fluctuations related to a circadian rhythm of salivary secretion and composition. All

recordings were performed by the same person. The whole saliva sample was collected in preweighed plastic tubes.

Unstimulated saliva was collected for 5 min with the patient seated in an upright position, with the head tilted forward. When possible, the tongue, cheek, and lip movements were limited during the procedure. At the end of the collection period, the patient had to expectorate saliva into the test tube. Afterwards, stimulated whole saliva samples were collected by asking patients to chew a small block of paraffin wax or chewing gum. All the saliva secreted for 5 min was then collected in a test tube. All test tubes were weighed before and after each collection using electronic scales, and the salivary flow rate was expressed in mL/min, which is nearly equivalent to g/min [26, 27]. A secretion rate < 0.1–0.2 mL/min for unstimulated flow and < 0.5–0.7 mL/min for stimulated flow was considered an objective sign of hyposalivation [25].

Assessment of hypersensitivity

A week before the DH evaluation, patients received an oral prophylaxis treatment (scaling and polishing procedures). A non-fluoride toothpaste (Toothpaste Total Protection, Istituto Erboristico L'Angelica - Coswell), a soft toothbrush (Oral-B Sensitive Advantage, Procter & Gamble) and oral hygiene instructions were provided before the start to standardize the patients' oral hygiene measures during the study. The level of sensitivity experienced by each patient was considered independent of the position of the hypersensitive tooth in the oral cavity [28]. The level of pain was assessed using a VAS, which grades the level of pain from 1 to 10, following the same procedure as in previous studies [23, 24]. The pain stimulus was given by one examiner with the same equipment yielding a similar air pressure each time, while the other operator performed the treatments. The subject's response was considered before the application of the material (pre-1), immediately after application (post-1), and 1 week (post-2), 4 weeks (post-3), and 12 weeks (post-4) after application to the oral environment. The same operator carried out the sensitivity test. None of the participants failed to complete the study, and none of them reported any adverse reactions.

Test materials

The following dental materials were used following the manufacturers' instructions: Vertise Flow™ (VF) (Kerr Corporation, Orange, CA, USA), a self-adhering composite; Universal Dentin Sealant (UDS) (Ultradent Products Inc., South Jordan, UT, USA), a non-polymerizable, high molecular weight resin sealant in an alcohol solvent; Clearfil Protect Bond (CPB) (Kuraray Noritake Dental, Osaka, Japan), a methacrylate-based self-etch adhesive system; and Flor-Opal® Varnish (FOV) (Ultradent Products Inc., South Jordan, UT, USA), a fluoride-based varnish (Table 1).

Sample size and statistical analysis

Following the same design as in a previous study and as found in other studies [24, 28, 29], each tooth was considered an independent statistical unit. The power (validity) of the study was computed with a post hoc analysis considering 216 teeth divided into 8 groups (2 principal groups related to the presence/absence of xerostomia and 4 sub-groups on the basis of the treatment) with 5 repeated measures. For a confidence interval of 0.95 and an alpha value of 0.05, the power was higher than 0.9.

Using a computer program (Microsoft Excel 2011 for Mac OsX, Version 14.4.2), the teeth were randomly assigned into four groups in both experimental groups. In group A, a total of 100 teeth were studied: 25 teeth treated with VF, 25 with UDS, 25 with CPB, and 25 with FOV (Fig. 1a). In group B, a total of 116 teeth were studied: 28 teeth treated with VF, 27 with UDS, 30 with CPB, and 31 with FOV (Fig. 1b).

The Shapiro–Wilk normality test was used to assess the normality distribution of the data. The median and interquartile ranges were used as a measure of central tendency and variability. The significant differences between the visual analogue scale (VAS) values of the different desensitizing materials were evaluated by performing a Kruskal–Wallis analysis, adjusting the statistical significance for the multiple comparisons (Bonferroni correction). Statistical differences between baseline VAS values and those obtained at other time-points were calculated using the Mann–Whitney *U* test. Additionally, significant differences between VAS values of the xerostomic and the normal-salivary group were calculated using the Mann–Whitney *U* test. The level of significance was set to 0.05. Statistical analysis was carried out using IBM® SPSS® Statistics, Version 21.0 (IBM Corporation©, Armonk, NY, USA) and STATA®13 (StataCorp, College Station, TX, USA).

