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INDIRIZZO IN ODONTOSTOMATOLOGIA PREVENTIVA

XXVII CICLO

Clinical evaluation of a self-adhering material as desensitizing agent in xerostomic patients for head and neck cancer.

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Abstract

Xerostomia is a common clinical symptom that may suffer patients with Head and Neck Cancers during and after radiotherapy. The aim of the present thesis were therefore: 1) to review the current state of knowledge of pathology, clinical complications and radiotherapeutic patient management, 2) to evaluate the aetiology of dentine hypersensitivity in conditions of reduced salivary flow resulting in the radiation exposure, 3) to evaluate the effectiveness of the materials commonly used in the treatment of hypersensitivity, when they work in conditions of hyposalivation.

Paper I is systematic review of actual management strategies for radiation-induced hypofunction and xerostomia in head and neck cancer patients. Paper II and III are based on the data of two split-mouth randomized clinical trial, where the efficacy of 4 different kinds of desensitizers has been assessed in the short and long term on patients with normal salivary flow. Paper IV is a long term evaluation based on the same experimental protocol applied on xerostomic patients.

The results showed that Dentine hypersensitivity is one among the multiple complications in the oral cavity that is possible diagnose in patients affected by xerostomia post radiotherapy. It may occur as a result of the combination between the typical etiologic factors and the reduction in salivary flow, that have a essential protective role for teeth and oral mucosa health. Dentine hypersensitivity arise from the tubular dentine exposure as a result of enamel loss and/or gingival root surface exposure and their occlusion is the first choice for the treatment. Unfortunately, there is still no gold standard for therapy of DH available today. In addiction, there is in the literature a lack of information about DH in xerostomic patients after radiotherapy.

The main conclusions from this thesis are that: 1) the radiation-induced xerostomia could be considered a multifactorial disease. It could depend on the type of cancer treatment and the cumulative radiation dose to the gland tissue. A preventive approach and the correct treatment of the particular radiotherapeutic patient can help to improve the condition of xerostomia. 2)The experimental data obtained from patients with normal salivary flow show that all the materials tested produced a reduction of dentine permeability. However, after 12-week controls, there was no significant statistical difference in the efficacy. 3) In xerostomic condition all the materials tested produced a significant reduction in the dentine sensibility. In light of the observed data, after 12-week controls there is no statistically significant difference between the desensitizers and they show a less stable behaviour compared to the normal salivation condition.

Key words: Xerostomia, head and neck cancers, radiotherapy, dentine hypersensibility, desensitising agents.

Contents

Original Papers

This thesis is based on the following four papers, which will be referred to in the text by their Roman numerals:

I. **Xerostomia induced by radiotherapy: an overview of the physio-pathology, clinical evidence and management of the oral damage.**
Pinna R, Campus G, Cumbo E, Mura I, Milia E.
Ther Clin Risk Manag. 2015;11.

II. **Short-term response of three resin-based materials as desensitizing agents under oral environmental exposure.**
Milia E, Castelli G, Bortone A, Sotgiu G, Manunta A, Pinna R, Gallina G.
Acta Odontol Scand 2013;71:599-609.

III. **Clinical evaluation of the efficacy of one self-adhesive composite in dental hypersensitivity.**
Pinna R, Bortone A, Sotgiu G, Dore S, Usai P, Milia E.
Clin Oral Investig. 2014; In press.

IV. **Clinical evaluation of a self-adhering material as desensitizing agent in xerostomic patients for head and neck cancer.**
Pinna R, Dore S, Sotgiu G, Milia E.
Ready for press.

Introduction

Xerostomia induced by radiotherapy in head and neck cancers.

Xerostomia is a term used to describe the subjective symptoms of a dry mouth often deriving from a lack of saliva. A large variety of causes can lead to xerostomia e.g. radiotherapy and chemotherapy(1-4), the chronic use of drugs (5-7), rheumatic and dysmetabolic diseases (8,9). Major salivary glands contribute to most of the secretion volume and electrolyte content of saliva (the parotid, submandibular, and sublingual glands, which account for 90% of saliva production), whereas minor salivary glands contribute little secretion volume and most of the blood-group substance (10).

Most patients diagnosed with head and neck cancer (HNC) receive radiotherapy as part of their cancer treatment. Head and neck cancer (HNC) actually includes many different malignancies. The most common type of cancer in the head and neck is squamous cell carcinoma, which originates in the cells that line the inside of the paranasal sinuses, nasal cavity, salivary glands, oral cavity, esophagus, pharynx and larynx (11). Worldwide, lip and oral cavity cancer along with thyroid cancer have the highest incidence; esophagus cancer is the most aggressive presenting a 4.9% mortality rate (Table 1). Similar findings regarding the incidence, mortality and prevalence of cancer in the European Union have been reported. The highest mortality rate belongs again to esophagus cancer with a predominance of 2.3% (Table 2).

HNC patients receive radiotherapy before, during, or after surgery as part of their cancer treatment. Routinely, HNC patients receive a dose between 50 and 70 Gy once a day for five days a week, (2 Gy per fraction) (12); on the other hand, if the radiotherapy protocol is just pre-operative, the total amount of radiation is usually lower. Conformal radiotherapy (CRT) is the most common type of radiotherapy used for the treatment of HNC; a special attachment to the radiotherapy machine carefully arranges the radiation beams to match the shape of the cancer, reducing the radiation to the surrounding healthy cells. Another similar type of radiotherapy used against HNC, known as intensity-modulated radiotherapy (IMRT), allows a more accurate delivery of specific radiation to be distributed to the tumor mass according to its location and severity, sparing the tissue and organs at risk, e.g., salivary glands (10). This radiation dose normally is used to destroy malignant cells and very often leads to the onset of salivary gland hypofunction and chronic xerostomia (13), that are the most common complications and occur to some degree in up to 100% of patients, severely impairing their quality of life (14).

The main problem, which correlates the xerostomia to radiotherapy is the anatomical location of the salivary glands. In fact, the salivary glands are superficially located compared to most head and neck tumors, and thus, the ionizing radiation has to pass through the salivary glands to effectively treat the tumor (15). There are differences among the various type of salivary glands; in fact, the submandibular gland is less radio

Tab. 1 – World Incidence, Mortality and 5-year prevalence of Head and Neck Cancer.

Cancer	Incidence			Mortality			5-year prevalence		
	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop
Lip, oral cavity	300373	2.1	4.0	145328	1.8	1.9	702149	2.2	13.5
Nasopharynx	86691	0.6	1.2	50828	0.6	0.7	228698	0.7	4.4
Other pharynx	142387	1.0	1.9	96090	1.2	1.3	309991	1.0	6.0
Oesophagus	455784	3.2	5.9	400156	4.9	5.0	464063	1.4	8.9
Larynx	156877	1.1	2.1	83376	1.0	1.1	441675	1.4	8.5
Thyroid	298102	2.1	4.0	39769	0.5	0.5	1206075	3.7	23.2

(%) = Risk of getting or dying from the disease before age 75 (%)
ASR (W) = Age-standardised rate (W)

Tab. 2 – European Union Incidence, Mortality and 5-year prevalence of Head and Neck Cancer.

Cancer	Incidence			Mortality			5-year prevalence		
	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	43847	1.6	4.9	14467	1.1	1.5	121633	1.7	28.4
Nasopharynx	3267	0.1	0.4	1494	0.1	0.2	9283	0.1	2.2
Other pharynx	26585	1.0	3.2	12583	1.0	1.4	67590	0.9	15.8
Oesophagus	34777	1.3	3.4	29845	2.3	2.8	38086	0.5	8.9
Larynx	28336	1.1	3.1	12248	1.0	1.2	94193	1.3	22.0
Thyroid	37440	1.4	5.4	3637	0.3	0.3	149044	2.1	34.8

(%) = Risk of getting or dying from the disease before age 75 (%)
ASR (W) = Age-standardised rate (W)

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sensitive than the parotid gland (16). From this point of view, the most severe and irreversible forms of salivary gland hypofunction result from the damage/loss of salivary acinar cells, giving rise to rapid and predictable compositional changes, reduction in saliva production and in the quality of the flow.
Radiotherapy can cause some temporary side effects. Although these may be worse if the treatment is combined with chemotherapy, they gradually disappear after the treatment has finished. Most radiotherapy side effects occur towards the middle and end of the course of treatment and continue during the first couple of weeks after the treatment. The effects can be mild or more troublesome, depending on the dose of radiotherapy and the length of treatment. Thus, the quantitative and qualitative salivary changes predispose the irradiated patient to a variety of problems.
The final degree of damage to gland tissue depends on individual patient characteristics, such as pre-treatment already done, age, and sex.
Xerostomia may affect the 80% of the patients who need radiotherapy as a primary treatment, as an adjunct to surgery, in combination with chemotherapy, or as palliation (17-19). Hyposalivation represents the biggest acute side effect in HNC radiotherapy. The reduced secretion rates and the alteration in the quality of saliva in irradiated patients are due to irreversible fibrosis and atrophy of the gland parenchyma (20), as well as damage to the extra glandular blood vessels or nerve structures (21). The major reduction of salivation after radiotherapy is observed in the period from the onset of radiotherapy to three months after completion. During radiotherapy, the first ten days are the worst ones as a massive decrease in saliva production occurs; especially in the first week, it could reduce by 50% to 60% (Fig. 1) (22). After this period the flow rate is reduced by less than 10% of the initial conditions (Fig. 2) (23). The salivary composition may change and it becomes more viscose than usual, so its colour may turn yellow, brown or even white (Fig. 3).
As a consequence of a reduction in the rate of saliva flow, which is correlated to the amount of radiation given to the patient, oral complications occur (16). The buccal mucosa has a dry and sticky appearance (Fig. 2). The normally moist, glistening appearance of the oral cavity is often replaced with a thin, pale, cracked appearance that is more susceptible to gingivitis and bleeding. Another frequent acute side effect is oral mucositis, which can be experienced by more than 50% of patients receiving HNC radiotherapy (Fig. 1). Some typical side effects are onset of erythema, edema and pain in the oral mucosa (24). Furthermore, the lack of saliva may lead to angular cheilitis, cracked lips (Fig. 4), periodontal disease, aching of the mouth and halitosis.
When part or all of the mouth is treated, the sense of taste may change quickly during the radiotherapy and some patients may even either lose their sense of taste completely or find that everything tastes the same (usually rather metallic or salty). Changes in taste are correlated to the direct irradiation of the taste buds, and also to the reduction in salivary flow rate that alters the ionic composition of saliva that is related to the sensation of taste (25).

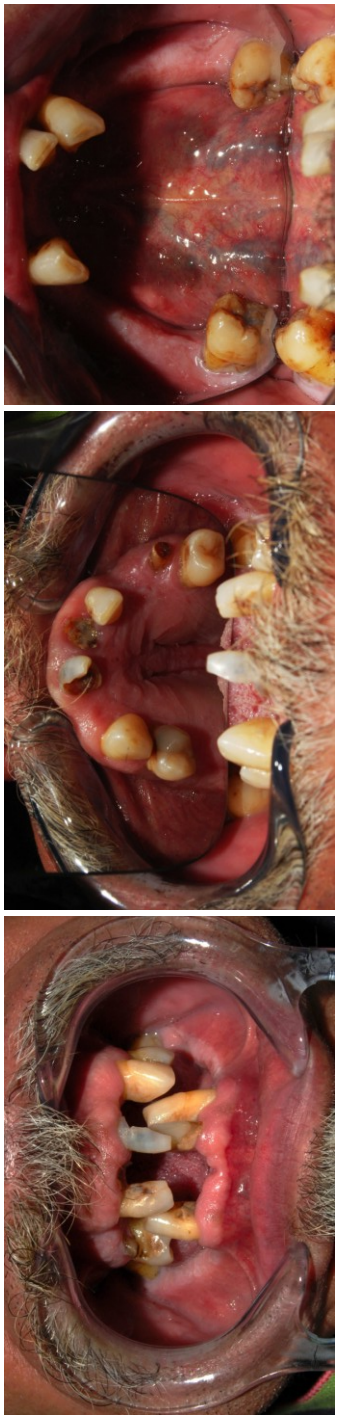

Fig. 1 - Condition of the oral cavity during the first week of radiation therapy.

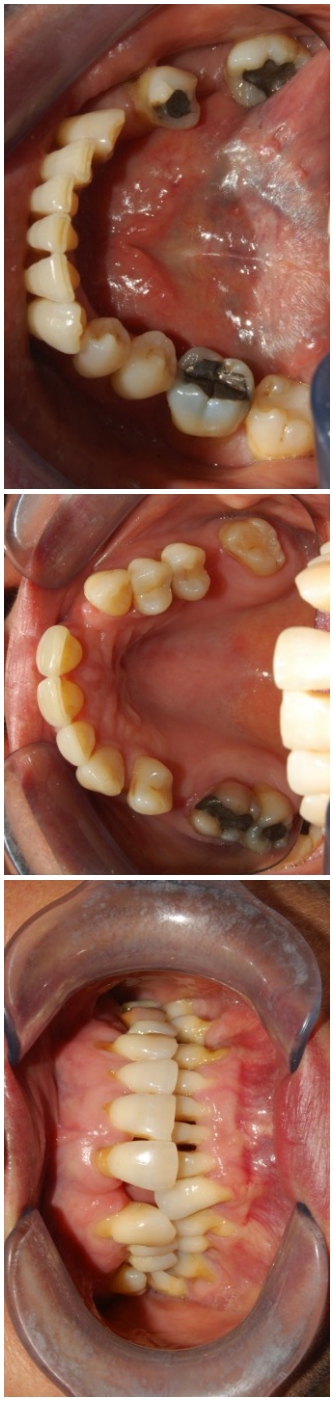

Fig. 2 - Condition of the oral cavity after three months of radiotherapy.

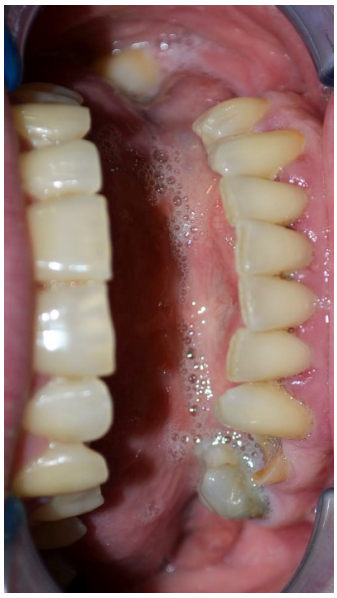

Fig. 3 - Appearance of saliva after radiotherapy.

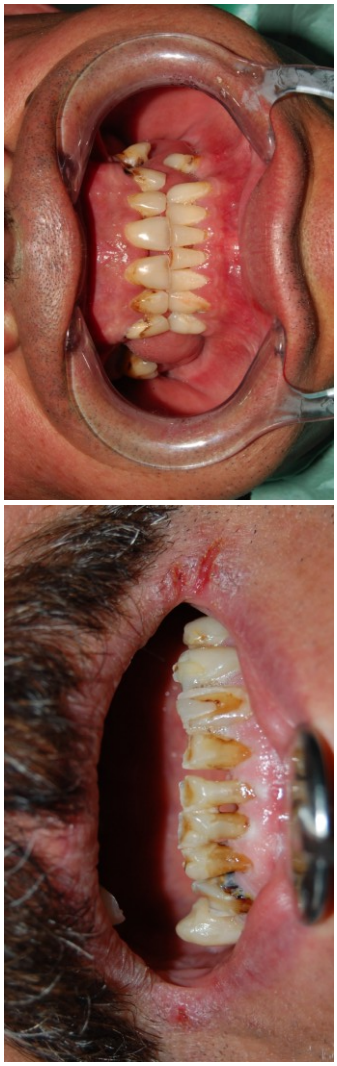

Fig. 4 - Oral and dental lesions after radiotherapy.

Moreover, the loss of saliva compromises mastication and nutrition. Some patients lose their appetite as a general effect of radiotherapy. Dryness of the mouth and lips can cause discomfort, ranging from a mild irritation to a severe burning sensation with difficulties in normal eating habits, particularly eating spicy or acidic food.
A sore, dry mouth can also make eating and swallowing difficult, because moistening of food is insufficient and oral mucosa surfaces are not wet and not lubricated enough (26). Furthermore an insufficient lubrication, due to a diminished salivary output, causes intolerance to prosthetic appliances, so more friction is present between the mucosa and the resin that can injure the delicate irradiated epithelial layer. In addition, the inadequate presence of saliva weakens the stability of prostheses in the mouth. Ulceration is more likely because the dry mucosa is more vulnerable to trauma.
A further complication that tends to occur later in irradiated patients is the increased risk of developing dental caries and oral infections, due to the alterations in the saliva flow and consequently in oral microflora (27). The decay is most often recurrent or primary and located at sites generally not usually susceptible to caries such as the cervical margins, incisal margins or the tips of teeth (Fig. 4).

Dentine Hypersensitivity in xerostomic patients after radiotherapy.

Saliva plays an essential role for the health condition of the oral cavity (28). Saliva components interact in related functions in the following general areas:
1) bicarbonates, phosphates, and urea act to modulate pH and the buffering capacity of saliva;
2) macromolecule proteins and mucins serve to cleanse, aggregate, and/or attach oral microorganisms and contribute to the dental plaque metabolism;
3) calcium, phosphates, and proteins work together as an antisolubility factor and modulate demineralization and remineralization of tooth surfaces;
4) immunoglobulins, proteins, and enzymes provide antibacterial action.
Thanks to the properties to humidify and lubricate the soft and hard tissue, saliva plays protective effects of the tissues, among which the preventing of mechanical damage. As regard to the tooth structural integrity, the buffering effect of the saliva is very important in the control of demineralization/remineralisation process (28-30). Physiologically saliva is supersaturated with respect to the tooth mineral content. Among the inorganic components, bicarbonate is related to saliva buffering capacity, while calcium, fluoride and phosphate are necessary for remineralisation allowing for the maintenance of tooth mineral integrity (31).
As a consequence of a reduction in the rate of saliva flow, which is correlated to the amount of radiation given to the patients, oral complications will occur (32). An increase of Dentine Hypersensitivity (DH) may represent one of the most common manifestations that affects patients after radiotherapy (33-36).

DH is characterized by a short and sharp sensation of pain arising from the tubular dentine exposure as a result of enamel loss and/or gingival root surface exposure due to attrition, abrasion, erosion, abfraction or gingival recession (37) (Fig 2). Any thermal, osmotic and mechanical stimuli induced by the application of tooth brushing, sweet and acid foods, hot or cold drinks may provoke pain referred to fluid shifts in the exposed dentinal tubules with activation of the pulp nerves, according to "Brännström's hydrodynamic theory" (37-40) (Fig. 5).
Therefore, the occlusion of the tubules by different materials may reduce the fluid movement inside the dentinal tubules and the clinical symptoms of DH (39). When reducing fluid movement by fully or partially occluding open dentine tubules, hypersensitivity could be diminished (41). Consequently, most desensitizing agents have been designed to cover the dentine surface with occlusion of the exposed tubules or penetration in the tubules, coating and sealing them (39,26-30) (Fig 6).
However, the efficacy of desensitizing agents is quite variable in long term, as reported in our previous studies and other clinical outcomes conditions (42 – 46). Clinical data show that the desensitizing capacity has been correlated to the ability of the material to resist in front of the interactions of saliva and other oral ambient interferences (46). Moreover, differences in the efficacy were attributed to the different chemistries of the materials and application modalities required by the desensitizer itself (47-50)..
Several different formulations of resin-based materials have being used in DH treatment. Four different kind can be summarized: 1) *varnishes*, usually with fluoride, creating a coat of calcium fluoride precipitates on the exposed surface and dentinal tubules (51,,52-54); 2) *adhesive monomeric systems*, with or without the etching phase, able to seal the exposed surface by a layer of interdiffusion in dentine and tubular resin plugs (47-49, 55); 3) *resin sealants* and 4) *flowable resin composites* able to form covers on the dentine surface (56) which sealing capacity in the time is influenced by the resin composition and the coupling between filler and matrix (57).

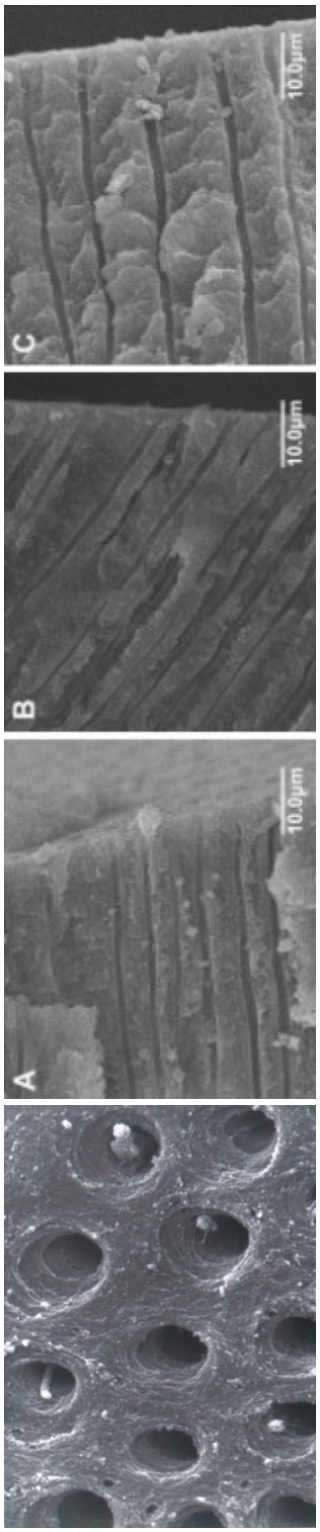

Fig. 5 - SEM micrograph of dentinal tubules.