Results

Salivary flow rates

In group A, the mean basal salivary flow rate was 0.15 mL/min (min. 0.06–max. 0.18), while the stimulated rate was 0.54 mL/min (min. 0.29–max. 066). In control group B, the salivary flow rate was 0.53 mL/min (min. 0.35–max. 0.98), while the stimulated rate was 1.27 mL/min (min. 0.89–max. 1.8).

VAS measurements

The median VAS scores at different time-points of each group are shown in Table 2. No statistically significant differences were observed at PRE-1 between the xerostomic group A and

Table 1 Desensitizing agents used in the study (manufacturer's data)

Material	Manufacturer	Components	Batch no.	Mode of application
Vertise Flow	Kerr Corporation	Glycerol phosphate dimethacrylate, Prepolymerized filler, 1-μ barium glass filler, Nano-sized colloidal silica, Nano-sized ytterbium fluoride methacrylate co-monomers, and nano-sized colloidal-silica,	3391829	1. Thoroughly brush, rubber cup polish and air dry at maximum air pressure for 5 s. 2. Rinse thoroughly for 15 s 3. Gently air dry for 3 s 4. Dispense with a dispensing tip 5. Brush a thin layer and bevelled area with moderate pressure for 15–20 s. 6. Light-cure for 40 s* 7. Saliva contact
Universal Dentin Sealant	Ultradent Products Inc.	Resin, Ethyl alcohol Ca, Cl, and Si as the highest ions in the resin matrix, also containing Al ion peaks	052809	1. Thoroughly isolate and dry area 2. Apply a thin coat of and gently air blow for 5–10 s 3. Saliva contact
Clearfil Protect Bond	Kuraray Noritake Dental	Primer: HEMA, MDP, hydrophilic dimethacrylate, MDPB, water Adhesive: HEMA, MDP, hydrophilic dimethacrylate, N, N-diethandiol-p-toluidine, CQ, silanized colloidal silica	041212	1. Apply Primer scrubbing gently for 20 s 2. Dry with mild air flow 3. Apply bond scrubbing for 10 s 4. Air flow gently for 5 s 5. Light-cure for 10 s 6. Saliva contact
Flor-Opal Varnish	Ultradent, Products Inc.	Sodium fluoride (4–6%) Ethyl alcohol (18.9–28.9%) Methyl salicylate (< 0.7%) Hydrogenated rosin (< 60%)	122005	1. Thoroughly brush, rubber cup polish or wipe teeth with a gauze prior to placement 2. With syringes connected, push varnish back and forth from syringe to syringe, at least 5 times, finishing with varnish in the Labelled syringe. 3. Lightly dry area to be treated 4. Apply a thin smooth layer to dry tooth using a painting motion 5. Saliva contact

*Curing conditions:

• LCUs, 1000 mW/cm^2, according to the manufacturer data (Optilux 501, Sybron)

• Light curing time, 20 s, according to the manufacturer instructions

the normal-salivation group B or between the different treatment groups. Interestingly, of 112 patients undergoing radiologic treatment for HNC and 74 patients enrolled in a dental check-up program, 42 patients developed dentin hypersensitivity (Fig. 1 a and b).

Effect of test materials

At POST-1 and POST-2, VF reduced VAS scores compared to baseline in both groups. Lower VAS values were found in group A compared to group B. However, at POST-3 and POST-4, the VAS scores were reduced compared to baseline, and values of VF were higher in group A than in group B. Statistically significant differences at each observation time between groups A and B were observed for VF.

At POST-1, POST-2, and POST-3, UDS reduced the VAS scores compared to baseline in both groups. Lower VAS values were found in group A compared to group B. Nevertheless, at POST-4, the VAS increased compared to baseline, and values of UDS were higher in group A than in group B. Statistically significant differences were observed at POST-1 and POST-2, while no statistically significant differences at POST-3 and POST-4 were observed between groups A and B for UDS.

At POST-1, POST-2, and POST-3, CPB reduced VAS scores compared to baseline in both groups. Lower VAS values were found in group A compared to group B (Figs. 2 and 3). However, at POST-4, the VAS scores were reduced compared to baseline, and values of CPB were higher in group A than in group B. Statistically significant differences were observed at POST-1, POST-2, and POST-4, while no statistically significant differences at POST-3 were observed between groups A and B for CPB.

At POST-1 and POST-2, FOV reduced the VAS scores compared to baseline in both groups. The VAS values were similar between group A and group B. However, at POST-3 and POST-4, the VAS scores were reduced compared to baseline, and the values of FOV were higher in group A compared to group B. No statistically significant differences were observed at POST-1 and POST-2, while statistically significant differences at POST-3 and POST-4 were observed between groups A and B for FOV.

Table 2 Descriptive and inferential analysis of visual analogue scale (VAS) values measured in group A at baseline and posttreatment

Material	Number	VAS PRE-1 Median (IQR)	VAS POST-1 Median (IQR)	VAS POST-2 Median (IQR)	VAS POST-3 Median (IQR)	VAS POST-4 Median (IQR)
Group A						
VertiseFlow™	25	4 (3–6)	0 (0–0)	0 (0–1)	2 (2–3)	3 (3–5)
Universal Dentin Sealant	25	4 (3–5)	2 (0–2)	1 (0–2)	1 (1–2)	3 (2–3)
Clearfil Protect Bond	25	4 (3–6)	0 (0–0)	0 (0–1)	2 (1–2)	3 (2–5)
Flor-Opal® Varnish	25	4 (3–6)	2 (1–3)	1.5 (1–2.5)	3 (2–4.5)	4 (2–5)
p value*		0.688	0.0001	0.0001	0.0002	0.131
Group B						
Vertise Flow™	28	4.0 (2.0–5.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.5 (1.0–2.0)	2.0 (2.0–3.0)
Universal Dentine Sealant	27	5.0 (3.0–6.0)	2.0 (2.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Clearfil Protect Bond	30	4.0 (3.0–6.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	2.0 (2.0–4.0)
Flor-Opal® Varnish	31	4.0 (3.0–5.0)	2.0 (2.0–3.0)	2.0 (1.0–3.0)	2.0 (2.0–3.0)	3.0 (2.0–3.0)
p value*		0.187	< 0.001	0.002	0.156	0.297

IQR interquartile range

*Kruskall-Wallis test

Effect of xerostomia

Comparing the data between groups A and B combined for all test materials, it was observed that at POST 1, a significant decrease in the VAS value compared to baseline (PRE 1) was noted immediately after the application of all the materials in group A as well as in group B (Table 2). After 1 week (POST-2), all the agents showed a stable reduction of VAS values in both groups. However, after 4 weeks (POST-3), in group A, the VAS score increased, whereas in group B, it stayed at a low level. Finally, at the end of the observation period (POST-4), the VAS values of group A increased again, while in group B, they were stable, with the exception of a small increase for those of FOV.

Discussion

In this study, we selected a group of patients who were xerostomic due to radiotherapy for HNC and suffered from DH. Patients began to complain of dentinal pain between 3 and 8 months after the radiation exposure. In group A, of 42 subjects, 24 were male and 18 were female, and the average age was 65 years. In group A, we tested the ability of four resin-based materials to relieve DH symptoms (VAS score reduction) up to 12 weeks after treatment, comparing these data to those from a group of normal-salivary patients, namely, group B, which was composed of 46 subjects, 19 male and 27 female, with an average age of 42 years. The intent was to detect whether the efficiency of a material would decrease in