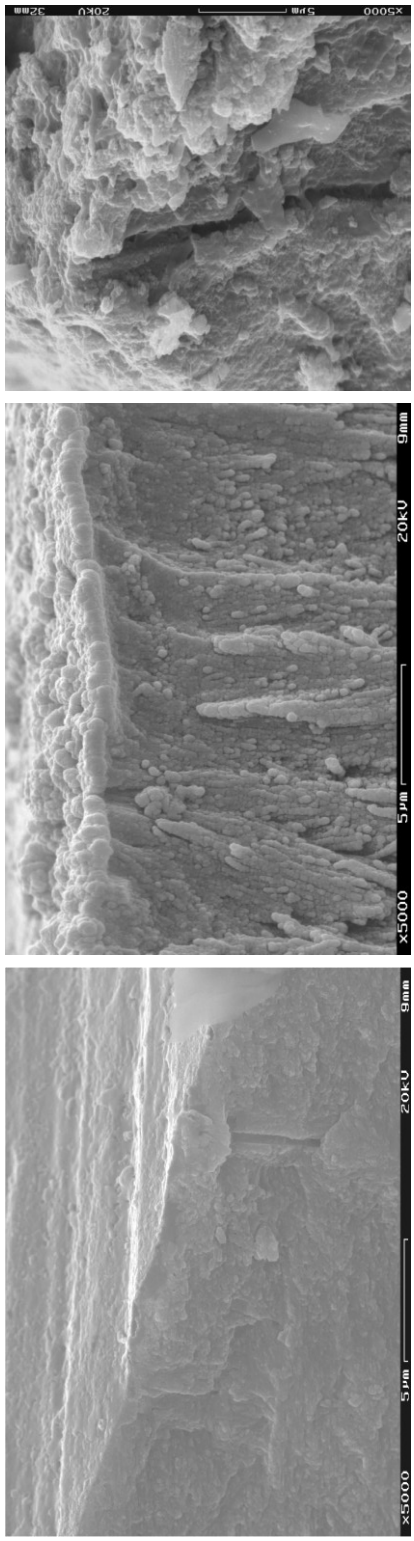

Fig. 6 – SEM micrograph of occlusion of the exposed tubules or penetration in the tubules by different dental materials

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Rational of the study.

Twenty-four patients about to start radiotherapy for HNC were subjected to dental check up at the Dental Clinic of the University of Sassari, during and after the treatment in 2013, alongside with an on-going evaluation study of DH patients with normal salivary flow. Few months after the end of radio-exposition, 8 patients began to complain DH. Our research team started to study if a correlation between their health status and the clinical symptoms has been already described in the literature. With a systematic approach, a literature search for articles related to the Radiotherapy Xerostomia and DH, published between 01/01/1990 and 31/06/2013, was conducted in the databases MEDLINE/PubMed, Scopus and The Cochrane Library, using combinations of the MeSH terms: [Head and Neck Cancer] OR [Salivary Hyposalivation] OR [Xerostomia] OR [Radiotherapy] AND [Dentin Hypersensitivity]. The electronic searches didn't identify any studies regarding the radiotherapeutic xerostomia and dentin hypersensitivity.
In the light of the results obtained, the research team decided to change the experimental protocol of the on-going study, adapting it to the clinical condition of patients undergoing radiation therapy.
The aim of the new clinical evaluation was to evaluate the 3-month efficacy of 4 kinds of dental materials used as desensitizing agents, especially focusing on the differences in DH reduction between the tested materials after the observation period. In addition, the difference of the desensitizing agent efficacy among xerostomic patients and patients with normal salivary flow was evaluated.

Aims

The owerall aim of this thesis was to collect knowledge about radiation-induced hypofunction, xerostomia and dentine hypersensitivity in head and neck cancer patients. In more detail, the aims of this thesis were:

- To review the current state of knowledge of pathology, clinical complications and radiotherapeutic patient management
- To evaluate the aetiology of dentine hypersensitivity in conditions of reduced salivary flow resulting in the radiation exposure
- To evaluate the effectiveness of the materials commonly used in the treatment of hypersensitivity, when they work in conditions of hyposalivation

Material and Methods

Paper I

Systematic Review methodology

Search strategy

A first systematic literature search for articles published between 01/01/1970 and 30/06/2013 was conducted in the databases MEDLINE/PubMed and The Cochrane Library, using combinations of the MeSH terms: [Saliva] OR [Salivary Glands] OR [Saliva Flow] OR [Salivation] OR [Salivary Gland Diseases] OR [Xerostomia] OR [Saliva in Xerostomia] OR [Dry Mouth] OR [Oral Dryness] OR [Composition Saliva Xerostomia] AND [Head and Neck Cancer] OR [Radiotherapy] OR [Radiation-induced Xerostomia] OR [Parotid-Sparing Intensity-Modulated Radiotherapy] AND [Quality of Life Analysis-Xerostomia] OR [Management Strategies Salivary Gland Hypofunction] OR [Prevention Xerostomia] OR [Treatment Xerostomia]. The search results were imported into a computerized database Review Manager 5.2. The search results from each of the electronic databases of MEDLINE/PubMed and The Cochrane Library were combined, and duplicated publications were eliminated. Subsequently, an update to include studies published up to 30/06/2013 was performed.

Criteria for selecting studies

After completing the search, articles for review were selected based on:

- English language
- Original data of cancer therapies protocols
- Oral complications associated with cancer therapies
- Human

Exclusion criteria

The reasons for exclusion were defined as follows:

- Studies without original and/or actual data
- Studies with data from previous publications
- Opinion papers
- Editorials

In this way, a preliminary set of potentially relevant publications, removing irrelevant citations according to the criteria was created. Two reviewers (RP and GC) independently screened the registered title and abstracts, author and references in two separate files (one for included abstracts and one for excluded abstracts) using a screening guide based on eligibility criteria. Studies rejected at this or subsequent stages were reported in the table of excluded studies. The full text of all potentially eligible

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studies in at least one screening was retrieved. Reviewers then evaluated the full text for inclusion using a screening guide and a second reviewer (RP) screened all the findings. When disagreement occurred, a third reviewer (IM) was consulted. For each review, the following information was recorded: Year, Authors, Journal, Aim and Number of Papers Reviewed; and for Clinical Trial Papers included: Year, Authors, Journal, Aim, Number of Patients and Results. All studies meeting the inclusion criteria then underwent validity assessment. Two examiners (RP and GC) read the papers independently. The qualities and relevance of each study were graded as follows: high (+++), medium (++) or low (+) using a study-quality checklist. External validity, internal validity and study precision were analysed to obtain an overall assessment of quality. The assessment was used as a basis for the discussion between the two examiners to grade the studies. In the case of disagreement, all authors discussed the paper until a consensus was reached.

Paper II

Elemental analysis

The elemental composition of Vertise Flow™, Universal Dentine Sealant and Flor-Opal® Varnish was investigated using an X-ray energy dispersive spectrometer (EDX) (INCA-X-acta, Oxford Instruments, Tubney Woods Abingdon, Oxfordshire, UK) in conjunction with an environmental scanning electron microscope (ESEM) (EVO® LS 25, Zeiss, Oberkochen, Germany). EDX was carried out using an accelerating voltage of 20 kV and ESEM was used for imaging of each sample at standardized magnification (200X, 1000X).

For the semi-quantitative X-ray analysis VF, UDS and FOV (0.5 mL) were weighed, placed in a thin layer over Perspex® slabs mounted on aluminum stubs (Agar Scientific, Stansted, UK). Three stubs were made for each tested material and the analysis was performed twice for each sample. The elemental analysis (weight % and atomic %) was performed in low-vacuum conditions (20 Pa). Atomic number, absorption, and fluorescence corrections were applied during the analysis with the ZAF correction method.

Experimental design

Subjects who had hypersensitive teeth were selected from an ongoing program of evaluating desensitizing agents at the Dental Clinic of the University of Sassari. Two clinicians selected patients complaining about hypersensitivity and who had reported this to the Department of Periodontology at the Dental Clinic. The protocol and informed consent forms were approved by the ethics committee at the University of Sassari (n° 1000/CE). The medical and dental history of the patients was collected, and

sensitive teeth were differentiated from other clinical conditions which frequently interfere with DH. All the subjects were thoroughly informed about the study's purpose, risks, and benefits. A total of 86 patients with hypersensitive teeth were collected after an intake period of 8 months. The study inclusion/exclusion criteria were the following: 1) patients were considered suitable for the study if they had sensitive teeth showing abrasion, erosion or recession with the exposure of the cervical dentine; 2) teeth with subjective or objective evidence of carious lesions, pulpitis, restorations, premature contact, cracked enamel, active periapical infection, or which had received periodontal surgery or root-planning up to 6 months prior to the investigation were excluded from the study. Other exclusion criteria were professional desensitizing therapy during the previous 3 months, or use of 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). As a consequence, the total study population included in the program was of 74 subjects, 43 female and 31 male, aged 27- 75 years (mean age ± standard deviation: 53 ± 7 years) with a total of 286 hypersensitive teeth (mean teeth for patient 2 ± 1). The level of sensitivity experienced by the patient was considered as independent of the position of the hypersensitive tooth in the oral cavity.

Morphological study

VF, UDS and FOV's, ability to occlude dentine tubules and their morphology on dentinal surfaces were evaluated in 30 selected patients, 18 female and 12 male, part of the total sample of 74 subjects with hypersensitive teeth. Patients had 30 hypersensitivity teeth (11 premolars, 13 incisors, 6 cuspids), whose Grade III mobility and significantly reduced response to periodontal treatment suggested the need for extraction.

A full medical and dental history was taken and all the teeth were carefully examined to confirm the diagnosis of DH. The nature and scope of the study was explained, and informed consent was obtained.

A week before treatment, patients received oral prophylaxis and were randomly assigned to three experimental groups *(N*=10 per group*)*. The treatments were carried out at random by one of the clinicians while the other assisted. The teeth were isolated with cotton rolls and the treatment with VF, UDS and FOV was performed as summarized in Table 1. As recommended, a halogen curing light (Optilux 501, Kerr Corporation, USA; 11mm exit window) under the standard curing mode (output wavelength range: 400–505 nm; output irradiance: 580–700mW/cm2) was used to allow light curing of VF. After the treatment, teeth were immediately extracted (*N*=5 per subgroup), subgroup 1, and after 7 days post-treatment (*N*=5 per subgroup), subgroup 2.

After extraction, samples were rinsed with distilled water at 37°C and fixed in a solution of 2.5% glutaraldehyde in 0.1 M PBS buffer (pH 7.2) for 72 h. In each sample, the

treated cervical dentine was sectioned from the remaining crown and roots of the tooth with a water-cooled saw (Isomet low-speed saw; Buehler, Lake Bluff, IL, USA) and then fractured into two halves in order to analyze the buccal surface and the longitudinal surface of the material-treated dentine surfaces. Samples were post-fixed in 1% osmium tetroxide, dehydrated in increasing concentrations of acetone (25% – 100%), dried by critical point drying, and metal-coated. Specimens were then observed using a scanning electron microscope (SEM) (Zeiss, DSM 962, Oberkochen, Germany). Observations were recorded at standardized magnifications (1000×, 3000×, 5000X).

Clinical study

The study population consisted of another 36 patients, 19 females and 17 males who were randomly selected from the total population of 74 subjects who had hypersensitive teeth. A total of 90 teeth (30 premolars, 44 incisors and 16 cuspids constituted the group of hypersensitive teeth for the clinical effectiveness of VF, UDS and FOV.
A week before the experiment, patients received oral prophylaxis. Non-fluoride toothpaste, soft toothbrush and oral hygiene instructions were also provided in order to have standardized habits during the period of the study.
Teeth were randomly assigned to three groups (N=30 per group) for the treatment with the three desensitizing agents (Table 1). At the baseline visit, they were reassessed for dentine hypersensitivity using the Visual Analogue Scores (VAS) of pain. Treatment was performed by one examiner, while the pain stimulus was given by the other examiner with the same equipment yielding similar air pressure each time.
The VAS scale consisted of a horizontal line that was 100 mm long, on which "no pain" was marked on the right-hand extremity and "unbearable pain" on the other. The patients expressed the intensity of the pain experienced by placing a mark at any point along the continuum. The distance, expressed in millimeters, from the right edge of "no pain" was used as the VAS score. Each patient was asked to rate the perception of discomfort after the application of air via a dental syringe at 45 to 60 psi, 1cm at the cervical third of the tooth after removing supragingival plaque with a low-speed handpiece with pumice powder and without fluoride. The adjacent teeth were covered by cotton rolls. The stimulus was delivered until reaction or up to a maximum duration of 10 seconds by the same examiner with the same equipment yielding similar air pressure each time. The subject's response was considered as the baseline measurement (PRE-1) -mean±standard deviation VAS score: 5.3±2.1. Before the application of the material (PRE-1), immediately after (POST-1), and after 7 days of oral environment (POST- 2), the same clinician carried out the sensitivity test.
To compare the efficacy of the treatments, teeth were evaluated as a statistical unit rather than a subject. Data were elaborated using parametric tests (ANOVA for more than two samples adjusted according to Sidak’s multiple testing) with a 5% significance level.

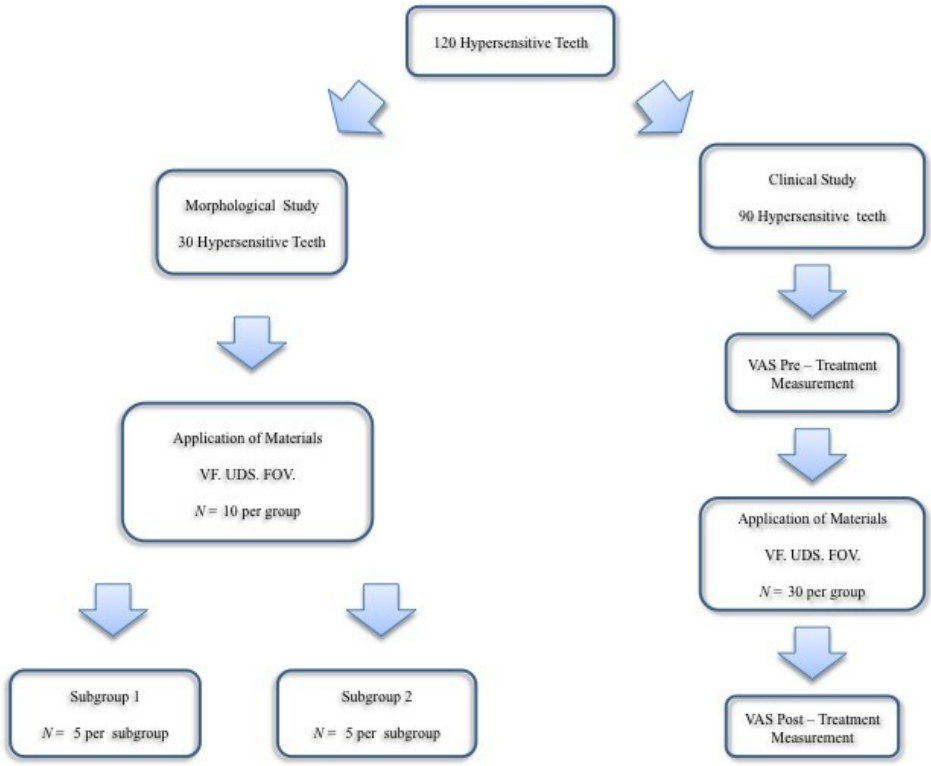

Fig. 7 - Summary of the experimental design to collect hypersensitivity teeth to test the efficiency of desensitising materials during the clinical study.

Paper III

Partecipants

The study was designed as a split-mouth randomized clinical trial. The protocol and informed consent forms were approved by the ethics committee at the University of Sassari (n° 1000/CE). Subjects who had hypersensitive teeth were selected from an on-going program of evaluating desensitizing agents at the Dental Clinic of the University of Sassari, Italy.

Two examiners selected patients complaining about hypersensitivity and who had reported this to the Department of Periodontology at the Dental Clinic. The medical and dental history of the patients was collected, and sensitive teeth were differentiated from other clinical conditions that frequently interfere with DH. To participate in the study, the subjects had to have two or three teeth that were hypersensitive to the stimulation with a blast of air.

All the subjects were thoroughly informed about the study's purpose, risks, and benefits. A total of 86 patients with hypersensitive teeth were collected. The study

inclusion/exclusion criteria were the following: 1) patients were considered suitable for the study if they had sensitive teeth showing abrasion, erosion or recession with the exposure of the cervical dentine; 2) teeth with subjective or objective evidence of carious lesions, pulpitis, restorations, premature contact, cracked enamel, active periapical infection, or which had received periodontal surgery or root-planning up to 6 months prior to the investigation were excluded from the study. Other exclusion criteria were professional desensitizing therapy during the previous 3 months, or use of 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). As a consequence, the total study population included in the program consisted of 46 patients, 27 females and 19 males who were randomly selected from the total population of 74 subjects who had hypersensitive teeth. A total of 116 teeth (52 incisors, 38 premolars, and 26 cuspidates) were included in the study.

Clinical Procedure

VF self adhering composite was compared to: Universal Dentin Sealant (UDS) (Ultradent Products Inc., South Jordan, UT, USA), a biocompatible, non-polymerizable, high molecular weight resin sealant in alcohol solvent, Clearfil Protect Bond (CPB), (Kuraray Noritake Dental, Osaka, Japan) a methacrilate-based resin, self-etching adhesive system, and Flor-Opal® Varnish (FOV), (Ultradent Products Inc., South Jordan, UT, USA), a fluoride-based varnish.

A week before the experiment, patients received oral prophylaxis. Non-fluoride toothpaste (Biorepair, Coswell), soft toothbrush (Oral-B Sensitive Advantage, Procter & Gamble) and oral hygiene instructions were also provided in order to have standardized habits during the period of the study.

In view of the treatment with the desensitizing agents, teeth were randomly assigned in to four groups (N=29 per group) (Fig. 8). The level of sensitivity experienced by each patient was considered as independent of the position of the hypersensitive tooth in the oral cavity 11]. The pain experience was assessed using a Visual Analogue Scores (VAS) graded from 1 to 10, according to the same procedure of a previous study (56). The pain stimulus was given by one examiner with the same equipment yielding similar air pressure each time, while the other one performed the treatments. The subject's response was considered before the application of the material (PRE-1), immediately after (POST-1), after 1 week (POST- 2), 4 weeks (POST- 3) and 12 weeks (POST-4) of 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.

Statistical Analysis

Shapiro-Wilk normality test was used to assess the normality distribution of the collected variables. Median and inter-quartile ranges were used as measures of central tendency and variability to describe quantitative variables. Statistical differences in the Visual Analogue Scale (VAS) values of VF, UDS, CPB and FOV were performed using the Kruskall-Wallis analysis at the different time-points, adjusting statistical significance for the multiple comparisons (Bonferroni correction). Statistical differences at the baseline VAS value and the other time-points were calculated performing the Mann–Whitney U test. 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).

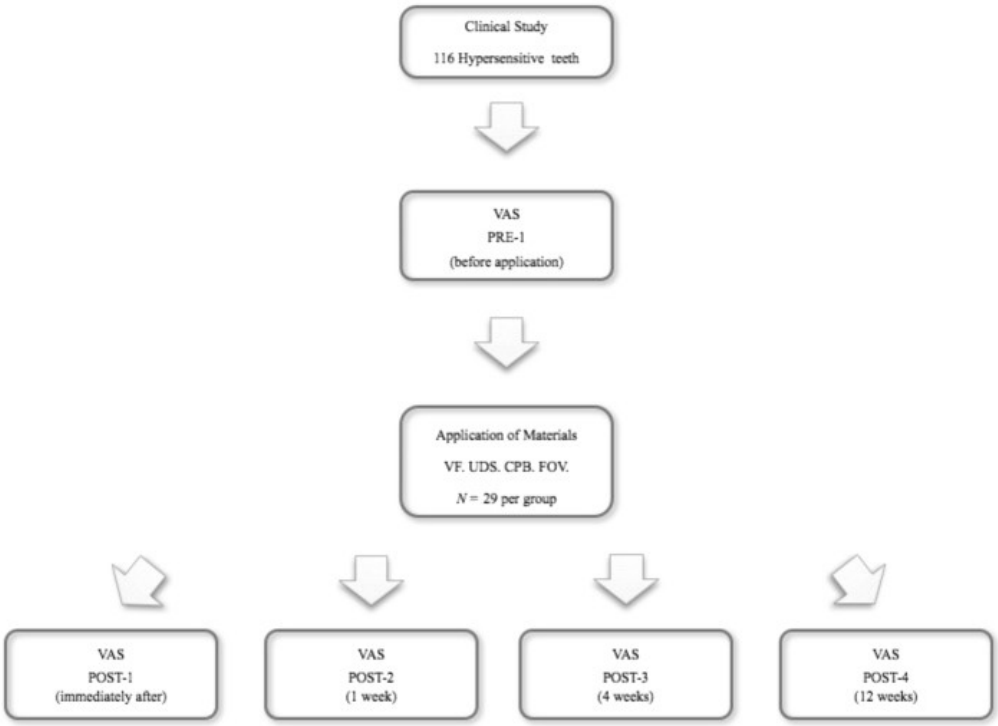

Fig. 8 - Summary of the experimental design to collect hypersensitivity teeth to test the efficiency of desensitising materials during the clinical study.