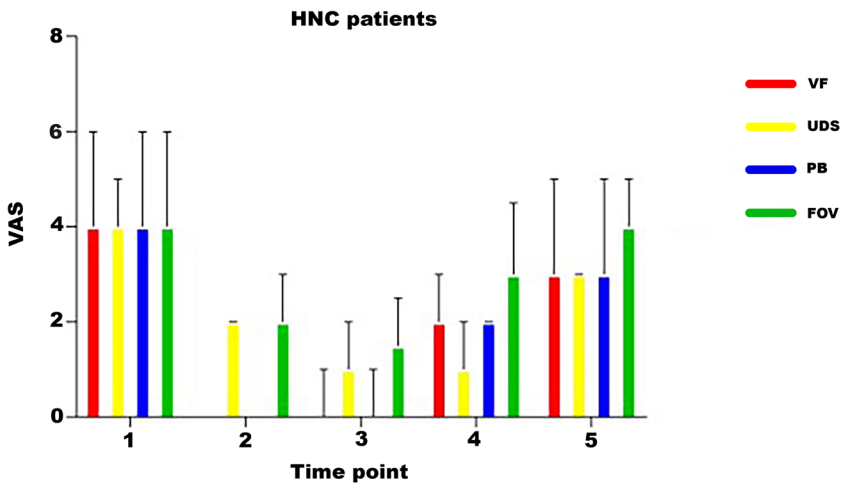

Fig. 2 Dentin hypersensitivity VAS score in HNC patients

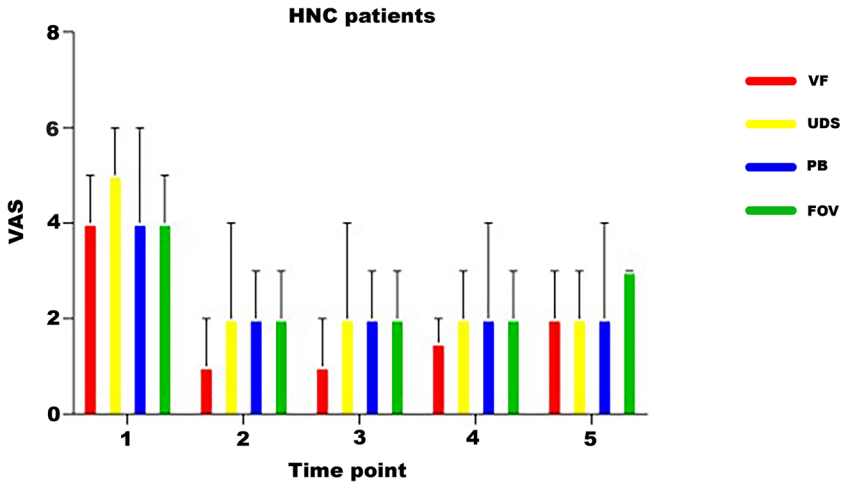

Fig. 3 Dentin hypersensitivity VAS score in healthy patients

hypo-salivary conditions. The first achievement of this investigation was that, interestingly, more than 50% of the HNC patients enrolled in the dental check-up program experienced DH. The average age of these patients was 65 years. Normally, DH is most prevalent in the age group of 30–40 years [30–32]. Comparing data between the group A xerostomic patients and group B healthy, normo-salivating patients, PRE-1 scores for DH pain were not significantly different between all groups; thus, the starting bases were the same for all groups. However, it was not possible to match the control group B concerning age and sex with group A, and this was mainly due to the different mean ages of the patients in the two groups and the different prevalence of the two diseases in the mean range and sex. In fact, in accordance with previous studies, HNC was found to be a disease of the approximately mid-60s age group [33]; here, the age was approximately 65 years, with a prevalence in men. Furthermore, the DH prevalence is highest in patient age groups between 20 and 40 [30, 34]. Here, we observed a mean age of 42 years and a prevalence in females.

Effect of xerostomia/radiation

Summarizing the data for all test materials, it was shown that in xerostomic radiation patients (group A), the effect of the applied desensitizing agents was good or even better initially but lasted a shorter period than that in the healthy control patients with normal salivation (group B). It can be assumed that the generally more aggressive oral environment in xerostomic patients may influence the clinical effectiveness of all desensitizing agents, though to a different extent and in different ways. This assumption can be related to the demineralizing effect produced by the acidic biofilm at the gingival margin between the restoration and the tooth [13], with no more remineralizing effect from the altered saliva [35, 36].

Additionally, as all tested desensitizing materials interfere with dentin, the possible influence of radiation on the dental hard tissue substrate may be relevant. Several studies have shown that radiotherapy could cause changes and damage to teeth that may result in alterations of the mechanical properties of their structures [37, 38]. Enamel and dentin can be severely affected by irradiation [32]. Irradiated enamel shows significant micromorphometric alterations, making it more vulnerable to acid attacks than sound enamel [39]. Radiation may also cause deep alterations and destruction of the organic matrix of dentin, causing a loss of structural stability that is manifested by the reduction of the microhardness [37]. Furthermore, the influence of radiation therapy for HNC on the bond strength of dental adhesives to dentin has been investigated by several authors [40, 41]. However, no significant difference was found between tested adhesive systems when applied on irradiated and nonirradiated dentin, probably because head and neck irradiation itself would not be able to change the mechanical properties of dentin, at least from an adhesion perspective.

Effect of test materials

In more detail, in xerostomic patients, VF and CPB significantly reduced the VAS scores at POST-1 and POST-2 compared to PRE-1, with no significant difference between them. This result can be attributed to the high bonding capacity of the self-adhesive materials on dentin. In addition, at the same time points, the VAS values of VF and CPB were lower in group A than in group B. This result could be ascribed to the lower-saturated saliva fluid environment of xerostomic patients, which might have led to a better performance of VF and CPB compared with the normal-saturated saliva fluids of the healthy group B. As delineated above, radiation-induced

changes in dentin may also be responsible, although the reported data on the influence of radiation on bond strength of adhesives to dentin are controversial [40–43]. However, at POST-3 and POST-4, both materials displayed a lower sealing capacity in dentin.

In the case of VF, the reduction in VAS values compared to baseline has been shown to be due to the ability of the self-adhering material to form a particle layer in tubular dentin, which tightly sealed the tubules and acted as a substrate for crystal growth within 7 days of being in the oral environment [23, 44]. The layer formation seemed to include calcium and phosphate ions dissolved in the VF firmly occluding the tubular orifices before curing. However, as with all resin materials, VF may experience a volumetric contraction on polymerization [45], and the internal stresses generated by this process could have resulted in gap formation with microleakage of salivary fluids, as was observed with the margins of restoration [46]. Therefore, we can speculate that the microleakage of salivary fluids was less pronounced in group A than in group B due to the reduced saliva flow rate in xerostomic patients, giving the xerostomic patients the advantage of a better seal of the composite to their tubular dentin, resulting in a greater reduction in DH at POST-1 and POST-2 compared with the normal-salivary environmental exposure of group B. However, the higher decline in effectiveness in group A compared with group B at POST-3 and POST-4 could be related to the greater susceptibility of VF being degraded in the acidic oral environment with the ongoing process of chemical breakdown on the radiation-impaired dentin. We can explain this finding by the richness of the VF matrix in filler leachable ions of Si, Yt, F, and Ba [23]. During its time in the oral environment, ion leaching could have allowed the permeation of water fluids into the spaces previously occupied by these ions. Additionally, water permeation exposes molecules of the resin that are located deeper within the matrix to the chemical hydrolysis of ester bonds in methacrylate materials [47]. Although this reaction is expected to be relatively slow at neutral pH values, variations in pH may lead to transient acid or base catalysis [45]. It may be possible that the acidic environment in group A may have caused faster degradation of local domains of the methacrylate network by *S. mutans* [13] in the acidic biofilm with the release of esterase enzymes, which greatly accelerate ester bond hydrolysis [47, 48]. These events may have led to on-going destruction of the sealing capacity of VF in Group A, which compared with the normal-salivary group B, had higher recurrent sensitivity at POST-3 and POST-4.

It is likely that the very similar performance of CPB and VF in the xerostomic group may be explained by the parallel behavior of the self-adhesive materials within the time of evaluation.

Although the reduction in saliva flow may have caused better efficiency of CPB at POST-1 and POST-2 in group A, as was the case with VF, we could suggest different reasons for the breakdown of CPB compared with VF within the 12-week control. In the present study, CPB, usually employed as an adhesive/sealer under a resin composite restoration, was evaluated for its desensitizing effect. After setting, the CPB hybrid layer in the dentin was left exposed to the oral environment without the usual resin restoration between it and the oral fluids [45]. It is well known that the surface roughness, heterogeneity, and porosity of the polymer make it extremely susceptible to being colonized and degraded in oral fluids [12]. Degradation phenomena of the hybrid interface have been shown to be particularly frequent at the gingival margin, where difficulty in cleaning allows attack by the proteins and microorganisms composing the oral biofilm [48]. Despite the same procedure of setting being used in the xerostomic group and in the control, a decrease in efficiency of the sealing was observed exclusively in group A between POST-3 and POST-4. Conversely, in the control normal-salivary patients, CPB was stable from POST-1 to POST-4, demonstrating that in a neutral pH environment, the CPB seal is able to resist exposure to oral fluids [49]. Therefore, we can explain the decrease in efficiency, which affected CPB in group A, as a result of factors probably mainly related to the xerostomic oral environment. We propose two major causes for the breakdown of CPB in group A: first, the esterase activities of *S. mutans* in the acidic biofilm at the margin of restorations causing hydrolysis of the bond, in the same manner exhibited by VF; and second, proteolytic degradation by matrix metalloproteinases (MMPs). More specifically, MMPs are a family of calcium-dependent zinc-containing proteolytic enzymes that are present in human saliva and capable of hydrolyzing hybrid layers [50]. MMPs require metal ions such as calcium or zinc to bind to the active site for their catalytic activation through a so-called cysteine switch [51]. More recently, it has been suggested that MMPs may become activated at the tooth and restoration interface by bacterial acid production [48]. Therefore, it might be suspected that the lactic acid production of S. *mutans* could have played a role in activating MMPs at the cervical margin of the CPB hybrid layer with a progressive loss in efficiency. This resulted in a lower significant difference in CPB performance in group A compared to group B.