Paper IV

Partecipants

The study was designed as a split-mouth randomized clinical trial. The protocol and informed consent forms were approved by the ethics committee at the University of Sassari (n° 1000/CE). Radio-therapeutic patients who had hypersensitive teeth were selected from an on-going program of evaluating desensitizing agents at the Dental Clinic of the University of Sassari, Italy.

During 2013, a total of 48 patients were visited at the Department of Radiology. 24 patients, which needed radiotherapy for HNC were collected. These groups of patients were subjected to a dental check-up with eventual teeth treatments, during and after the radiotherapy. Few months later the end of the radio-exposition, 8 patients began to complain HD.

To participate in the study all the subjects were thoroughly informed about the study's purpose, risks, and benefits.

The study inclusion criteria were the following:

- A relative good general health status;
- A clinical reduction of salivary flow;
- Two or three teeth that were hypersensitive to the stimulation with a blast of air.

In addition, patients were considered suitable for the study if they had sensitive teeth showing abrasion, erosion or recession with the exposure of the cervical dentine.

The study exclusion criteria were:

- teeth with subjective or objective evidence of carious lesions, pulpitis, restorations, premature contact, cracked enamel, active periapical infection;
- received periodontal surgery or root-planning up to 6 months prior to the investigation;
- professional desensitizing therapy during the previous 3 months
- use of 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).

Clinical Procedure

Saliva collection

All salivary assessments were performed in the absence of acute sialadenitis. The flow rate was determined in every person according to the method described by Sreebny (58). Saliva was collected in a standardised manner. Patients were instructed not to eat, drink, or smoke for 90 minutes before the sialometric assessment. All assessments were performed at a fixed time of the day, between 10 am and 1 pm, in order to minimise fluctuations related to a circadian rhythm of salivary secretion and composition. All

assessments were performed by the same observer. Whole saliva was collected in pre-weighed plastic tubes using an electronic scale.
Unstimulated salivary secretions were collected for 5 min with the patient seated in an upright position and with the tilted head. When possible the tongue, cheeks and lips movements were limited during the procedure. At the end of the collection period, the patient had to expectorate saliva into the test-tube.Stimulated whole saliva was collected asking to patients to chew a small block of paraffin wax or chewing gum. All the saliva secreted for 5 min was then collected in the test-tube.Measuring vessels were weighed after each collection using an electronic scale, and salivary flow rate was expressed in ml/min, which is nearly equivalent to g/min (59). A secretion rate < 0.1-0.2 ml/min for unstimulated flow and < 0.5-0.7 ml/min for stimulated flow was considered as an objective sign of hyposalivation.

Assessment of hypersensitivity and desensitizing agents application.
A week before the experiment, patients received oral prophylaxis. Non-fluoride toothpaste (Biorepair, Coswell), soft toothbrush (Oral-B Sensitive Advantage, Procter & Gamble) and oral hygiene instructions were also provided in order to have standardized habits during the period of the study. The level of sensitivity experienced by each patient was considered as independent of the position of the hypersensitive tooth in the oral cavity (30). The pain experience was assessed using a Visual Analogue Scores (VAS) according the methodology described in the previous studies.
The following dental materials were used following manufacture instructions: Vertise Flow^{TM} (VF) (Kerr Corporation, Orange, CA, USA), a self-adhering composite; Universal Dentin Sealant (UDS) (Ultradent Products Inc., South Jordan, UT, USA), a biocompatible, non-polymerizable, high molecular weight resin sealant in alcohol solvent; Clearfil Protect Bond (CPB), (Kuraray Noritake Dental, Osaka, Japan) a methacrilate-based resin, self-etching adhesive system, and Flor-Opal® Varnish (FOV), (Ultradent Products Inc., South Jordan, UT, USA), a fluoride-based varnish.
All 8 patients were considered eligible and agreed to take part in the study. In view of the treatment with the desensitizing agents, teeth were randomly assigned into four groups (N= per group) (Fig. 9). None of the participants failed to complete the study neither reported any adverse reactions.

Statistical Analysis
Shapiro-Wilk normality test was used to assess the normality distribution of the collected variables. Median and inter-quartile range were used as measures of central tendency and variability to describe quantitative variables. Statistical differences between Visual Analogue Scale (VAS) values of Vertise FlowTM, Universal Dentine Sealant, Clearfil Protect Bond and Flor-Opal® Varnish were evaluated performing Kruskall-Wallis analysis at different time points, adjusting statistical significance for the multiple comparisons (Bonferroni correction). Statistical differences between baseline

VAS values and those obtained at other time-points were calculated performing the Mann–Whitney U test. 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).
Statistical differences between VAS values of xerostomic group and normo-salivation group were calculated performing the Mann–Whitney U test. Statistical analysis was carried out using STATA®13 (StataCorp, College Station, TX, USA).

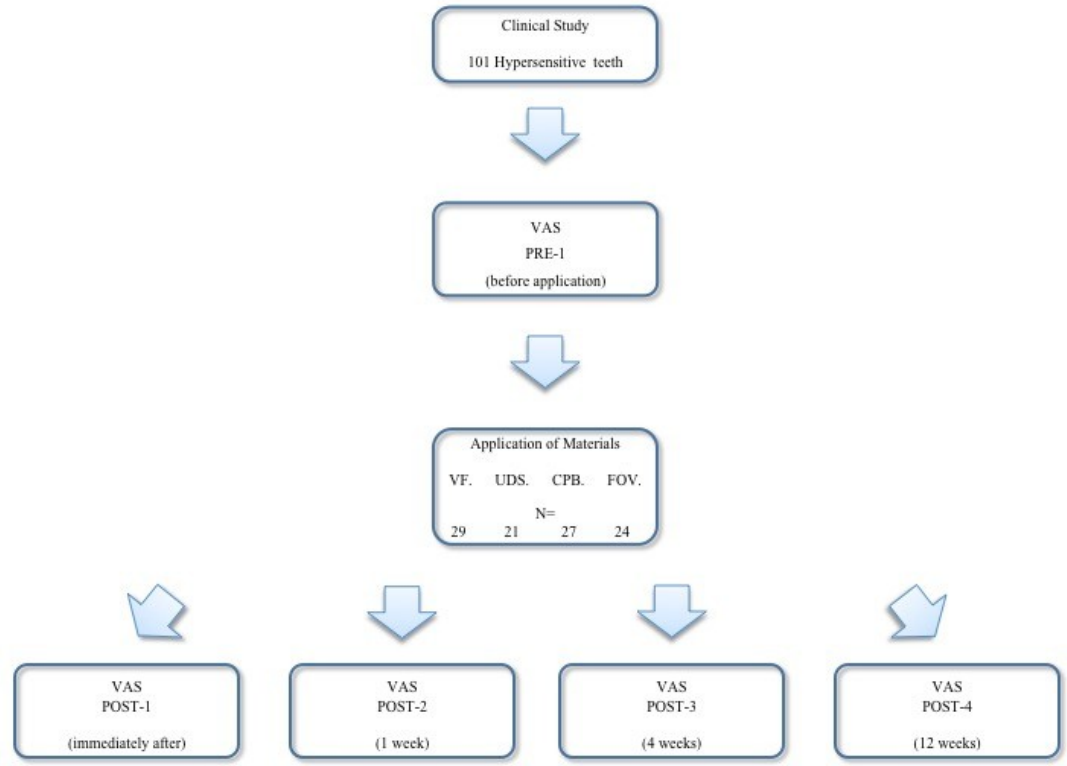

Fig. 9 - Summary of the experimental design to collect hypersensitivity teeth to test the efficiency of desensitising materials during the clinical study.

Results

Review research result
(Paper I)

The electronic searches identified about a thousand titles and abstracts, and after reviewing the titles 411 studies were evaluated. Subsequently, during the review of the abstract, 336 studies were excluded. The final analysis included 70 articles that conformed to the criteria for the present review (Fig. 10). Although animal studies have been excluded, important information regarding the experimental results on two of the papers was considered useful and therefore they were discussed.

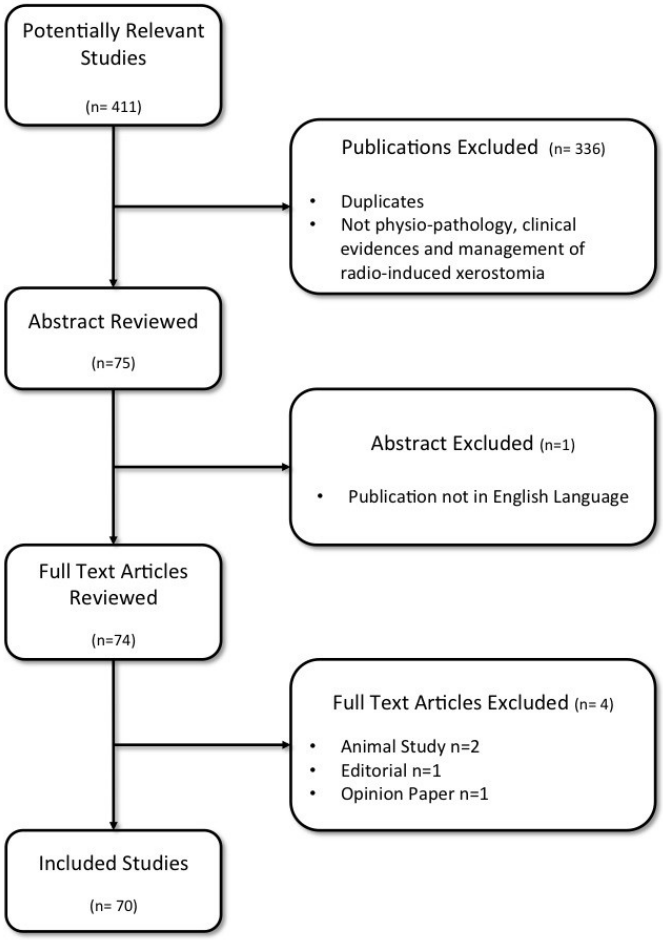

Fig. 10 - Search Flowchart.

Laboratory and Clinical Analysis of short-term evaluation of DH treatment
(Paper II)

Elemental analysis
VF treatment left a layer of highly visible randomly distributed 5 to 40 μm particles. Spectra of silicion (Si), ytterbium (Yb) alumina (Al) were highest in the layer in which also phosphorus (P), calcium (Ca), barium (Ba) and fluoride (F) were found.
UDS treatment left fine, dispersed particles of about 0.5 μm in a thin and smooth layer. Spots on these particles showed very high pecks of Ca and chlorine (Cl). The semi-quantitative analysis obtained by scanning different areas of the matrix highlighted Ca and Cl associated with Si and other oxides of Al, iron (Fe), chrome (Cr), potassium (K), sulphur (S), magnesium (Mg), titanium (Ti) and zinc (Zn). FOV treated samples showed a layer of particles embedded in a smooth matrix rich in sodium (Na) and F peaks and with traces of Si and P.

Morphological study
On the surface of the exposed dentine (ED) to the oral fluids, VF formed a thick, irregular coat that completely masked the underlying tubular dentine. Cracks were also noted in ED. Longitudinal sections showed a coating about 3 μm thick composed of a matrix with crystal-like particles of different sizes. Tubule orifices were tightly blocked by the material and plugs of resin-like material were found inside the tubules. After 7 days of exposure to the oral environment (subgroup 2), tubular orifices were still not visible on ED treated dentin surface which showed cracks and gap formations. Crystal-like precipitates were dissolving, but the tubular apertures remained occluded.
UDS formed a smooth amorphous layer that contained particles about 0.5 μm in diameter, over dentine. Particles had a tendency to form clusters and adhered to the underlying dentine completely occluding the tubular orifices. Longitudinal sections showed the dentine surface covered by a coating of UDS that was about 0.4 μm thick, and plug-like structures in the tubules. After exposure to oral environment for 7 days (subgroup 2), the dentine surface treated with UDS showed a residual coating of dentine with different representations of crystal-like particles. Longitudinal sections showed a thick granular surface and peritubular dentine masking the intratubular space. Occasionally, small areas of separation between the surface coating and the dentine subsurface demonstrated the presence of a barrier-like structure with tag-like structures reproducing the tubular dentine.
FOV treated dentine surface exhibited an amorphous layer with dispersed particles leaving most of the tubules partially occluded. Transverse sections of exposed dentine revealed a thick coating of varnish almost blocking the tubular apertures. After 7 days of exposure to the oral environment (subgroup 2), ED showed areas of solubilization of a surface coating with disclosure of the underling smear layer. The solubilization

process involved the tubular blocks of varnish on ED simultaneously showing crystal-like precipitates with reduction of the tubular diameter.

Clinical Study

The mean VAS scores are shown in Table 3. There was no difference among baseline VAS scores of all groups (P > 0.05). After treatment, all teeth exhibited statistically significant reductions in VAS in Post-1. Teeth treated with VF had lower VAS scores immediately after Post-1 control (VF vs. FOV: P =0.034). After 7 days of exposure to oral fluids (POST-2) there was no significant difference among tested materials, according to Sidak's multiple testing adjustment. However, when compared with baseline data, all the VAS scores at post-treatment evaluation points were significantly decreased (P < 0.05).

Tab. 3 – Visual Analogue Scale (VAS) values measured in 30 patients baseline and post-treatment.

	Vertise flow mean (SD)	Universal Dentine Sealant mean (SD)	Flor-Opal Varnish mean (SD)	Anova one way
PRE-1	5.4 (2.2) *	5.8 (2.3) $^{\circ}$	4.7 (1.9)	NS
POST-1	0.5 (1.1) *	0.6 (0.8) $^{\circ}$	1.9 (1.5) †	NS $^{*\circ}$ 0.04 *† 0.02 $^{\circ\dagger}$
POST-2	1.7 (1.2) *	1.2 (1.1) $^{\circ}$	1.8 (1.5) †	NS $^{*\circ}$ 0.01 *† 0.03 $^{\circ\dagger}$
Anova one way	<0.01	<0.01	<0.01	

Values expressed as means and standard deviation.

Clinical Analysis of long-term evaluation of DH treatment (Paper III)

The sample size based on the initial assumptions showed a statistical power higher than 80%. Table 4 shows the median VAS scores at the different time-points.

At baseline (VAS score), no significant statistical differences were observed (p-value >0.05) among the groups. After the applications of the materials, statistical significant decrease of the VAS values was observed proceeding from Post-1 to Post-4 control. Teeth treated with VF showed lower VAS scores at Post-1 control when compared to UDS (p-value >0.001), CPB (p-value =0.001), and FOV (p-value >0.001), while at Post-2, a significant statistical reduction of the value was demonstrated in VF in comparison to UDS (p-value =0.001) and FOV (p-value =0.001). As far as the Post-3 and Post-4 controls, no significant differences were detected in VF efficiency in respect to any other materials. Also, post-treatment values showed a significant decrease in the VAS score in all of the groups in comparison to the baseline values (Tab. 5).

Table 4 - Descriptive and inferential analysis of Visual Analogue Scale (VAS) values measured in patients at baseline and post-treatment.

Material	n	VAS PRE1 Median (IQR)	VAS POST1 Median (IQR)	VAS POST 2 Median (IQR)	VAS POST3 Median (IQR)	VAS POST 4 Median (IQR)
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: Inter-Quartile Range
**Kruskal-Wallis* test

Table 5 - Differences of Visual Analogue Scale (VAS) between baseline and post-treatment values.

	VAS PRE1 - VAS POST1 Difference (*p-value*)	VAS PRE1 - VAS POST2 Difference (*p-value*)	VAS PRE1 - VAS POST3 Difference (*p-value*)	VAS PRE1 - VAS POST4 Difference (*p-value*)
Vertise FlowTM	3.0 (<0.001)	3.0 (<0.001)	2.5 (<0.001)	2.0 (<0.001)
Universal Dentine Sealant	3.0 (<0.001)	3.0 (<0.001)	3.0 (0.001)	3.0 (<0.001)
Clearfil Protect Bond	2.0 (<0.001)	2.0 (<0.001)	2.0 (<0.001)	2.0 (<0.001)
Flor-Opal® Varnish	2.0 (<0.001)	2.0 (<0.001)	2.0 (<0.001)	1.0 (<0.001)

Difference: Difference between median Visual Analogue Scale (VAS) values.

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Clinical Analysis of long-term evaluation of DH treatment in radio-induced xerostomia
(Paper IV)

The mean basal salivary flow rate was 0.24 ml/min (minimum 0.06 – maximum 0.42) while the stimulated rate was of 0.54 ml/min (minimum 0.29 – maximum 0.86).
The median VAS scores at different time-points is shown in Table 6. No statistically significant differences between the baseline VAS scores were observed (p-value >0.05). Following the exposure to the materials, a statistically significant VAS decreases was observed from Post-1 to Post-3; no statistical differences were detected in the final point. Teeth treated with Vertise FlowTM and Universal Dentine Sealant showed lower VAS scores at Post-1 in in comparison to those treated with Clearfil Protect Bond (p-value <0.0001), and Flor-Opal® Varnish (p-value <0.0001). On the other hand, statistically significant lower VAS values were showed for Vertise FlowTM and Universal Dentine Sealant in Post-2 when compared to Flor-Opal® Varnish (p-value =0.0002 and p-value<0.0001, respectively). Significantly higher VAS values were reported in regard to Flor-Opal® Varnish, Universal Dentine Sealant (p-value =0.0003) and Clearfil Protect Bond (p-value =0.0002). Conversely, no significant differences were detected at Post-4. In the case of Universal Dentine Sealant and Clearfil Protect Bond, the baseline, Pre-1, and the post-treatment values Post-4 showed significant VAS score decreases, This wasn't in the case of Vertise FlowTM and Flor-Opal® Varnish (Tab. 7).
Moreover, no statistically significant differences (p-value >0.05) were detected at the baseline VAS when the xerostomic group was compared to the healthy (Table 8). Statistically lower VAS values were showed in the normo-salivation group treated with Vertise FlowTM , Clearfil Protect Bond and Flor-Opal® Varnish at Post-4 (p-value <0.05) (Table 9).

Tab. 6 - Descriptive and inferential analysis of Visual Analogue Scale (VAS) values measured in patients at baseline and post-treatment.

	n	VAS PRE1 Median (IQR)	VAS POST1 Median (IQR)	VAS POST 2 Median (IQR)	VAS POST3 Median (IQR)	VAS POST 4 Median (IQR)
Vertise Flow™	29	4 (3-6)	0 (0-0)	0 (0-1)	2 (2-3)	3 (3-5)
Universal Dentine Sealant	21	4 (3-5)	2 (0-2)	1 (0-2)	1 (1-2)	3 (2-3)
Clearfil Protect Bond	27	4 (3-6)	0 (0-0)	0 (0-1)	2 (1-2)	3 (2-5)
Flor-Opal® Varnish	24	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*

IQR: Inter-Quartile Range
**Kruskall-Wallis* test

Tab. 7 - Differences of Visual Analogue Scale (VAS) between baseline and post-treatment values.

	VAS PRE1 - VAS POST1 Difference (*p-value*)	VAS PRE1 - VAS POST2 Difference (*p-value*)	VAS PRE1 - VAS POST3 Difference (*p-value*)	VAS PRE1 - VAS POST4 Difference (*p-value*)
Vertise FlowTM	4(<0.001)	4 (<0.001)	2 (0.003)	1 (0.251)
Universal Dentine Sealant	2 (<0.001)	3 (<0.001)	3 (0.001)	1 (0.008)
Clearfil Protect Bond	4 (<0.001)	4 (<0.001)	2 (<0.001)	1 (0.018)
Flor-Opal® Varnish	2 (<0.001)	2.5 (<0.001)	1 (0.030)	0 (0.193)

Difference: Difference between median Visual Analogue Scale (VAS) values.

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Tab. 8 - Comparison of Visual Analogue Scale (VAS) between groups at baseline.

	Normo-salivation group		Xerostomic group		
	n	VAS POST 4 Median (IQR)	n	VAS POST 4 Median (IQR)	p-value
Vertise Flow™	28	2 (2-3)	29	3 (3-5)	0.003
Universal Dentine Sealant	27	2 (1-3)	21	3 (2-3)	0.059
Clearfil Protect Bond	30	2 (2-4)	27	3 (2-5)	0.012
Flor-Opal® Varnish	31	3 (2-3)	24	4 (2-5)	0.003

Tab. 9 - Comparison of Visual Analogue Scale (VAS) between groups at the end of treatment

	Normo-salivation group		Xerostomic group		
	n	VAS PRE1 Median (IQR)	n	VAS PRE1 Median (IQR)	p-value
Vertise Flow™	28	4 (2-5)	29	4 (3-6)	0.329
Universal Dentine Sealant	27	5 (3-6)	21	4 (3-5)	0.167
Clearfil Protect Bond	30	4 (3-6)	27	4 (3-6)	0.961
Flor-Opal® Varnish	31	4 (3-5)	24	4 (3-6)	0.530

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Discussion

Management of patients with radio-induced xerostomia
(Paper I)

The treatment of xerostomia has four aims: increasing existing saliva flow or replacing lost secretions, the control of the state of oral health, the control of dental caries and the treatment of possible infections (60).
Therapy options in xerostomia depend on the presence of residual secretion or the absence of it. When residual secretory capacity is present, it is advisable to regularly stimulate the salivary glands by mechanical or gustatory stimuli as supportive oral care. The use of sugarless chewing gum or candy containing xylitol or sorbitol can be recommended as a means of stimulating extra salivary flow to aid caries management and lubrication. Nocturnal oral dryness can be alleviated by applying a small amount of dentifrice on smooth dental surfaces, especially using anti-xerostomia dentifrices that contain three salivary enzymes, lactoperoxidase, glucose oxidase and lysozyme, specifically formulated to activate intra-oral bacterial systems.
The salivary flow can be also stimulated by the use of cholinergic pharmaceutical preparations, such as pilocarpine or cevimeline. These two parasympathomimetic drugs are approved by the Food and Drug Administration for treatment of xerostomia; pilocarpine is approved for Sjögren's Syndrome and radiotherapy induced xerostomia, while cevimeline seems to be more specifically for Sjogren's Syndrome. If some residual function of salivary glands remains, acupuncture could be a good alternative treatment for alleviating radio-induced xerostomia (61) . The way this works remains poorly understood, but it seems that acupuncture modulates central nervous system processes (62), increasing the concentration of salivary neuropeptides, which seem capable of modulating the complex process of salivary secretion (63). However, the results of systematic reviews do not indicate the efficacy of acupuncture in the treatment of xerostomia due to the current lack of relevant randomized clinical trials (64 ,63-66).
When stimulation of salivary secretion fails, patients can be given palliative oral care in the form of application of mouthwashes and saliva substitutes. Although the daily use of a mouthwash or one of the saliva substitutes, which are formulated to mimic natural saliva, is strongly recommended , they do not stimulate salivary gland production. Commercially available products come in a variety of formulations including solutions, sprays, gels and lozenges. In general, they contain an agent to increase viscosity, such as carboxymethylcellulose (CMC) or hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), polyglycerylmethacrylate (PGM) (64), minerals such as calcium and phosphate ions and fluoride, preservatives such as methyl or propylparaben, and flavouring and related agents. In order to minimize problems related to the absence of or reduced secretion of saliva, all patients should be encouraged to take an active role in the management of their xerostomia; so a daily mouth

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examination, checking for red, white or dark patches, ulcers or tooth decay, is highly recommended.
Patients with reduced saliva should also be encouraged to consider visiting their dentist more frequently because they have got a greater susceptibility to dental problems. Dentures and acrylic appliances should not be worn during sleep and they should be kept clean by soaking them overnight in chlorhexidine. Sometimes, lubricants, vaseline and or glycerin based, put on the lips and under dentures, may relieve drying, cracking, soreness and mucosal trauma (67).
Patients with decreased salivary flow also should be made aware of the necessity to comply with suggested oral hygiene regimens after exposure to acid-producing food sources. Recommendations for professional and home fluoride treatments should be considered carefully for patients with salivary dysfunction, especially those with high caries rates and exposed root surfaces. A modified diet can be useful to minimize the effects of xerostomia, for instance, they should avoid sugary or acidic foods and avoid also dry, spicy, astringent or excessively hot or cold foods that are more irritating, while eating foods such as carrots or celery may also help patients with residual salivary gland function. The addition of flavour enhancers such as herbs, condiments and fruit extracts may make food more palatable to patients complaining of their food tasting bland, papery, salty or otherwise unpleasant; at the same time, taking frequent sips of water throughout the day and sucking on ice chips is helpful (68).

Clinical evaluation of the efficacy of different desensitizers in dental hypersensitivity of patients with normal salivary flow.
(Paper II and III)

A 12-week evaluation was kept in consideration due to the fact that significant differences among the desensitizer effects may appear in long-term estimation of the agents (43,44,46). Factors involved in the efficiency of the desensitizers are first of all the intrinsic material performance, strictly related to the different formulation (52) and the active ingredient of the materials (45,55). The leach of ions by resins may affect the sealing capacity of the desensitizing agents in oral fluids (69.70). Another factor is the stability of the tubular occlusions produced by the agents, which is related to the composition of the blocks (53) finally derived by the interaction of the material components with the oral fluids (53,71).

Data obtained in this study demonstrated that of the VAS value was reduced after the application of VF and the other desensitizing agents when compared to the baseline. However, different responses could be observed in the post-treatment controls as a consequence of the material composition and interaction capacity in dentine under oral environment (Fig. 11).

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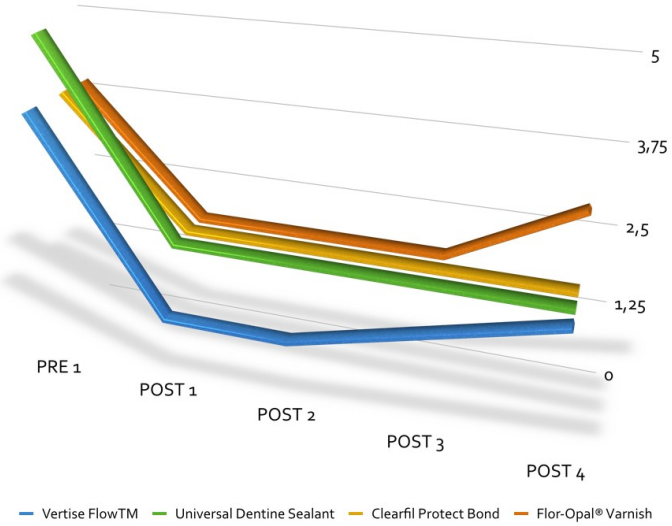

Fig. 11 – Trend of VAS Scores.

Compared with the baseline, VF showed the ability to significantly reduce the sensitivity immediately after the application, however lowering its efficiency within the 12-week post-treatments, as a possible loss of the resin sealing in dentine under oral fluids exposure. Under SEM, VF layer covered the exposed surface of dentine leading to tubular seals and reduction of sensitivity. The reduction of the tubular orifices can explain the significant decrease of DH, as any substance that causes a decrease of tubular radius is able to reduce clinical symptoms of DH by reducing fluid conductance (58). It is like, however, that the same chemical components of the composite mass might be responsible for the deterioration of the physico-mechanical properties of the resin cover within the 12-week controls. A hydrolytic breakdown has been supposed in VF in water mostly related to the presence of leachable ions of Si, Yt, F, and Ba (57), that may have allowed the permeation of water molecules into the spaces previously occupied by these ions (72,73). This process may explain a possible reduction of the strength of resin–filler interface, a weakening of the mechanical properties, and the chemical bond of VF in dentine.

UDS revealed Ca, Cl, and Si as the highest ions in the resin matrix, also containing Al ion peaks (56). Clinically, the behaviour of the resin sealant was different to that of the self-adhesive composite. In comparison to VF, UDS produced a slowly but continue decrease of the VAS showing the higher most stable desensitizing effect at the 12-week controls. Results may be related to the different composition and filler treatment in UDS in respect to VF (56), leading to a filler-polymer bond probably less attackable by water degradation under oral exposure. Moreover, the different behavior of UDS in respect to VF, may suggest that the 12-weeks of oral environment would be essential for the sealant expression.

Clinically, CPB showed a significant decrease of the VAS in POST-1, that remained stable within the 12-week controls. The significant decrease in DH immediately after CPB application may be related to the high bonding capacity in tubular dentine. The strong adhesion in dentine may be the result of the 1) chemical bonding of the acidic functional monomer 10-MDP contained in the CPB allowing for a ionic interaction to the calcium in dentine (74), and 2) micromechanical bonding due to the fluoro-alumino-silicate glasses in the filler capable to react with the acidic monomer following a typical glass-ionomer acid–base reaction (75). Still, the reduction in efficiency observed within the 12-week controls may be explained in the incapacity of the resin adhesive to resist in face to the fluid exposure unless a composite cover is performed (75).
FOV, a resin varnish rich in Na and F, and Si and P traces (56)., clinically demonstrated low efficiency in DH when compared to the other materials. FOV showed a higher VAS score after the 12-week control. The initial reduction of VAS value by FOV may be explained by the presence of a cover of varnish on dentine with precipitation of crystallites of calcium fluoride or phosphate containing calcium fluoride in the opening of the tubules (42,53). This mechanism of covering, previous observed in vivo (56), is able to reduce the tubular apertures in exposed dentine with a decrease of tubular fluid conductance and DH (58), as was observed in POST-1. However, the progressive decline in effectiveness demonstrated the inability of the resin varnish to produce a firm seal in dentine (53,76) within the 12-week controls under environment.
As a result of these investigations, all the materials tested produced a reduction of dentine permeability. However, after 12-week controls, there was no significant statistical difference in the decrease of the VAS irrespective of the desensitizing agent employed.

Clinical evaluation of the efficacy of different desensitizers in dental hypersensitivity of patients with radio-induced xerostomia
(Paper IV)

Due to the lack of information about DH in radiotherapeutic xerostomia, this study was undertaken to investigate the effectiveness of four different desensitizing agents with the purpose to identify the material of choice. Also, the response of the hyposalivary group was compared to a group of normosalivary patients in order to understand differences between the two groups.
All the eight patients (101 teeth) completed the 12-week evaluation study. Data obtained in demonstrated that of the VAS value was significantly reduced after the application of all the materials (Tab. 6). This is really evident for VF and CPB, both showing an overall specular behaviour (Fig. 12). It could be speculated that the reduced presence of saliva, as found among the patients, was a determinant factor in this result.

In fact, one of the major factors in the reduction of the adhesive bond in dentine is the hydrolysis of the adhesive material within water exposure (77). In an oral environment with low saliva volume these materials could be able to increase their performance.At the same time, it could be speculated that the clinical condition of xerostomia, may lower the bonding in time. The occlusal stress, thermal stress and chemical attack by acid and enzymes may affect the adhesive sealing, compromising the integrity of the adhesive restoration (77). Consequently, comparing the data with those obtained in our previous evaluation (78), both the materials may have behaved overall in a less stable manner (Fig. 12).
However, after 12-week controls, both VF and CPB showed a dramatically decrease of performance with reduction of the VAS scores in a similar manner to those observed at PRE-1 (Fig. 12). As reported in the previous study (78) (Fig. 12), UDS produced a slow but continue decrease of the VAS scores (Fig. 12). The results may be related to the proper composition of UDS and the presence of fillers in the resin mass of (56). Unlike it was previously reported, at 12-week controls UDS VAS decreases showing similar values to those noted at PRE-1, similarly to VF and CPB (Fig. 12).
As regard to FOV, it demonstrated the lower efficiency in DH when compared to the other materials (Fig. 12). As previous observed in vivo (56), the reduction of VAS scores in FOV is due to precipitation of crystallites of calcium fluoride or phosphate containing calcium fluoride in the opening of the tubules. In this study, FOV showed the higher VAS scores after the 12-week control. It could be speculated that the reduction of saliva might have affected the performance of the varnish as in the case of UDS and FOV. In light of these data, the first null hypothesis has been accepted: after 12-week controls there is no statistically significant difference among all desensitizers (Tab. 6). Conversely, the second null hypothesis was rejected except in the case of UDS, which didn't show an evident statistically significant difference (Tab. 9).

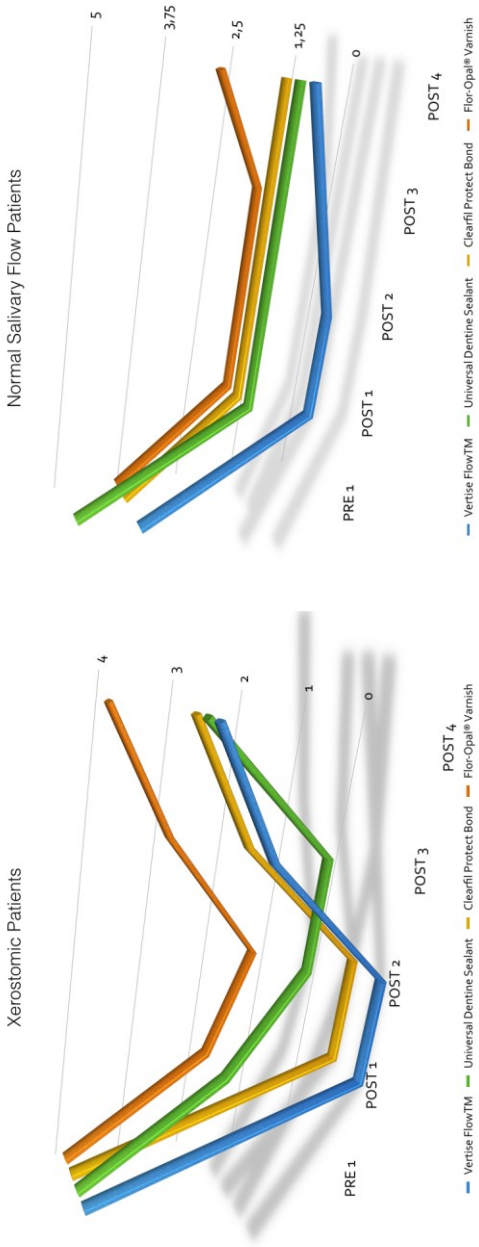

Fig. 12 – Trend VAS Scores

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Conclusions

From the results of these studies the following conclusions were drawn:

Xerostomia is a subjective symptom of a dry mouth often deriving from a lack of saliva that often suffer patients undergoing radiation therapy for the treatment of Head and Neck Cancers. HNC patients receive a radiation dose normally used to destroy cancer cells. The superficial anatomical position of salivary glands, compared to most head and neck tumors, causes the exposition to ionizing radiation, which very often leads to the onset of salivary gland hypofunction and chronic xerostomia (I).

- Dentine hypersensitivity is a common and painful syndrome, predominately located on the cervical part of the tooth buccal surface. Dentine hypersensitivity arise from the tubular dentine exposure as a result of enamel loss and/or gingival root surface exposure, according to "Brännström's hydrodynamic theory". The occlusion of the tubules by different materials may reduce the fluid movement inside the dentinal tubules and the clinical symptoms of DH. Unfortunately, there is already no gold standard for treatment of DH available today, able to guarantee a stable seal on dentin over (II,III).
- Dentine hypersensitivity is one among the multiple complications in the oral cavity which is possible diagnose in patients affected by xerostomia post radiotherapy. It may occur as a result of the combination between the typical etiologic factors and the reduction in salivary flow, because it is lacking the essential protective role of saliva for tooth structural integrity, which consists in the buffering effect and demineralization / remineralization process control (IV).
- The experimental data obtained from patients with normal salivary flow show that all the materials tested produced a reduction of dentine permeability. However, after 12-week controls, there was no significant statistical difference in the efficacy, irrespective of the desensitizing agent employed. This is a possible consequence of deterioration of the physical-mechanical properties of the resin cover in dentine (II,III).
- In xerostomic condition all the materials tested produced a significant reduction in the dentine sensibility. In light of the observed data, the materials show a less stable behaviour compared to the normal salivation condition. After 12-week controls there is no statistically significant difference between the desensitizers. It is a possible consequence of deterioration of the physical-mechanical properties of the materials, that it could be related to the loss of the protective effect of saliva. Unfortunately it is not possible to indicate a long term therapeutic gold standard among the materials tested (IV).

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Therapeutics and Clinical Risk Management

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REVIEW

Xerostomia induced by radiotherapy: an overview of the physiopathology, clinical evidence, and management of the oral damage

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Background: The irradiation of head and neck cancer (HNC) often causes damage to the salivary glands. The resulting salivary gland hypofunction and xerostomia seriously reduce the patient's quality of life.

Purpose: To analyze the literature of actual management strategies for radiation-induced hypofunction and xerostomia in HNC patients.

Methods: MEDLINE/PubMed and the Cochrane Library databases were electronically evaluated for articles published from January 1, 1970, to June 30, 2013. Two reviewers independently screened and included papers according to the predefined selection criteria.

Results: Sixty-one articles met the inclusion criteria. The systematic review of the literature suggests that the most suitable methods for managing the clinical and pathophysiological consequences of HNC radiotherapy might be the pharmacological approach, for example, through the use of cholinergic agonists when residual secretory capacity is still present, and the use of salivary substitutes. In addition, a modified diet and the patient's motivation to enhance oral hygiene can lead to a significant improvement.

Conclusion: Radiation-induced xerostomia could be considered a multifactorial disease. It could depend on the type of cancer treatment and the cumulative radiation dose to the gland tissue. A preventive approach and the correct treatment of the particular radiotherapeutic patient can help to improve the condition of xerostomia.

Keywords: radiation-induced xerostomia, salivary gland hypofunction, management strategies

Introduction

Xerostomia is a term used to describe the subjective symptoms of a dry mouth deriving from a lack of saliva. A large variety of causes can lead to xerostomia, eg, radiotherapy and chemotherapy,[1–4] the chronic use of drugs,[5–7] and rheumatic and dysmetabolic diseases.[8,9]

Saliva is an important host defense component of the oral cavity. Major salivary glands contribute to most of the secretion volume and electrolyte content of saliva (the parotid, submandibular, and sublingual glands, which account for 90% of saliva production), whereas minor salivary glands contribute little secretion volume and most of the blood-group substance.[10] Saliva components interact in related functions in the following general areas:

1) bicarbonates, phosphates, and urea act to modulate pH and the buffering capacity of saliva;
2) macromolecule proteins and mucins serve to cleanse, aggregate, and/or attach oral microorganisms and contribute to the dental plaque metabolism;

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3) calcium, phosphates, and proteins work together as an antisolubility factor and modulate demineralization and remineralization of tooth surfaces;
4) immunoglobulins, proteins, and enzymes provide antibacterial action.

Objectively, patients affected by xerostomia have a hypofunction of the salivary output[11,12] leading to functional oral disorders such as sore throat, altered taste, dental decay, changes in voice quality, and impaired chewing and swallowing function.[13] These factors may ultimately cause reduced nutritional intake and weight loss and significantly affect general health and quality of life of the subjects involved.

Head and neck cancer (HNC) actually includes many different malignancies. The most common type of cancer in the head and neck is squamous cell carcinoma, which originates in the cells that line the inside of the paranasal sinuses, nasal cavity, salivary glands, oral cavity, esophagus, pharynx, and larynx.[14] Worldwide, lip and oral cavity cancer along with thyroid cancer has the highest incidence; esophagus cancer is the most aggressive presenting a 4.9% mortality rate (Table 1).

Similar findings regarding the incidence, mortality, and prevalence of cancer in the European Union have been reported. The highest mortality rate belongs again to esophagus cancer with a predominance of 2.3% (Table 2).

Other less common types of HNCs include salivary gland tumors, lymphomas, and sarcomas.[15]

The way a particular HNC behaves depends on the primary site in which it arises, and the spread to the lymph nodes in the neck is relatively common.

A patient may receive radiation therapy before, during, or after surgery. Some patients may receive radiation therapy alone without surgery or any other treatment; others may receive radiation therapy and chemotherapy at the same time. The timing of radiation therapy depends on the type of cancer and on the goal of the treatment (cure or palliation). Radiotherapy treats cancer by using doses of high-energy X-rays to destroy the cancer cells while avoiding as much harm as possible to normal cells. The treatment is usually given every weekday with a pause at the weekend; some protocols are based on more than one irradiation a day, and occasionally include therapy during the weekend. The treatment will usually last 3–7 weeks, depending on the type and size of the cancer. Most of the time, patients with HNC treated with radiotherapy receive a dose between 50 Gy and 70 Gy once a day for 5 days a week (2 Gy per fraction);[4] on the other hand, if the radiotherapy protocol is just preoperative, the total amount of radiation is usually lower. Conformal radiotherapy is the most common type of radiotherapy used for the treatment of HNC; a special attachment to the radiotherapy machine carefully arranges the radiation beams to match the shape of the cancer, reducing the radiation to the surrounding healthy cells. Another similar type of radiotherapy used against HNC, known as intensity-modulated radiotherapy, allows a more accurate delivery of specific radiation to be distributed to the tumor mass according to its location and severity, sparing the tissue and organs at risk, eg, salivary glands.[10]

Aims

The aim of the study is to systematically determine the current treatment option for cancer-/radiation-induced xerostomia among patients treated for HNC, and to describe the strategic prevention and management enhancements.