UDS, a proprietary resin sealant enriched by ions [23], produced a slow but continuous decrease in the VAS from POST-1 to POST-3. Additionally, at POST-3, UDS showed the highest and most stable effect of all the agents. Moreover, the VAS values in group A were lower than those in the normal-salivary group B at points 2 and 3. Nevertheless, at the 12-week control, the VAS scores of UDS increased, showing similar values to those noted at PRE-1 and behaving similarly to VF and CPB in the xerostomic group, with a lower efficiency than that of the normal-salivary group.

We can explain the sealing capacity of UDS in terms of its ability to form an interdiffusion layer in dentin, resulting in

thick barrier-like and tag-like structures in the exposed tubules within 7 days of oral exposure [23]. In comparison to group B, the better efficiency observed in group A at POST-1 and 2 could be explained by a reduction of oral environmental fluids, which, at first, seemed to enhance the sealing of UDS as well as that of all the resin-based agents tested in this study. Moreover, compared with the other resin-based agents, the high concentration of Ca and Cl ions in addition to the ions of Si and Al might have rendered the UDS seal more capable of resisting the oral environmental stress of xerostomia, resulting in its higher desensitizing efficiency at POST-3. Nevertheless, at the POST-4 control, UDS lost its sealing capacity, producing an increase in the VAS values in DH, with no significant differences between it and the other desensitizing agents.

Comparing the data obtained in group A at POST-4 to those in group B, we can presume that the acidic environment of xerostomia could have affected the capacity of UDS, as was observed in the case of the other resins within the whole period of the study. This resulted in a lower significant difference in the performance of UDS between group A and group B.

Compared to all the other materials, FOV demonstrated the lowest efficiency in treating DH in xerostomic radiation patients and in the control group. Despite the slightly better efficiency of FOV in the xerostomic group compared with the normal-salivary group at POST-4, the data demonstrated that this kind of dentin coat could not resist oral stress regardless of environmental alteration. In group A, as well as in the control group, FOV showed the highest VAS scores after the 12-week exposure, highlighting its independence of any clinical variables.

The first null hypothesis was that there would be no significant differences in the effectiveness between the desensitizing agents after up to 12 weeks after application. This hypothesis cannot be rejected for the POST-3 control in group B and for the POST-4 controls of both groups because there were no statistically significant differences between the materials tested in both groups (Table 2). However, the null hypothesis could be rejected for other time periods because there were statistically significant differences between the test materials.

The second hypothesis was that there would be no significant difference between the xerostomic patients and normal-salivary patients. This null hypothesis could be rejected for VF, CBP, and the FOV, as there were statistically significant differences between group A and group B. However, the null hypothesis could not be rejected for the UDS because they were no statistically significant differences between the two groups.

Conclusions

In light of these results and taking into account the limitations of the present study, we conclude that radiation-treated HNC patients with hyposalivation may be a new risk group for DH. Concerning the treatment outcome, the application of tested desensitizing products initially leads to a reduction in symptoms to the levels in patients with normal salivary flow or even better. However, this effect is less long lasting in radiated xerostomic patients. These patients should therefore be informed that reapplication of desensitizing agents might have to be performed more often than in patients with normal saliva flow conditions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The protocol and informed consent forms were approved by the Ethics Committee of the University of Sassari (no. 1000/CE).

The study followed CONSORT guidelines and was registered at the US National Institutes of Health (ClinicalTrials.gov) # NCT02766127.

Informed consent Informed consent was obtained from all individual participants included in the study.

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