Materials and methods

Systematic review methodology

Search strategy

A first systematic literature search for articles published between January 1, 1970 and June 30, 2013 was conducted in the databases MEDLINE/PubMed and the Cochrane Library, using combinations of the MeSH terms: [Saliva] OR [Salivary Glands] OR [Saliva Flow] OR [Salivation] OR [Salivary Gland Diseases] OR [Xerostomia] OR [Saliva in Xerostomia] OR [Dry Mouth] OR [Oral Dryness]

Table 1 Word incidence, mortality, and 5-year prevalence of head and neck cancer

Cancer	Incidence			Mortality			5-year prevalence		
	Number	%	ASR (W)	Number	%	ASR (W)	Number	%	Proportion
Lip, oral cavity	300,373	2.1	4.0	145,328	1.8	1.9	702,149	2.2	13.5
Nasopharynx	86,691	0.6	1.2	50,828	0.6	0.7	228,698	0.7	4.4
Other pharynx	142,387	1.0	1.9	96,090	1.2	1.3	309,991	1.0	6.0
Esophagus	455,784	3.2	5.9	400,156	4.9	5.0	464,063	1.4	8.9
Larynx	156,877	1.1	2.1	83,376	1.0	1.1	441,675	1.4	8.5
Thyroid	298,102	2.1	4.0	39,769	0.5	0.5	1,206,075	3.7	23.2

Note: % = risk of getting or dying from the disease before age 75.
Abbreviation: ASR (W), age-standardized rate (W).

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Table 2 European Union incidence, mortality, and 5-year prevalence of head and neck cancer

Cancer	Incidence			Mortality			5-year prevalence		
	Number	%	ASR (W)	Number	%	ASR (W)	Number	%	Proportion
Lip, oral cavity	43,847	1.6	4.9	14,467	1.1	1.5	121,633	1.7	28.4
Nasopharynx	3,267	0.1	0.4	1,494	0.1	0.2	9,283	0.1	2.2
Other pharynx	26,585	1.0	3.2	12,583	1.0	1.4	67,590	0.9	15.8
Esophagus	34,777	1.3	3.4	29,845	2.3	2.8	38,086	0.5	8.9
Larynx	28,336	1.1	3.1	12,248	1.0	1.2	94,193	1.3	22.0
Thyroid	37,440	1.4	5.4	3,637	0.3	0.3	149,044	2.1	34.8

Note: % = risk of getting or dying from the disease before age 75.
Abbreviation: ASR (W), age-standardized rate (W).

OR [Composition Saliva Xerostomia] AND [Head and Neck Cancer] OR [Radiotherapy] OR [Radiation-induced Xerostomia] OR [Parotid-Sparing Intensity-Modulated Radiotherapy] AND [Quality of Life Analysis-Xerostomia] OR [Management Strategies Salivary Gland Hypofunction] OR [Prevention Xerostomia] OR [Treatment Xerostomia]. The search results were imported into a computerized database Review Manager 5.2. The search results from each of the electronic databases of MEDLINE/PubMed and the Cochrane Library were combined, and duplicated publications were eliminated. Subsequently, an update to include studies published up to June 30, 2013, was performed.

Criteria for selecting studies

After completing the search, articles for review were selected based on:

- English language
- Original data of cancer therapy protocols
- Oral complications associated with cancer therapies
- Human.

Exclusion criteria

The reasons for exclusion were defined as follows:

- Studies without original and/or actual data
- Studies with data from previous publications
- Opinion papers
- Editorials.

In this way, a preliminary set of potentially relevant publications, removing irrelevant citations according to the criteria, was created. Two reviewers (RP and GC) independently screened the registered title and abstracts, and author and references in two separate files (one for included abstracts and one for excluded abstracts) using a screening guide based on eligibility criteria. Studies rejected at this stage or subsequent stages were reported in the table of excluded studies (Table 3). The full text of all potentially eligible studies in at least one screening was retrieved. Reviewers then evaluated the full text for inclusion using a screening guide and a second reviewer (RP) screened all the findings. When disagreement occurred, a third reviewer (IM) was consulted. For each review, the following information was recorded: year, authors, journal, aim, and number of papers reviewed (Table 4); and for clinical trial papers included: year, authors, journal, aim, number of patients, and results (Table 5). All studies meeting the inclusion criteria then underwent validity assessment. Two examiners (RP and GC) read the papers independently. The qualities and relevance of each study were graded as follows: high (+++), medium (++), or low (+) using a study-quality checklist. External validity, internal validity, and study precision were analyzed to obtain an overall assessment of quality. The assessment was used as a basis for the discussion between the two examiners to grade the studies. In the case of disagreement, all authors discussed the paper until a consensus was reached.

Results

The electronic searches identified about 1,000 titles and abstracts, and after reviewing the titles, 411 studies were evaluated. Subsequently, during the review of the abstract, 336 studies were excluded. The final analysis included 70 articles that conformed to the criteria for the present review (Figure 1). Although animal studies have been excluded, important information regarding the experimental results on two of the papers was considered useful and therefore they were discussed.

Table 3 Papers excluded

Reference	Year	Authors	Journal	Reason
19	1991	Vissink et al	*J Oral Pathol Med*	Animal study
70	1998	Davies	*Br Med J*	Editorial
46	1998	Spielman	*J Dent Res*	Animal study
51	2000	Kuntz et al	*Int J Pharm Compound*	Opinion paper
3	2005	Waltimo et al	*Schweiz Monatsschr Zahnmed*	Article in German

Table 4 Reviews included

Reference	Year	Authors	Journal	Aim	Number of papers reviewed	Qualities and relevance of studies included score
–	1976	Mandel and Wotman	*Oral Sci Rev*	Narrative – Identification of the pathological conditions which give rise to hyposalivation and evaluation of a method for the saliva collection and analysis	104	++
23	1977	Dreizen et al	*Postgrad Med*	Narrative – To evaluate the main injury of the surrounding tissues during radiotherapy for oral cancer that can have devastating physical and psychological consequences for the patients	13	++
45	1994	Atkinson and Wu	*J Am Dent Assoc*	Narrative – To evaluate the three most common known causes (medication, radiation therapy, and Sjögren's syndrome) of salivary gland dysfunction and their clinical management	62	+++
17	1996	Scully and Epstein	*Eur J Cancer B Oral Oncol*	Narrative – To discuss the etiopathogenesis and current means available for preventing, ameliorating, and treating radiation therapy complications, as well as indicating research directions	282	+++
1	1998	Bivona	*N Y State Dent J*	Narrative – To evaluate generally physiopathological features and clinical management of Sjögren's syndrome	16	++
61	2000	Dyke	*Int J Pharm Compound*	Narrative – To evaluate physiopathological features and clinical management of Sjögren's syndrome	19	+
–	2000	Shaw et al	*Br J Oral Maxillofac Surg*	Narrative – The aim of this article is to review the current literature concerning the implications and management of these oral implications of cancer treatment	42	++
18	2000	Sreebny	*Int Dent J*	Systematic – This paper reviews the role of saliva, the prevalence of oral dryness, and consequent importance of salivary flow as well as the relationship between xerostomia and salivary gland hypofunction among the causes of oral dryness. Other aspects: association between saliva and SS and esophageal function; use of saliva as diagnostic tool	134	+++
47	2002	Pedersen et al	*Oral Dis*	Narrative – This paper reviews the role of human saliva and its compositional elements in relation to the gastrointestinal functions of taste, mastication, bolus formation, enzymatic digestion, and swallowing	161	+
2	2003	Cassolato and Turnbull	*Gerodontology*	Narrative – To outline for clinicians the common etiologies, clinical identification, and routine therapeutic modalities available for individuals with xerostomia	86	+++
12	2004	Porter et al	*Oral Surg Oral Med Oral Pathol Oral Radiol Endod*	Narrative – To create an update of the etiology and management of xerostomia	229	+++
14	2008	Argiris et al	*Lancet*	Narrative – To review the epidemiology, molecular pathogenesis, diagnosis and staging, and the latest multimodal management of squamous cell carcinoma of the HNC	153	+++
–	2008	Chan and Liebsch	*J Surg Oncol*	Narrative – To describe mechanism of action, applications, and safety of protons in HNC therapy	31	+++

(*Continued*)

Table 4 (*Continued*)

Reference	Year	Authors	Journal	Aim	Number of papers reviewed	Qualities and relevance of studies included score
63	2008	Sagar	*Curr Treat Options Oncol*	Narrative – To describe the effectiveness of acupuncture to control the symptoms of cancer patients, with an evidence-based approach	59	++
55	2010	Ramos-Casals et al	*JAMA*	Systematic – To summarize evidence on primary Sjögren's syndrome drug therapy from randomized controlled trials	74	+
10	2010	Jensen et al	*Support Care Cancer*	Systematic – To assess the literature for management strategies and economic impact of salivary gland hypofunction and xerostomia induced by cancer therapies and to determine the quality of evidence-based management recommendations	154	+++
10	2010	Jensen et al	*Support Care Cancer*	Systematic – To assess the literature for prevalence, severity, and impact on quality of life of salivary gland hypofunction and xerostomia induced by cancer therapies	203	+++
66	2010	O'Sullivan and Higginson	*Acupunct Med*	Systematic – To systematically review evidence on clinical effectiveness and safety of acupuncture in irradiation-induced xerostomia in patients with HNC	51	+++
41	2013	Radvansky et al	*Am J Health Syst Pharm*	Narrative – To evaluate current strategies for preventing and managing radiation-induced dermatitis, mucositis, and xerostomia, with an emphasis on pharmacologic interventions	52	++
67	2013	Zhuang et al	*Integr Cancer Ther*	Systematic – To evaluate the preventive and therapeutic effect of acupuncture for radiation-induced xerostomia among patients with HNC	46	+++

Abbreviation: HNC, head and neck cancer.

Physiopathological and clinical consequences in cancer therapy

Each of the reviews concerning the physiopathological and clinical consequences are listed in Table 6.

Physiopathological consequences

A total of five articles reported the physiopathological effects of radiation therapy on salivary glands parenchyma: one systematic review, one narrative review, one pilot study, one animal experimentation study, and one cohort study.[16–20] Radiotherapy-induced xerostomia could be considered a multifactorial disease. On the one hand, the damage to the oral cavity has been strongly related to the radiation dose, fraction size, volume of irradiated tissue, fractionation scheme, and type of ionizing irradiation, but on the other, it may be difficult to distinguish changes caused by radiotherapy itself from those related to the malignant disease, the concomitant systemic diseases, and the medication needed for the treatment of the cancer.[16,17]

The salivary glands are superficially located compared to most head and neck tumors, and thus, the ionizing radiation has to pass through the salivary glands to effectively treat the tumor.[18] Tissues with a rapid turnover rate are more susceptible than tissues with a slow one and even with the most accurate therapeutic protocol, X-rays cause unwanted changes in non-tumoral tissues. Despite the fact that salivary gland cells turnover is slow, production and quality of saliva change after radiation, so they are not as radioresistant as they are supposed to be.[19] There are differences among the various types of salivary glands; in fact, the submandibular gland is less radiosensitive than the parotid gland.[20] From this point of view, the most severe and irreversible forms of salivary gland hypofunction result from the damage/loss of salivary acinar cells, giving rise to rapid and predictable compositional changes, and reduction in saliva production and in the quality of the flow.

Radiation-induced changes in saliva

Nineteen articles analyzed the effects of the radiotherapy on salivary flow and composition, and the changes in microbial population: one narrative review, four randomized controlled trials, nine cohort studies, and five cross-sectional studies.[21–40]

Table 5 Clinical trial papers included

Reference	Year	Authors	Journal	Aim	Number of patients	Results	Qualities and relevance of studies included score
35	1974	Brown et al	*J Dent Res*	To assess the effects of radiation-induced xerostomia on the human oral microflora	30	Cariogenic microorganisms gain prominence at the expense of non-cariogenic microorganisms in concert with saliva shutdown	+++
49	1974	Chen and Webster	*Cancer*	One hundred and one cases of head and neck cancer were subjected to oral culture for *Candida albicans* before, during, and 1 month after radiotherapy	101	Thirty percent of the patients had a positive culture before radiotherapy. During the course of radiotherapy, almost half of the negative patients turned positive. The severity of the acute radiation reaction of the oropharyngeal mucosa was not related to the apparent presence or absence of *C. albicans*. Amphotericin B (1 cm^3 [100 mg] four times daily) converted about one-third of the positive patients to negative	++
24	1975	Ben-Aryeh et al	*Int J Oral Surg*	Flow rate, pH, electrolytes, protein, and phosphate evaluation of whole saliva in 15 healthy individuals and 15 patients with malignant tumors in the head and neck region before and during irradiation therapy	30	The most significant finding was the increased sodium content. Irradiation reduces the reabsorption ability of the tubuli, causing the sodium content of the saliva to increase	++
25	1976	Dreizen et al	*Cancer*	Saliva and serum electrolyte concentrations were monitored in 30 patients given a course of xerostomia-producing cancer radiotherapy	30	The xerostomic saliva was more concentrated and had a greater salinity than the pretreatment saliva in each instance. In contrast, none of the serum electrolytes measured was significantly altered by the subtotal salivary shutdown	++
28	1981	Abelson and Mandel	*J Dent Res*	To evaluate the impact of the saliva on plaque in vivo, following exposure to a sucrose substrate, in ten caries-resistant and ten caries-susceptible subjects under varying conditions of salivary access	20	The study results indicate that saliva plays a major role in mediating plaque pH and qualitatively reflects caries status	+
–	1981	Anderson et al	*Oral Surg Oral Med Oral Pathol*	To evaluate the alterations of electrolyte and protein concentrations in patients receiving localized, fractionated, neutron and gamma irradiation for the treatment of cancer	5	There were concurrent decrease in salivary flow rate, pH, and sodium chloride and bicarbonate concentration. The decrease in sodium chloride concentration and flow rate was inconsistent with an irradiation-induced ductal sodium resorption defect	+++
36	1981	Keene et al	*Caries Res*	To evaluate the prevalence of *Streptococcus mutans* in both preradiation and irradiation patients	39	*S. mutans* were detected in 82% of the irradiated patients and 100% of the preradiotherapy patients. In the irradiated group without current caries, *S. mutans* prevalence was inversely related to the number of elapsed years postradiotherapy	+++
34	1981	Izutsu et al	*Oral Surg Oral Med Oral Pathol*	Albumin concentrations were measured in whole and parotid saliva samples collected from patients who were undergoing various cancer treatment protocols and had a high incidence of stomatitis	7	The salivary albumin increases always preceded and often occurred in the absence of stomatitis, suggesting that the whole saliva albumin level may be a useful measure and predictor of this condition	++

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26	1981	Marks et al	*Int J Radiat Oncol Biol Phys*	To establish a dose–response curve for the human parotid, selective measurements of right and left parotid salivary flow were done for 15 age-matched control patients whose parotids were not irradiated, 17 patients who had both parotids irradiated, and 12 whose parotids were irradiated by unilateral electron beam technique	46	In this study there clearly exists a dose–response correlation for the late effects of radiation on parotid salivary flow. Indeed, parotid salivary flow progressively decreased with increasing doses of radiation. A change in the pH of saliva that, especially at high doses, becomes acidic was found	++
33	1986	Makkonen et al	*Oral Surg Oral Med Oral Pathol*	To analyze the radiation-induced changes in the flow rate and protein composition of stimulated whole saliva in eleven patients treated for malignant conditions of the head and neck	11	It is concluded that the observed qualitative changes in whole saliva components are net effects caused by the cancer itself, radiation therapy given, systemic diseases, or medications, as well as mucosal inflammations	++
11	1987	Fox et al	*J Am Dent Assoc*	Describes the responses to a questionnaire of oral findings and QOL in patients with reduced saliva flow. Moreover, an objective measurement of the major saliva output unstimulated and stimulated	100	In this study there exists a correlation between clinical symptoms and low-rate salivary flow. The questionnaire clearly helps to identify xerostomic patients and allows appropriate management to begin	+
37	1988	Hase and Birkhed	*Arch Oral Biol*	The aim was to study the effect of different salivary secretion rates on glucose clearance in saliva and on pH change in dental plaque in man, in normal and hyposalivation conditions		The pH changes in dental plaque after the mouth rinse with glucose at extremely low secretion rate were significantly more pronounced than the normal flow rate. Thus, the salivary secretion rate affects both the glucose clearance in saliva and the pH changes in dental plaque in man	+
16	1991	Maciejewski et al	*Radiother Oncol*	To evaluate the effects and efficacy of the application of 2% silver-nitrate solution for several days before radiotherapy in 16 patients treated for squamous cell carcinoma of the oral cavity or oropharynx	16	The application of solutions and astringents is effective in modifying the development of acute side effects of radiotherapy and to decrease signs, symptoms, and suffering by modulating the biological status of critical normal tissue before the onset of radiotherapy. Unfortunately, their application before radiotherapy has not given significant results in order to promote reparative processes	++
29	1993	Lingström and Birkhed	*Acta Odontol Scand*	To evaluate plaque pH and oral retention after consumption of starchy snack products at normal and low salivary secretion rate	10	All products resulted in greater pH falls and remained at a low level for a longer period during low secretion rate. There were no differences in concentration of carbohydrates in saliva after consumption of starchy snack products. Low secretion rate increased the oral retention for all products	+
32	1993	Valdez et al	*Cancer*	To evaluate whether the sialogogue pilocarpine given during radiation therapy may reduce the severity of xerostomia and salivary dysfunction. The patients, requiring head, neck, or mantle radiation therapy, took either 5 mg of pilocarpine or placebo four times daily for 3 months, beginning the day before radiation therapy. Subjective complaints and salivary functions were assessed	10	The stimulation with pilocarpine may reduce the severity of salivary dysfunction and associated oral symptoms during radiation therapy	+

(*Continued*)

Table 5 (*Continued*)

Reference	Year	Authors	Journal	Aim	Number of patients	Results	Qualities and relevance of studies included score
60	1997	Bagheri et al	*Eur J Clin Pharmacol*	To compare the effects of yohimbine, an alpha-2 adrenoceptor antagonist, and anethole trithione, a reference drug in the treatment of dry mouth, in patients treated with psychotropic drugs (tricyclic antidepressants or neuroleptics) and suffering from xerostomia	10	The study results show that under experimental conditions, yohimbine, but not anethole trithione, stimulates salivary secretion after a 5-day treatment in patients receiving antidepressants or neuroleptics and suffering from dry mouth	+
48	1997	Ramirez-Amador et al	*Oral Med Oral Pathol Oral Radiol Endod*	To quantitate oral *Candida* colonization, assessing symptoms, and response to antifungal management, especially *Candida*, and evaluate the influence of smoking and dentures	46	When salivary glands are included in the field of radiation, xerostomia occurs causing progressive increases in oral *Candida* colonization. Because 17.4% developed clinical candidiasis during radiotherapy and the question of fungal resistance remains speculative, a recommendation for the prophylactic use of antifungal medication is unresolved	+++
31	1998	Almståhl and Wikström	*J Dent Res*	To evaluate the effect of hyposalivation on the oral microflora	38	The results indicated that a low salivary secretion rate mainly promotes a flora associated with the development of caries	+++
38	1998	Ravald and List	*Swed Dent J*	The investigation is designed to study caries and periodontal conditions in a selected group of patients with 1°SS. Clinical examination includes registrations of dental caries, restorations, and periodontal condition	21	The patients with 1°SS face a high risk of developing both coronal and root caries due to xerostomia. The periodontal conditions are similar to those found in patient groups in general dentistry	++
13	1999	De-Graeff et al	*Oral Oncol*	To describe prospectively the QOL and mood in patients with oral or oropharyngeal cancer treated with surgery radiotherapy	75	After treatment, a gradual improvement in emotional functioning occurred. Surgical treatment for oral or oropharyngeal cancer results in significant deterioration of physical functioning and symptoms during the first year, especially when combined with radiotherapy	+++
–	1999	International Commission on Radiological Protection		This new website report presents data on 99mTc-furifosmin, 99mTc-EC, 99mTc-ECD, and various monoclonal antibodies and antibody fragments labeled with 99mTc, 111In, 123I, and 131I			+++
59	1999	Hamada et al	*Am J Med Sci*	To evaluate the efficacy of AT, a cholagogue, for xerostomia signs management	49	The results indicate that AT sufficiently stimulates salivation and improves xerostomia	+++
39	2001	Almståhl et al	*Oral Microbiol Immunol*	To compare lactoferrin, amylase, and MUC5B concentrations in stimulated whole saliva collected from subjects with radiation-induced hyposalivation, subjects with pSS, and subjects with hyposalivation of unknown origin or due to medicines. In addition, the data in relation to the presence of selected microbial species that have been associated with oral disorders were analyzed	75	The saliva composition in subjects with hyposalivation of unknown origin or due to medicines was close to that in the healthy controls. All three hyposalivation groups tended to display a decrease in the concentrations of MUC5B and amylase. None of the microbial species analyzed correlated with concentration of MUC5B in saliva	+++

20	2001	Burlage et al	*Radiother Oncol*	It was studied whether differences in acute radiosensitivity exist between parotid and submandibular/sublingual glands	18	The results revealed that salivary flow rates decreased dramatically during the first 2 weeks of radiotherapy. Neither recovery nor significant differences were observed between the production of saliva from the parotid and submandibular/sublingual glands during the 13-week observation period	+++
21	2001	Epstein et al	*Head Neck*	To assess the QOL, oral function, and oral symptoms in a cohort of patients during and after radiation therapy, by QLQ-C30, with an added oral symptom and function	20	The EORTC QLQ-30 questionnaire with the oral assessment addendum provides a measure of the QOL and oral function in head and neck cancer patients and may provide useful outcome measures for assessment of oral care prevention and management strategies in these patient populations	++
9	2001	Moore et al	*Oral Surg Oral Med Oral Pathol Oral Radiol Endod*	The study evaluates the prevalence of dry-mouth symptoms (xerostomia), the prevalence of hyposalivation in this population, and the possible interrelationships between salivary dysfunction and diabetic complications	676	Subjects with type 1 diabetes who had developed neuropathy more often reported symptoms of dry mouth as well as symptoms of decreased salivary flow rates	+
42	2002	Wijers et al	*Head Neck*	The first aim of the study was to evaluate the degree of xerostomia in 39 long-term survivors treated between 1965 and 1995 by conventional 2D radiation therapy and currently without evidence of disease. The second aim was to develop a concise instrument to evaluate the subjective aspects of xerostomia	39	In this survey, 64% of the long-term survivors, after treatment by conventional 2D radiation therapy for a malignancy in the head and neck region, still experienced a moderate-to-severe degree of permanent xerostomia	++
56	2004	Hendrickson et al	*J Emerg Med*	A report of a case of unintentional overdose of oral pilocarpine tablets that resulted in bradycardia, mild hypotension, and muscarinic symptoms in a patient with Sjögren's syndrome	1		++
53	2004	Koseki et al	*Oral Dis*	To investigate oral symptoms and clinical parameters in dry eye patients	224	The sensation of a dry mouth and changes in oral soft tissues, dental caries, and oral *Candida* frequently occurred in dry eye patients	++
30	2006	Eliasson et al	*Eur J Oral Sci*	To investigate the secretion rate from palatal, buccal, and labial glands, and to analyze the IgA concentrations in relation to age, sex, circulatory disease, diabetes, medication, smoking, and pregnancy	142	The results did not suggest any effect of aging on the secretion capacity of minor salivary glands, but the IgA concentration seemed to increase with age. Women had lower buccal and labial saliva secretion rates, and lower levels of IgA in buccal saliva, than men. For whole saliva, resting, but not stimulated, saliva secretion rates were reduced with age, and the secretion rate of stimulated whole saliva was lower in women than in men	+

(*Continued*)

Table 5 (*Continued*)

Reference	Year	Authors	Journal	Aim	Number of patients	Results	Qualities and relevance of studies included score
57	2007	Chambers et al	*Int J Radiat Oncol Biol Phys*	To assess the safety of long-term cevimeline treatment of radiation-induced xerostomia in patients with head and neck cancer; and to assess the efficacy of cevimeline in these patients	255	Cevimeline 45 mg three times daily was generally well tolerated over a period of 52 weeks in subjects with xerostomia secondary to radiotherapy for cancer in the head and neck region	+++
57	2007	Chambers et al	*Int J Radiat Oncol Biol Phys*	To study the efficacy and safety of cevimeline in two double-blind trials enrolling patients with head and neck cancer in whom xerostomia developed after radiotherapy	500	Cevimeline was well tolerated by patients with xerostomia after radiotherapy for head and neck cancer, and oral administration of 30–45 mg of cevimeline three times daily increased unstimulated salivary flow	+++
4	2009	Brand et al	*Br Dent J*	To assess the severity of xerostomia in HSCT patients and to investigate the association of xerostomia with other chronic oral complications	89	HSCT patients have more severe xerostomia, which is associated with other oral complaints	+
8	2009	Busato et al	*Oral Surg Oral Med Oral Pathol Oral Radiol Endod*	To evaluate the impact of xerostomia on the QOL of adolescents with DMI	56	Xerostomia is frequent and has a negative impact on QOL of adolescents with DMI	+++
54	2010	Tomiita et al	*Mod Rheumatol*	To evaluate the efficacy and safety of orally administered pilocarpine hydrochloride for juvenile-onset SS patients	5	The results of this study suggest that orally administered pilocarpine is safe and effective for treating xerostomia in juvenile-onset SS patients	+
39	2010	Almstähl et al	*Arch Oral Biol*	To analyze the frequency of different *Lactobacillus* spp. in relation to the pH-lowering potential of the plaque	30	There were large intra- and interindividual variations in frequencies of *Lactobacillus* spp. and *Lactobacillus* counts, but no specific species could be related to plaque acidogenicity	+++
52	2010	Almeida and Kowalski	*Braz J Otorhinolaryngol*	To report on the experience with pilocarpine on the treatment of xerostomia in thyroid cancer patients submitted to adjuvant RIT	84	Pilocarpine seems to relieve xerostomia complaints in thyroid cancer patients because it is able to stimulate salivary flow, but the observed side effects made the patients refuse long-term therapy continuation	+++
43	2011	Sher et al	*Int J Radiat Oncol Biol Phys*	A retrospective study of all patients treated at the Dana-Farber Cancer Institute for HNCUP with IMRT between August 2004 and January 2009. The primary endpoint was overall survival; the secondary endpoints were locoregional and distant control, and acute and chronic toxicity	24	In a single-institution series, IMRT-based chemoradiotherapy for HNCUP was associated with superb overall survival and locoregional control. The xerostomia rates were promising, but the aggressive therapy was associated with significant rates of esophageal stenosis	++
7	2011	Villa et al	*J Am Dent Assoc*	To estimate the prevalence of the subjective perception of dry mouth in dental patients in Italy, to relate these estimates to the patients' ages and sexes, and to determine whether xerogenic medications taken by these patients were associated with complaints of xerostomia	1,201	The authors found that medication use and age were highly significant risk factors for dental patients reporting xerostomia	++

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6	2011	Villa and Abati	*Aust Dent J*	To examine the symptoms and risk factors associated with self-reported xerostomia	601	Participants reported having dry mouth in 19.6% of cases. Older individuals were significantly more likely to report dry mouth, and the prevalence of xerostomia increased with advancing age. The prevalence of xerostomia in patients taking one or more drugs was significantly higher compared to medication-free patients, and increased with increasing numbers of medications used. Finally, individuals with a nervous or mental disorder, or who wore removable dentures, were five times more likely to develop xerostomia than patients without disorder or dentures	++
44	2012	Schoenfeld et al	*Int J Radiat Oncol Biol Phys*	To analyze the recent single-institution experience of patients with salivary gland tumors who had undergone adjuvant IMRT, with or without concurrent chemotherapy	35	Treatment of salivary gland malignancies with postoperative IMRT was well tolerated with a high rate of local control. Chemoradiotherapy resulted in excellent local control in a subgroup of patients with adverse prognostic factors and might be warranted in select patients	++

Abbreviations: EC, ethylenedicysteine; ECD, N,N′-1,2-ethylenediylbis-L-cysteinediethylester; AT, anethole trithione; QLQ, Quality of Life Questionnaire; IgA, immunoglobulin A; HSCT, hematopoietic stem cell transplantation; QOL, quality of life; DM1, type 1 diabetes mellitus; RIT, radioactive iodine therapy; HNCUP, head and neck squamous cell carcinoma; IMRT, intensity-modulated radiotherapy; 2D, two-dimensional.

Figure 1

Salivary flow

One of the main problems resulting from tissue damage generated by radiation therapy is the reduction of salivary flow. The radiation level necessary to cause severe dysfunction to gland tissue is >52 Gy. Below this threshold, the radiation damage generally has a transient and reversible duration.[12] Routinely, HNC patients receive a total of 50–70 Gy, the radiation dose normally used to destroy malignant cells, which very often leads to the onset of chronic xerostomia.[21] The major reduction in salivation after radiotherapy is observed in the period from the onset of radiotherapy to 3 months after completion. During radiotherapy, the first 10 days are the worst ones as a massive decrease in saliva production occurs; especially in the first week, it could reduce by 50%–60%.[22] After this period, the flow rate is reduced by <10% of the initial conditions.[23]

Chemical and immunochemical alterations

Radiotherapy can also induce alterations in electrolytes and antibacterial systems. Salivary electrolyte levels are altered, with an increase in the concentrations of sodium, chloride, calcium, and magnesium, while potassium is only

Table 6 Reviews included related to physiopathological and clinical consequences in cancer therapy

Reference	Year	Authors	Journal	Aim	Number of papers reviewed	Qualities and relevance of studies included score
Physiopathological consequences						
17	1996	Scully and Epstein	*Eur J Cancer B Oral Oncol*	Narrative – To discuss the etiopathogenesis and current means available for preventing, ameliorating, and treating these complications, as well as indicating research directions	282	+++
18	2000	Sreebny	*Int Dent J*	Systematic – This paper reviews the role of saliva, the prevalence of oral dryness, and consequent importance of salivary flow as well as the relationship between xerostomia and salivary gland hypofunction among the causes of oral dryness. Other aspects: associations between saliva and SS and esophageal function; use of saliva as diagnostic tool	134	+++
Radiation-induced changes of saliva						
23	1977	Dreizen et al	*Postgrad Med*	Narrative – To evaluate the main injury to surrounding tissues during radiotherapy for oral cancer that can have devastating physical and psychological consequences for the patients	13	++
Radiotherapy clinical consequences						
45	1994	Atkinson and Wu	*J Am Dent Assoc*	Narrative – To evaluate the three most common known causes (medication, radiation therapy, and Sjögren's syndrome) of salivary gland dysfunction and their clinical management	62	+++
47	2002	Pedersen et al	*Oral Dis*	Narrative – This paper reviews the role of human saliva and its compositional elements in relation to the gastrointestinal functions of taste, mastication, bolus formation, enzymatic digestion, and swallowing	161	
41	2013	Radvansky et al	*Am J Health Syst Pharm*	Narrative – To evaluate current strategies for preventing and managing radiation-induced dermatitis, mucositis, and xerostomia, with an emphasis on pharmacologic interventions	52	++

slightly affected.[24] Saliva also reduces the buffering capacity in irradiated patients due to a reduction of bicarbonate concentration in parotid saliva.[25,26] Saliva becomes, moreover, highly viscous, and reduces its pH from about 7.0 to 5.0[25,27] with slow recovery to the neutral pH in dental plaque after a sugar rinse.[28,29] The permanence of the acidic pH in dental plaque was related to the reduced buccal gland saliva flow[30] as the secretion from the buccal glands, closely delivered to the teeth surfaces, could affect the dental plaque more than the whole saliva during resting conditions.

Changes also involve the nonimmune and immune antibacterial systems. The concentrations of immunoproteins (eg, secretory immunoglobulin A), lysozyme, and lactoferrin are increased, as well as the serum and non-salivary components.[31–34] However, the decrease in salivary flow rate is greater than the increase in immunoprotein and lysozyme levels, and this results in significant immunoprotein deficit. Since the reduction of the oral clearance, immunologic mechanisms and buffering capacity of saliva are altered, and the host protection decreases giving rise to changes in the oral flora.[35]

Microbial changes

All of these radiation-induced changes cause a different oral flora growth and acidogenic, cariogenic microorganisms are more present than non-cariogenic microorganisms. Unfortunately, even if there is an increase in immunoprotein and lysozyme levels, a significant immunoprotein deficit occurs due to the decrease in salivary flow rate. *Streptococcus mutans*, *Lactobacillus* spp., and *Candida* spp. are the

most prevalent in the plaque of irradiated patients.[30,36–38] In a longitudinal study, Brown et al assessed the effects of radiation-induced xerostomia on the human oral microflora and on the subsequent development of dental caries.[35] Five intraoral specimens consisting of resting saliva, gingival sulcus fluid, dental plaque, lingual swabs, and stimulated whole saliva were collected from each patient two times during 1 week before radiation, one time per week during radiotherapy, at 3-month intervals during the first postradiation year, and at 6-month intervals thereafter. During irradiation, the development of xerostomia was matched by a parallel and pronounced shift in certain microbial populations at each intraoral site assessed. The most prominent changes were the increase in *S. mutans* and species of *Lactobacillus*, *Candida* (primarily *Candida albicans*), and *Staphylococcus*, with parallel decreases in *Streptococcus sanguis* and species of *Neisseria* and *Fusobacterium*. Microbial differences were relatively minimal between the groups of patients receiving radiotherapy who used a fluoride gel and a nonfluoride gel during the irradiation period. However, there was a more rapid decrease in the level of *S. sanguis* in the plaque of the patients using the nonfluoride gel compared with those patients using the fluoride gel, and the subsequent development of dental caries differed greatly. The increased number of *Lactobacilli* was correlated to a high acidic potential of the plaque and the use of fluoride was associated with a protective effect in the prevention of dental decay during xerostomia.

The findings that a high frequency, number, and proportion of *Lactobacillus* spp. occur in irradiated patients were strengthened by a study of Almståhl et al who analyzed the saliva oral microbiota in subjects with hyposalivation using a rinsing technique and a cultivation technique. Results indicated that the salivary secretion rate, pH, and buffer capacity were the more important factors in the increase in *Lactobacillus* spp. A marked increase in *C. albicans* was also characteristic of the irradiated patients.[39]

In a more recent study, Almståhl et al evaluated the frequency of different *Lactobacillus* spp. in relation to the pH-lowering potential of the supra-gingival plaque in irradiated patients in comparison to primary Sjögren's syndrome patients and controls with normal salivary secretion.[40] The irradiated subjects had finished their bilateral radiation treatment (64.6 Gy) 3–5 years before participating in the study. Interproximal plaque pH was measured by the microtouch method[30] before and up to 60 minutes after a 10% sugar rinse.[29] The measurements were performed at two sites: in the anterior and in the premolar/molar region. Data indicated that the most common species were *Lactobacillus fermentum*, *Lactobacillus rhamnosus*, and *Lactobacillus casei*. In anterior sites, both the hyposalivated group subjects with high *Lactobacillus* counts had an increased plaque acidogenicity compared to those with low counts. In posterior sites, subjects with high *Lactobacillus* counts had a lower final pH compared with those with low counts. Authors concluded that hyposalivation patients often harbor several different *Lactobacillus* spp. in their supragingival plaque. There were, however, large differences in number and proportion of *Lactobacilli* between individuals and between anterior and posterior dental sites, but no specific species could be related to plaque acidogenicity.

Radiotherapy clinical consequences

In eleven articles, the clinical consequences that may arise as a result of HNC radiation therapy have been described: three narrative reviews, one randomized clinical trial, one animal experimentation study, four cohort studies, and two cross-sectional studies.[20,36,41–50] Radiotherapy can cause some temporary side effects. Although these may be worse if the treatment is combined with chemotherapy, they gradually disappear after the treatment has finished. Most radiotherapy side effects occur toward the middle and end of the course of treatment and continue during the first couple of weeks after the treatment. The effects can be mild or more troublesome, depending on the dose of radiotherapy and the length of treatment. Thus, the quantitative and qualitative salivary changes predispose the irradiated patient to a variety of problems.

Radiation therapy in HNC is inevitably associated with damages to the oral tissues and, in addition, the clinical consequences of radiotherapy include also dermatitis and osteoradionecrosis.[41] In fact, salivary glands are often involved and, as a result, patients may have a salivary gland hypofunction, even if 3D planning and unilateral irradiation have considerably reduced the side effects by minimizing the dose to normal tissues. However, the final degree of damage to gland tissue depends on individual patient characteristics, such as pretreatment already done, age, and sex.

Xerostomia may affect 80% of the patients who need radiotherapy as a primary treatment, as an adjunct to surgery, in combination with chemotherapy, or as palliation.[42–44] Hyposalivation represents the biggest acute side effect in HNC radiotherapy and, in general, is always associated with oral function problems, such as chewing and swallowing, or caries at a later stage. Normally, during radiotherapy, salivary composition may change and it becomes more viscose than usual, so its color may turn yellow, brown, or even white

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(Figure 2). Furthermore, salivary glands with high flow rates before the initiation of radiotherapy show less reduction in salivary flow rate. As a consequence of the reduction in the rate of saliva flow, which is correlated to the amount of radiation given to the patient, oral complications occur.[20]

The buccal mucosa has a dry and sticky appearance (Figure 3). The normally moist, glistening appearance of the oral cavity is often replaced with a thin, pale, cracked appearance that is more susceptible to gingivitis and bleeding. Another frequent acute side effect is oral mucositis, which can be experienced by >50% of patients receiving HNC radiotherapy. Some typical side effects are onset of erythema, edema, and pain in the oral mucosa.[41] Patients may also exhibit a dry irritated tongue with an erythematous appearance of the dorsal surface, the hard or soft palate, the commissures of the mouth, and under-removable prostheses.[43] Furthermore, the lack of saliva may lead to angular cheilitis, cracked lips (Figure 4), periodontal disease, aching of the mouth, and halitosis.

When part or all of the mouth is treated, the sense of taste may change quickly during the radiotherapy, and some patients may even either lose their sense of taste completely or find that everything tastes the same (usually rather metallic or salty). Changes in taste are correlated to the direct irradiation of the taste buds, and also to the reduction in salivary flow rate that alters the ionic composition of saliva that is related to the sensation of taste.[46]

Moreover, the loss of saliva compromises mastication and nutrition. Some patients lose their appetite as a general effect of radiotherapy. Dryness of the mouth and lips can cause discomfort, ranging from a mild irritation to a severe burning sensation with difficulties in normal eating habits, particularly eating spicy or acidic food. A sore, dry mouth can also make eating and swallowing difficult because moistening of food is insufficient and oral mucosa surfaces are not wet and not lubricated enough.[47]

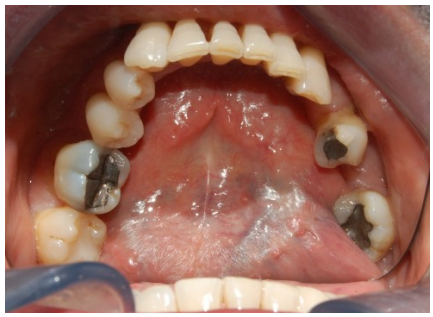

Figure 3 Dry and sticky appearance of oral mucosa in a radiotherapeutic patient.

Furthermore, an insufficient lubrication, due to a diminished salivary output, causes intolerance to prosthetic appliances, so more friction is present between the mucosa and the resin that can injure the delicate irradiated epithelial layer. In addition, the inadequate presence of saliva weakens the stability of prostheses in the mouth. Ulceration is more likely because the dry mucosa is more vulnerable to trauma.

A further complication that tends to occur later in irradiated patients is the increased risk of developing dental caries and oral infections, due to the alterations in the saliva flow and consequently in oral microflora.[36] The decay is most often recurrent or primary and located at sites generally not usually susceptible to caries such as the cervical margins, incisal margins, or the tips of teeth (Figure 4).

Another issue is the high incidence of yeast infections during xerostomia.[48] An example being the *C. albicans* infection, which is very common in both dentate and edentulous individuals and allows a colonization of oral mucosae[49] increasing the risk of oral mucosal infections.[50]

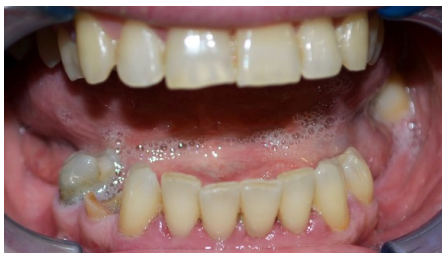

Figure 2 Viscous appearance of the saliva in a radiotherapeutic patient.

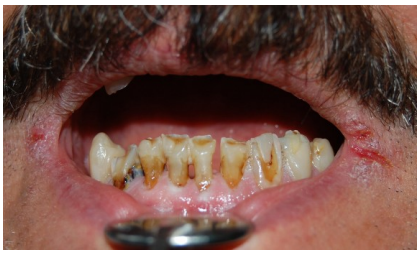

Figure 4 Cheilitis and cracked lips, and teeth cervical caries in a radiotherapeutic patient.

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Another acute side effect of radiotherapy is dermatitis, which can be experienced by up to 95% of patients.[41] The skin over the face and neck is very likely to gradually redden or darken and become sore. At the same time, the mouth and throat become sore and inflamed after a couple of weeks of treatment and mouth ulcers may occur; the voice may also become hoarse.

Discussion

The treatment of xerostomia has four aims: increasing existing saliva flow or replacing lost secretions, the control of the state of oral health, the control of dental caries, and the treatment of possible infections.[51]

Therapy options in xerostomia depend on the presence of residual secretion or the absence of it. When residual secretory capacity is present, it is advisable to regularly stimulate the salivary glands by mechanical or gustatory stimuli as supportive oral care. The use of sugarless chewing gum or candy-containing xylitol or sorbitol can be recommended as a means of stimulating extra salivary flow to aid caries management and lubrication. Nocturnal oral dryness can be alleviated by applying a small amount of dentifrice on smooth dental surfaces, especially using anti-xerostomia dentifrices that contain three salivary enzymes, lactoperoxidase, glucose oxidase, and lysozyme, specifically formulated to activate intraoral bacterial systems.

The salivary flow can also be stimulated by the use of cholinergic pharmaceutical preparations, such as pilocarpine or cevimeline. These two parasympathomimetic drugs are approved by the Food and Drug Administration for treatment of xerostomia; pilocarpine is approved for Sjögren's syndrome and radiotherapy-induced xerostomia, while cevimeline seems to be more specific for Sjögren's syndrome. Pilocarpine, a natural alkaloid, is a parasympathomimetic agent with β-adrenergic effects that activates cholinergic receptors,[52] stimulating the residual function of the salivary glands. The recommended dose is 5 mg orally three times a day.[53] Severe adverse effects are rare, but side effects associated with the use of the drug are vomiting, sweating, headache, increased urinary frequency, wheezing, watery eyes, and nausea, and gastrointestinal intolerance. Hypotension, rhinitis, diarrhea, and visual disturbances can also occur.[54,55] Normally, these are moderate in intensity and last for a short period of time. Patients with asthma, high blood pressure, heart diseases, and in therapy with β-blockers cannot use pilocarpine because this drug is a nonselective antagonist of muscarinic receptors and, therefore, it can interfere with the cardiac and respiratory functions in those patients. For the same reason, pilocarpine, stimulating muscarinic receptors in the central nervous system, can cause onset of agitation, confusion, and parkinsonian-like syndromes.[56]

Cevimeline is analogous to acetylcholine, which binds to muscarinic acetylcholine receptors in exocrine glands, specifically the M1 and M3 subtypes present, for instance, in the epithelium of the salivary and lachrymal glands, leading to an increase in exocrine gland secretion including saliva and sweat. M2 and M4 receptor sites predominate in cardiac and respiratory tissues. This receptor subtype selectivity is presumed to mitigate the systemic adverse effects of muscarinic–cholinergic stimulation.[56] It is rapidly absorbed from the gastrointestinal tract, reaching peak concentrations in approximately 90 minutes without food. The duration of its sialogogic effect seems to be unclear. Clinical trials have shown it to be more effective than placebos in relieving the symptoms of a dry mouth. The recommended dose is 30 mg orally three times a day, but in two clinical trials, it has been shown that the use of cevimeline in treating radiation-induced xerostomia, increasing the dose to 45 mg, was well tolerated by patients, with an increase of unstimulated salivary flow.[57,58] This medication is not recommended for patients with uncontrolled asthma, narrow-angle glaucoma, or iritis. Excessive sweating and nausea are the most frequently reported adverse effects with cevimeline. Rhinitis, diarrhea, and visual disturbances, especially at night, can also occur.

Another medication is anethole trithione that is a bile secretion-stimulating drug, or cholagogue. It increases the secretion of acetylcholine and stimulates the parasympathetic nervous system, and so as a result, we have the stimulation of salivation from serous acinar cells. This medication has been used for many years in the treatment of chronic xerostomia, but reports differ regarding its efficacy. While some studies report improvements in salivary flow rates in drug-induced xerostomia, trials in patients with Sjögren's syndrome show conflicting results. Side effects reported include abdominal discomfort and flatulence. Dosages of 75 mg three times daily may be effective in treating patients with mild-to-moderate symptoms of xerostomia, but further research is needed to establish its safety and efficacy in this setting.[59]

Yohimbine has also been used in patients with xerostomia and it is an alpha-2 adrenergic antagonist, which induces an increase in cholinergic activity peripherally. In one randomized, double-blind, crossover study, the effect of this medication was compared to that of anethole trithione in patients treated with psychotropic medications. Patients given yohimbine 6 mg three times daily for 5 days showed

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significantly increased saliva flow ($P<0.01$) when compared with anethole trithione 25 mg three times daily.[60]

Human interferon alfa (IFN-α) is currently undergoing clinical trials to determine the safety and efficacy of low-dose lozenges in the treatment of salivary gland dysfunction and xerostomia. In one study, IFN-α lozenges at dosages of 150 IU given three times daily for 12 weeks resulted in a significant increase in stimulated whole saliva ($P=0.04$) when compared with placebos.[61]

If some residual function of salivary glands remains, acupuncture could be a good alternative treatment for alleviating radio-induced xerostomia.[62] The way this works remains poorly understood, but it seems that acupuncture modulates central nervous system processes,[63] increasing the concentration of salivary neuropeptides, which seem capable of modulating the complex process of salivary secretion.[64] There are some studies that provide encouraging results, suggesting an effective increase in salivary flow, while others do not detect statistically significant differences in the increase in salivary flow between the treated subjects and controls.[65] However, the results of systematic reviews do not indicate the efficacy of acupuncture in the treatment of xerostomia due to the current lack of relevant randomized clinical trials.[64–67]

When stimulation of salivary secretion fails, patients can be given palliative oral care in the form of application of mouthwashes and saliva substitutes. Although the daily use of a mouthwash or one of the saliva substitutes that are formulated to mimic natural saliva, is strongly recommended, they do not stimulate salivary gland production. Commercially available products come in a variety of formulations including solutions, sprays, gels, and lozenges. In general, they contain an agent to increase viscosity, such as carboxymethylcellulose or hydroxypropylmethylcellulose, hydroxyethylcellulose, and polyglycerylmethacrylate,[65] minerals such as calcium and phosphate ions and fluoride, preservatives such as methyl or propylparaben, and flavoring and related agents.

Also homeopathic remedies such as olive oil, aloe vera gel, and rape oil spray may be effective alternatives in the palliative management of xerostomic patients.[68,69]

In order to minimize problems related to the absence of or reduced secretion of saliva, all patients should be encouraged to take an active role in the management of their xerostomia; so a daily mouth examination, checking for red, white, or dark patches, ulcers, or tooth decay, is highly recommended.

Patients with reduced saliva should also be encouraged to consider visiting their dentist more frequently because they have got a greater susceptibility to dental problems. Teeth should be cleaned at least twice a day, so brushing and flossing regularly and the daily use of fluoride and chlorhexidine rinses may also be useful in preventing caries by reducing amounts of *Streptococcus* and *Lactobacillus* in the mouth. For daily use, a special dentifrice (eg, children's toothpaste or anti-xerostomia dentifrices) is recommended, since the taste of a regular dentifrice may be too strong for these patients.

Dentures and acrylic appliances should not be worn during sleep and they should be kept clean by soaking them overnight in chlorhexidine. Sometimes, lubricants, Vaseline and/or glycerin based, put on the lips and under dentures, may relieve drying, cracking, soreness, and mucosal trauma.[61]

Patients with decreased salivary flow should also be made aware of the necessity to comply with suggested oral hygiene regimens after exposure to acid-producing food sources. Recommendations for professional and home fluoride treatments should be considered carefully for patients with salivary dysfunction, especially those with high caries rates and exposed root surfaces. A modified diet can be useful to minimize the effects of xerostomia; for instance, they should avoid sugary or acidic foods and also avoid dry, spicy, astringent, or excessively hot or cold foods that are more irritating, while eating foods such as carrots or celery may also help patients with residual salivary gland function. The addition of flavor enhancers such as herbs, condiments, and fruit extracts may make food more palatable to patients complaining of their food tasting bland, papery, salty, or otherwise unpleasant; at the same time, taking frequent sips of water throughout the day and sucking on ice chips are helpful.[70]

Conclusion

The resulting salivary gland hypofunction and xerostomia arising from radiotherapy for HNC can cause a serious diseased condition. The stomatologic complications could depend on the type of cancer treatment and the cumulative radiation dose to the gland tissue. They can be reversible or irreversible, transient, or enduring. The best approach to manage the radiotherapeutic patient begins with a careful clinical assessment of the individual case, followed by preventive therapy aimed to reduce oral complications when possible. Therefore, the clinician must keep this kind of patients under careful control in order to palliate the symptoms of xerostomia and improve their quality of life.

Disclosure

The authors report no conflicts of interest in this work.

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ORIGINAL ARTICLE

Short-term response of three resin-based materials as desensitizing agents under oral environmental exposure

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Abstract

Objective. This paper focuses on clinical responses after 7 days of oral exposure to two resin-based materials as desensitizing agents compared to a fluoride varnish and on morphological and analytical study as a means to elucidate the mechanism of action. Materials and methods. The elemental composition of Vertise Flow (VF), Universal Dentine Sealant (UDS) and Flor-Opal Varnish (FOV) were investigated by using an X-ray energy dispersive spectrometer (EDX) in conjunction with a scanning electron microscope (SEM). SEM morphology of the material-treated dentine surfaces and pain reduction ability according to the Visual Analogue Scale (VAS) were evaluated in selected hypersensitive teeth. Post treatments and 7 day controls were recorded with SEM and VAS measurements. Clinical data was analysed with the Student's t-test for paired data, with a 5% significance level. Results. Silicon, ytterbium and alumina were the most present elements in VF, whilst calcium, chloride, silicon and alumina were highest in UDS. Within a 7 day oral environment all the tested materials modified the treated-dentine surfaces showing tubular occlusion of different morphology. Clinically, the efficacy of all materials was similar after a 7-day examination. However, VAS scores were significantly reduced if compared with the baseline ($p < 0.05$). Conclusions. Within the limits of this study, data indicate that both resins are effective in sealing tubules and reducing VAS. A resin-related effect on the dentine's morphology was observed, which may influence the long-term response of the resins in the treatment of dental hypersensitivity, which requires further investigation.

Key Words: adhesive resins, dentine hypersensitivity, fluoride, ultrastructure, VAS

Introduction

Dentine hypersensitivity (DH) is a common and painful syndrome existing within 4–74% of the adult population [1]. DH is characterized by a short and sharp sensation of pain arising from the tubular dentine exposure to the oral environment as a result of enamel loss and/or gingival root surface exposure due to attrition, abrasion, erosion, abfraction or gingival recession [2]. The most widely accepted mechanism of DH is Brännstrōm's [2] hydrodynamic theory, whereby thermal, drying, tactile or chemical stimuli promote fluid shifts in the exposed dentinal tubules, causing pain by activation of the pulp nerves [3].

Therefore, the occlusion of the tubules by different materials may reduce the fluid movement inside the dentinal tubules and the clinical symptoms of DH [4].

Thus, the efficacy of desensitizing materials has been evaluated by direct measurement of fluid flow through dentine, or dentine permeability, using in vitro fluid filtration systems [4–9] or an in vivo Visual Analogue Scale (VAS) measurement of pain [10–14] and has been correlated with various stimuli that induce pain in the exposed dentine [15]. Furthermore, the material-treated dentine surfaces have been investigated using a scanning electron microscope (SEM) [6,16]. However, when the occlusion of the tubules was superficial or not adherent to the tubular wall, daily tooth brushing, saliva or consumption of acidic beverages easily opened the dentinal tubules, leading to short-term desensitization effects.

Some treatments of DH employ inorganic biomaterials [15–19] and organic biomaterials or resin-based materials [20–23].

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The binding quality of biomaterials influences DH treatment outcomes, as biomaterials can bind to the exposed dentine surface and within the openings of the dentinal tubules to mediate the formation of a tight seal [24–27]. In vitro studies recently showed stable tubular occlusion through the use of calcium silicate cements [16], which are largely used as bioactive materials in dentistry. However, the clinical use of calcium silicate cements (i.e. mineral trioxide aggregate (MTA) and Portland Cement (PC)) is limited, due to the long setting time entailing possible oral interferences with bio-activity capacity [28]. Thus, selected accelerants (i.e. calcium chloride) have been suggested to accelerate the setting of MTA and PC, increasing their acceptance in wider clinical situations [29–32].

With regard to the resin-based materials, the desensitizing effect has been attributed to the formation of a resin seal in the exposed dentine with tubular occlusions by resin plugs [9,23,31]. Nevertheless, different data are reported when resin-based materials were used in the treatment of DH, which may reflect different approaches and reactivities of resins [7,9,23,31] and a possible degradation of the polymer matrix in an oral environment [32,33]. Unfortunately, objective and comparative research on resin-based materials is often hindered by the scarcity of specific information about some of their chemical components, such as the proprietary monomers. Descriptive terms are often used to indicate the working mechanism avoiding the disclosure of active ingredients in the resin matrix. Even if some resin properties may be deducted through chemical analysis [32,34] it is paramount to know their behaviours in oral environment conditions [10,27,29,30].

In light of the considerations above and of the scarcity of resin-based materials indicated to treat DH, we decided to conduct both an elemental analysis and a morphological and clinical assessment of the efficacy of Vertise® Flow (VF) (Kerr Corporation, Orange, CA), a self-adhering resin composite, that is suggested for DH treatment, and Universal Dentine Sealant (UDS) (Ultradent, South Jordan, UT), a desensitizing resin sealant, whilst controlling for the influence of the oral environment which can trigger different responses. As a control group we used a fluoride-containing varnish.

The null-hypothesis was that the three resins will not reduce the VAS measurement of pain, either initially or after 7 days of exposure to oral fluids.

Materials and methods

VF is a proprietary self-adhering flowable resin composite. Wej et al. [33] recently reported that VF included an organic matrix of glycerol phosphate dimethacrylate (GPDM), proprietary methacrylate co-monomers, a filler of pre-polymerized particles of barium glass, nano-sized colloidal silica and nano-sized ytterbium fluoride.

UDS is described by the manufacturer as a biocompatible, non-polymerizable, high molecular weight proprietary resin sealant in an alcohol solvent.

In this study Flor-Opal® Varnish (FOV) (Ultradent, South Jordan, UT), a 5% sodium fluoride (NaF) varnish, was used as a control group due to the ability of fluoride to react with calcium ions in dentinal fluid to produce tubular occlusion by insoluble CaF_2 crystals [6,20,21] with dentine permeability reduction [10,23,35–37]. (Table I shows the components and modes of application of the materials tested in this study).

Elemental analysis

The elemental composition of VF, UDS and FOV was investigated using an X-ray energy dispersive spectrometer (EDX) (INCA-X-acta, Oxford Instruments, Tubney Woods, Abingdon, Oxfordshire, UK) in conjunction with an environmental scanning electron microscope (ESEM) (EVO® LS 25, Zeiss, Oberkochen, Germany). EDX was carried out using an accelerating voltage of 20 kV and ESEM was used for imaging of each sample at standardized magnification (200×, 1000×).

For the semi-quantitative X-ray analysis, VF, UDS and FOV (0.5 mL) were weighed, placed in a thin layer over Perspex® slabs mounted on aluminum stubs (Agar Scientific, Stansted, UK). Three stubs were made for each tested material and the analysis was performed twice for each sample. The elemental analysis (weight percentage and atomic percentage) was performed in low-vacuum conditions (20 Pa). Atomic number, absorption and fluorescence corrections were applied during the analysis with the ZAF correction method.

Experimental design

Subjects who had hypersensitive teeth were selected from an ongoing programme evaluating desensitizing agents at the Dental Clinic of the University of Sassari. Two clinicians selected patients complaining about hypersensitivity and who had reported this to the Department of Periodontology at the Dental Clinic. The protocol and informed consent forms were approved by the ethics committee at the University of Sassari (n° 1000/CE). The medical and dental history of the patients was collected and sensitive teeth were differentiated from other clinical conditions which frequently interfere with DH. All the subjects were thoroughly informed about the study's purpose, risks and benefits. A total of 86 patients with hypersensitive teeth were collected after an intake period of 8 months. The study inclusion/exclusion criteria were the following: (1) patients

were considered suitable for the study if they had sensitive teeth showing abrasion, erosion or recession with the exposure of the cervical dentine; (2) teeth with subjective or objective evidence of carious lesions, pulpitis, restorations, premature contact, cracked enamel, active periapical infection or which had received periodontal surgery or root-planning up to 6 months prior to the investigation were excluded from the study. Other exclusion criteria were professional desensitizing therapy during the previous 3 months or use of 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). As a consequence, the total study population included in the programme was of 74 subjects, 43 female and 31 male, aged 27–75 years (mean age ± standard deviation: 53 ± 7 years) with a total of 286 hypersensitive teeth (mean teeth for patient 2 ± 1). The level of sensitivity experienced by the patient was considered as independent of the position of the hypersensitive tooth in the oral cavity [12].

Morphological study

VF, UDS and FOV's ability to occlude dentine tubules and their morphology on dentinal surfaces were evaluated in 30 selected patients, 18 female and 12 male, part of the total sample of 74 subjects with 30 hypersensitive teeth. Patients had 30 hypersensitivity teeth (11 premolars, 13 incisors, six cuspids), whose Grade III mobility and significantly reduced response to periodontal treatment suggested the need for extraction [38,39].

A full medical and dental history was taken and all the teeth were carefully examined to confirm the diagnosis of DH. The nature and scope of the study was explained and informed consent was obtained.

A week before treatment, patients received oral prophylaxis and were randomly assigned to three experimental groups (n = 10 per group). The treatments were carried out at random by one of the clinicians, while the other assisted. The teeth were isolated with cotton rolls and the treatment with VF, UDS and FOV was performed as summarized in Table I. As recommended, a halogen curing light (Optilux 501, Kerr Corporation, Orange, CA, USA; 11 mm exit window) under the standard curing mode (output wavelength range: 400–505 nm; output irradiance: 580–700 mW/cm^2) was used to allow light curing of VF. After the treatment, teeth were immediately extracted (n = 5 per sub-group) in sub-group 1 and after 7 days post-treatment (n = 5 per sub-group) in sub-group 2.

After extraction, samples were rinsed with distilled water at 37°C and fixed in a solution of 2.5% glutaraldehyde in 0.1 M PBS buffer (pH 7.2) for 72 h. In each sample, the treated cervical dentine was sectioned from the remaining crown and roots of the tooth with a water-cooled saw (Isomet low-speed saw; Buehler, Lake Bluff, IL) and then fractured into two halves in order to analyse the buccal surface and the longitudinal surface of the material-treated dentine surfaces. Samples were post-fixed in 1% osmium tetroxide, dehydrated in increasing concentrations of acetone (25–100%), dried by critical point drying and metal-coated. Specimens were then observed using a scanning electron microscope (SEM) (Zeiss, DSM 962, Oberkochen, Germany). Observations were recorded at standardized magnifications (1000×, 3000×, 5000×).

Clinical study

The study population consisted of another 36 patients, 19 females and 17 males, who were randomly selected from the total population of 74 subjects who had hypersensitive teeth. A total of 90 teeth (30 premolars, 44 incisors and 16 cuspids) constituted the group of hypersensitive teeth for the clinical effectiveness of VF, UDS and FOV.

A week before the experiment, patients received oral prophylaxis. Non-fluoride toothpaste, soft toothbrush and oral hygiene instructions were also provided in order to have standardized habits during the period of the study.

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

Code	Material	Manufacturer	Components	Batch no.	Mode of application
VF	VertiseÔ Flow	Kerr Corporation (Orange, CA)	GPDM, methacrylate monomers, barium glass, silica, ytterbium fluoride*	122005	apply flow on a thin layer, scrubbing for 20 s, gently air-dry for 20 s, light cure 10 s
UDS	Universal Dentine Sealant	Ultradent (South Jordan, UT)	resin, alcohol	052809	Brush 30 s, paint a thin layer and gently air-dry for 5–10 s, saliva contact
FOV	Flor-OpalÔ Varnish	Ultradent (South Jordan, UT)	natural resin, sodium fluoride	122005	Brush 30 s, apply a smooth layer, scrubbing for 5–10 s, saliva contact

GPDM, glycerol phosphate dimethacrylate.
* [33].

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Teeth were randomly assigned to three groups (n = 30 per group) for the treatment with the three desensitizing agents (Table I). At the baseline visit, they were reassessed for dentine hypersensitivity using the Visual Analogue Scores (VAS) of pain. Treatment was performed by one examiner, while the pain stimulus was given by the other examiner with the same equipment yielding similar air pressure each time.

The VAS scale consisted of a horizontal line that was 100 mm long, on which 'no pain' was marked on the right-hand extremity and 'unbearable pain' on the other. The patients expressed the intensity of the pain experienced by placing a mark at any point along the continuum. The distance, expressed in millimetres, from the right edge of 'no pain' was used as the VAS score. Each patient was asked to rate the perception of discomfort after the application of air via a dental syringe at 45–60 psi, 1 cm at the cervical third of the tooth after removing supragingival plaque with a low-speed handpiece with pumice powder and without fluoride. The adjacent teeth were covered by cotton rolls. The stimulus was delivered until reaction or up to a maximum duration of 10 s by the same examiner with the same equipment yielding similar air pressure each time. The subject's response was considered as the baseline measurement (PRE-1) mean ± standard deviation VAS score: 5.3 ± 2.1. Before the application of the material (PRE-1), immediately after (POST-1) and after 7 days of oral environment (POST- 2), the same clinician carried out the sensitivity test.

To compare the efficacy of the treatments, teeth were evaluated as a statistical unit rather than a subject. Data were elaborated using parametric tests (ANOVA for more than two samples adjusted according to Sidak's multiple testing) with a 5% significance level.

Figure 1 summarizes the experimental design used for the SEM morphological study and the clinical study in order to test different desensitizing materials.

Results

Elemental analysis

VF treatment left a layer of highly visible randomly distributed 5–40 nm particles (Figure 2). Spectra of silicion (Si), ytterbium (Yb) and alumina (Al) were highest in the layer in which also phosphorus (P),

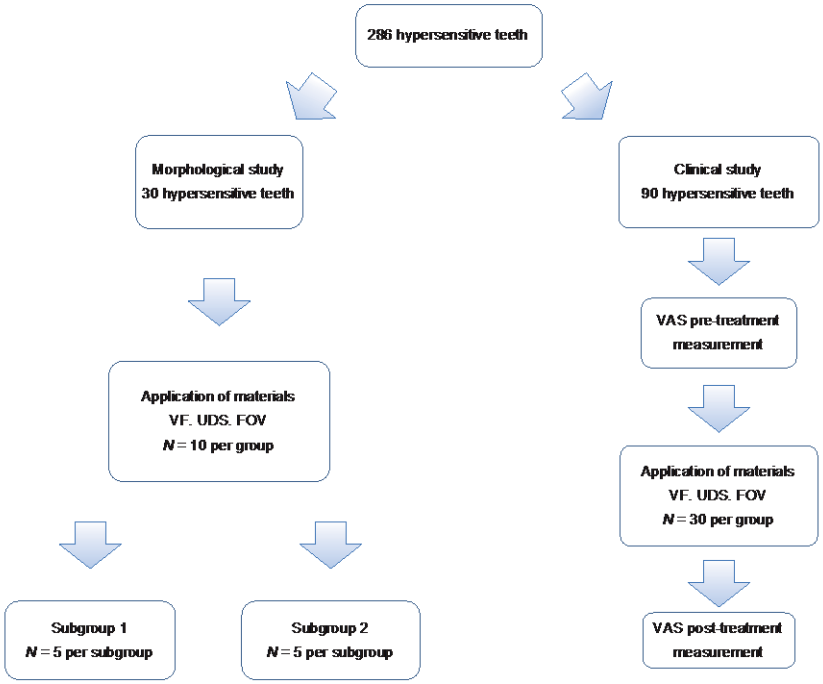

Figure 1. Summary of the experimental design to collect hypersensitive teeth and test different desensitising materials for the SEM morphological study and the clinical study.

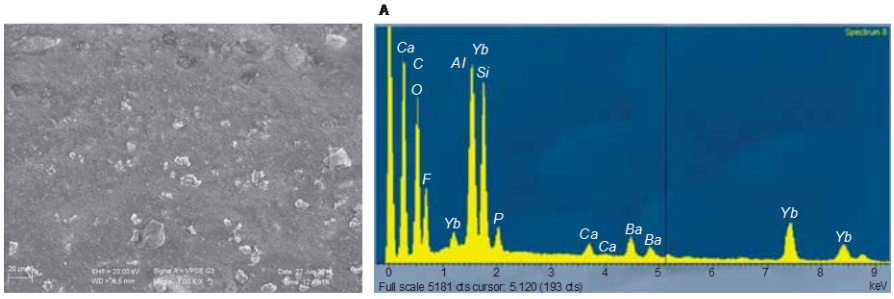

Figure 2. EDX analysis of VertiseÔ Flow self-etching composite showing the ESEM morphological aspect of the self-etching composite composed by an amorphous matrix of nano-particles and highly visible randomly distributed 5–40 nm particles. EDX analysis in (A) reveals Si, Yb and F as the most represented elements in the matrix in which Al, P, Ca and Ba are also present.

calcium (Ca), barium (Ba) and fluoride (F) were found (Figure 2A).

UDS treatment left fine, dispersed particles of ~ 0.5 mm in a thin and smooth layer (Figure 3). Spots on these particles showed very high peaks of Ca and chlorine (Cl) (Figure 3A). The semi-quantitative analysis obtained by scanning different areas of the matrix highlighted Ca and Cl associated with Si and other oxides of Al, iron (Fe), chrome (Cr), potassium (K), sulphur (S), magnesium (Mg), titanium (Ti) and zinc (Zn) (Figure 3B).

FOV-treated samples showed a layer of particles embedded in a smooth matrix (Figure 4) rich in sodium (Na) and F peaks and with traces of Si and P (Figure 4A).

Morphological study

On the surface of the exposed dentine (ED) to the oral fluids, VF formed a thick, irregular coat that completely masked the underlying tubular dentine (Figures 5A and B). Cracks were also noted in ED. Longitudinal sections showed a coating ~ 3 mm thick composed of a matrix with crystal-like particles of different sizes. Tubule orifices were tightly blocked by the material and plugs of resin-like material were found inside the tubules (Figure 5C). After 7 days of exposure to the oral environment (sub-group 2), tubular orifices were still not visible on ED treated dentin surface, which showed cracks and gap formations (Figure 5D). Crystal-like precipitates were

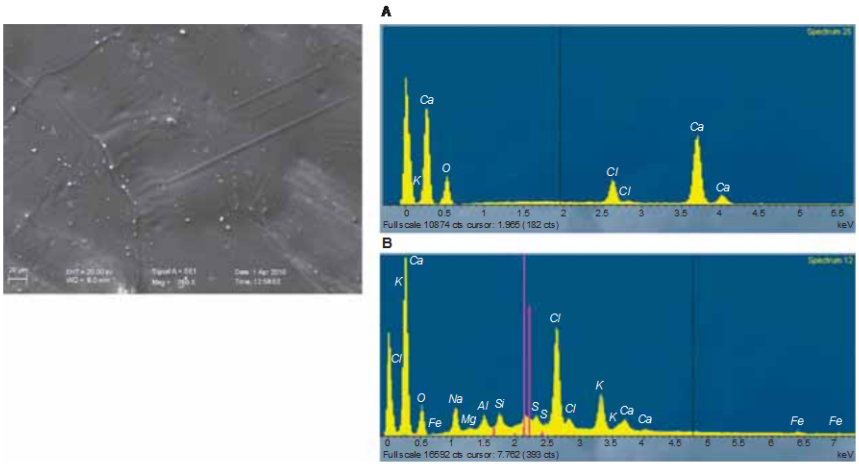

Figure 3. EDX analysis of Universal Dentin Sealant showing the ESEM morphology of the sealant composed by a smooth matrix with dispersed particles of ~ 0.5 mm. (A) EDX composition of the particles with very high peaks of Ca and Cl and (B) the semi-quantitative analysis obtained by scanning different areas in the matrix evidencing Ca and Cl peaks associated to Si and Al peaks as well as traces of Fe, Cr, K, S, Mg, Ti and Zn.

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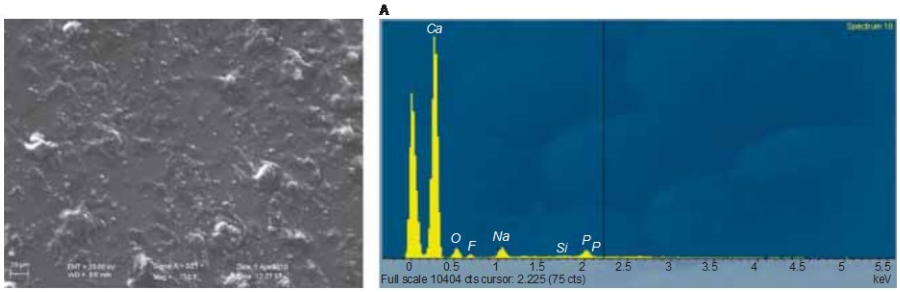

Figure 4. EDX analysis of Flor-Opal® Varnish showing the ESEM morphology of amorphous layer with particles and (A) the semi-quantitative analysis identifying Na and F as the main elemental components. Si and P are also retrieved in traces in the varnish.

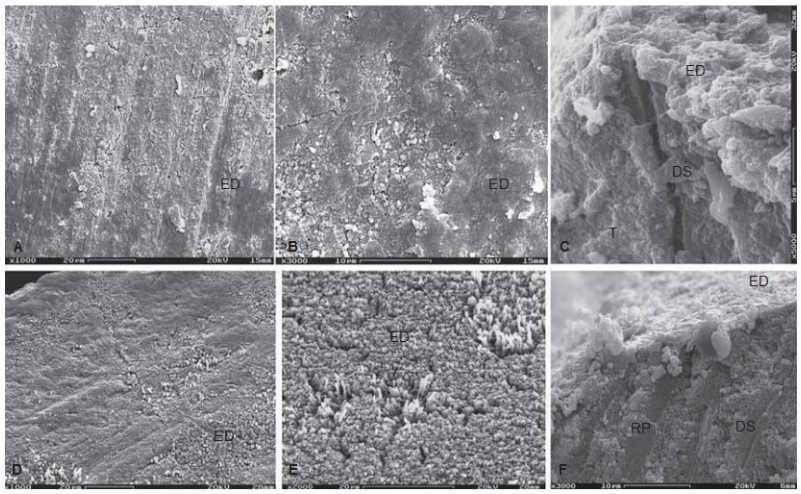

Figure 5. Representative SEM micrographs of Vertise® Flow self-adhering composite immediately after application on the dentine (A, B) and after environmental exposure (D, E). (A and B) Two images at different magnifications of the dense, irregular layer containing particles masking the tubular dentine and showing cracks which could be caused by dehydration of the samples during the preparation procedure for the SEM. Longitudinal sections of exposed dentine (C) show the 3 mm thick coating with crystal-like filler particles of Vertise® Flow. An interdiffusion layer of the self-adhering resin composite in the dentine cannot be disclosed by SEM under the standardized magnifications used in this study. Environmental exposure in (D) and (E) shows the cracks, which, compared with pre-aged images in (A) and (B), appear wider on the dentine surface, along with gaps. Crystal-like particles were also observed on the exposed surface. Longitudinal sections of exposed dentine (F) show the tubular occlusions by resin plug (RP) and the reduction of tubular diameter by the presence of crystal-like filler particles. ED, exposed dentin; T, tubule; RP, resin plug; DS, dentin sub-surface.

dissolving (Figure 5E), but the tubular apertures (Figure 5F) remained occluded.

UDS formed a smooth amorphous layer that contained particles ~ 0.5 mm in diameter, over dentine (Figure 6A). Particles had a tendency to form clusters and adhered to the underlying dentine completely occluding the tubular orifices (Figure 6B). Longitudinal sections showed the dentine surface covered by a coating of UDS that was ~ 0.4 mm thick and plug-like structures in the tubules (Figure 6C). After exposure to oral environment for 7 days (sub-group 2), the dentine surface treated with UDS showed a residual coating of dentine with different representations of crystal-like particles (Figure 6D). Longitudinal sections showed a thick granular surface and peritubular dentine masking the intratubular space (Figure 6E).

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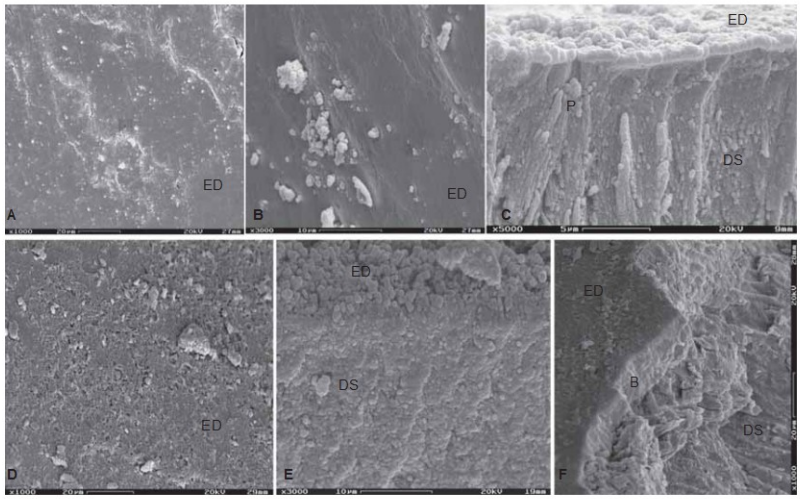

Figure 6. Representative SEM micrographs of Universal Dentin Sealant on the exposed dentin surfaces showing the smooth amorphous layer with particles (A) forming clusters (B). The thick layer of varnish completely covers the tubular orifices. Longitudinal sections of exposed dentine (C) detect the penetration of the resin sealant into dentinal tubules forming varnish-tags inside the tubule. Exposure to oral fluids for 7 days may have solubilized the varnish allowing exposure of the underling smear layer on ED (D). Transverse sections of exposed dentine show a thickening of inter-diffusion and peritubular dentine (E). Fractures between the exposed surface and the inter-diffusion reveal that inter-diffusion forms a barrier-like structure (B) with tag-like structures reproducing tubular dentine morphology after 7 days exposure. ED, exposed dentine; T, tubule; DS, dentine sub-surface.

Occasionally, small areas of separation between the surface coating and the dentine sub-surface demonstrated the presence of a barrier-like structure, with tag-like structures reproducing the tubular dentine (Figure 6F).

FOV-treated dentine surface exhibited an amorphous layer with dispersed particles leaving most of the tubules partially occluded (Figures 7A and B). Transverse sections of exposed dentine revealed a thick coating of varnish almost blocking the tubular apertures (Figure 7C). After 7 days of exposure to the oral environment (sub-group 2), ED showed areas of solubilization of a surface coating with disclosure of the underling smear layer (Figure 7D). The solubilization process involved the tubular blocks of varnish on ED simultaneously showing crystal-like precipitates with reduction of the tubular diameter (Figure 7E).

Clinical study

The mean VAS scores are shown in Table II. There was no difference among baseline VAS scores of all groups ($p > 0.05$). After treatment, all teeth exhibited statistically significant reductions in VAS in Post-1. Teeth treated with VF had lower VAS scores immediately after Post-1 control (VF vs FOV: $p = 0.034$). After 7 days of exposure to oral fluids (POST-2) there was no significant difference among tested materials, according to Sidak's multiple testing adjustment. However, when compared with baseline data, all the VAS scores at post-treatment evaluation points were significantly decreased ($p < 0.05$).

Discussion

Extensive tubular occlusion and permeability reduction reported for various classes of materials when treating DH reflect intrinsic material performance, but they show differences in terms of experimental design and execution [22]. As suggested by Gillam et al. [40], in vitro evaluation of desensitizing agents is gathered by using human dentine discs with fluid filtration systems for hydraulic conductance measurement (i.e. dentinal permeability) [3] under simulated oral cavity conditions. SEM images are made of the morphological changes in material-treated dentine surfaces before and after exposure to oral fluids to determine the stability of tubular occlusion [5,7,8,16,18]. One advantage of these studies is that the physical and chemical influences that affect tubular occlusion (i.e. toothbrush, dietary acids and saliva) can be evaluated separately to simplify interpretation of data and within a specific time framework. However, morphological evidence of

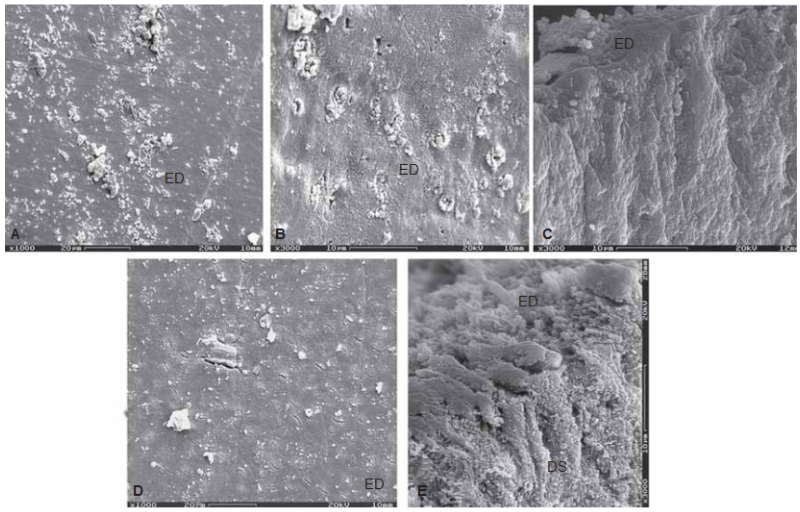

Figure 7. Representative SEM micrographs of the exposed dentine surface after application of Flor-Opal® Varnish showing a layer with dispersed particles (A and B) that partially obliterated tubule orifices. Longitudinal sections (C) showing the thick cover of varnish which blocks the tubular orifices. Exposure to oral fluids for 7 days largely solubilized the varnish leaving a surface of smear layer on ED (D). Transverse sections of exposed dentine (F) show the solubilization of the tubular blocks of varnish in ED and crystal-like precipitates just below the tubular apertures (E). ED, exposed dentine; T, tubule; DS, dentine sub-surface.

Table II. Visual Analogue Scale (VAS) values measured in 30 patients at baseline and post-treatment.

	*Vertise flow M (SD)	°Universal Dentine Sealant M (SD)	†Flor-Opal Varnish M (SD)	Anova one-way
PRE-1	5.4 (2.2)*	5.8 (2.3)°	4.7 (1.9)	NS
POST-1	0.5 (1.1)*	0.6 (0.8)°	1.9 (1.5)†	NS* 0.04*† 0.02°†
POST-2	1.7 (1.2)*	1.2 (1.1)°	1.8 (1.5)†	NS* 0.01*† 0.03°†
Anova one-way	< 0.01	< 0.01	< 0.01	

Values expressed as means and standard deviation.
*Vertise Flow; °Universal Dentin Sealant; †Flor-Opal Varnish.

materials' performance in oral environment conditions as well as the longevity of the tubular occlusion under environmental stress may not be correctly predicted for the in vivo situation. Furthermore, prolonged exposure to environmental fluids would be essential to observe the behaviours of different materials on dentine. For instance, instability of the resins in an oral environment [9] and in simulated oral cavity conditions [33] increased within months of observation. The formation of bio-apatite by calcium-silicate cements has been observed as a gradual transformation of amorphous calcium phosphate exposed to oral fluids, within a time framework of between a few hours and up to 2 months, yielding phase mixtures richer in apatite [24,26,27].

In light of such considerations, this study aimed to assess the response of newly introduced proprietary resin-based materials as desensitizers under oral environment conditions. With this assessment we decided: (1) to conduct an ESEM-EDX examination in order to investigate the semi-quantitative elemental composition and micro-morphology of the matrices; this might reveal information regarding their mode of action [32,34,41]; (2) to investigate the SEM morphology of the material-treated dentine and the tubular occlusions after exposure to oral fluids (and environment) which might reveal the materials' behaviour on the dentine surface and their occlusion capacity [24,27,33]; and (3) to compare the morphological features with the clinical

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outcomes of the resins by employing VAS measurement of pain, which might allow for correlation between form and function of the tubular seals [9,38].

The morphological and clinical studies were conducted on hypersensitive teeth as part of a study population of 286 hypersensitive teeth using the same exclusion/inclusion criteria, in order to compare data on teeth as homogeneous as possible. Even if the in situ SEM-replica technique was utilized to accurately trace the material-treated tooth surfaces [9], the use of extracted specimens might show information on dentine cross-sections with the interpretation of peritubular and intratubular dentine interactions of the desensitizers after exposure to oral fluids.

Furthermore, a NaF varnish was used in our investigation as a control due to the effect of fluoride on tubular occlusions [6,38] as well as in the reduction of the VAS measurement of pain [10,11,13].

Data clearly showed that environmental interaction modifies the morphological aspect of all the material-treated dentine surfaces and tubular occlusion. However, different responses could be observed as a consequence of the material composition and interaction capacity with the dentine in an oral environment.

In the control group, FOV fluorine varnish was somewhat solubilized from the ED surfaces and in the tubule occlusions as possible evidence of lack of bonding between the varnish and the dentine [10] after 7 days in the oral cavity. At the same time, crystal-like precipitates were observed in the tubules with a reduction of the tubule's radius. These observations are interpreted as a consequence of the complex series of chemical and physical interactions involving the F ions in the varnish and the Ca and P in the dentine, which produce a mechanical obstruction of the tubules by precipitation of Ca-P phases [6]. Markowitz and Pashley [14] claimed that any substance that causes a decrease of tubular radius is able to reduce clinical symptomatology of DH by reducing fluid conductance. Therefore, the presence of crystal-like precipitates inside the tubules would have produced a relief of DH. Following treatment of hypersensitive dentine with FOV, we clinically observed a decreased of the VAS measurement compared to the baseline, in POST 1, immediately after the application, and in 7 days of exposure after treatment. Compared to the baseline, the reduction in VAS was significant in both POST-1 and POST-2, but it was not in POST-2 if compared with POST-1 values. It is likely that, immediately after treatment with FOV, the tubules were occluded by both CaF_2 crystals and varnish but that, over the 7 day post-treatment time, the varnish solubilized leading tubules partially occluded with CaF_2 crystals. These results support other clinical studies on the ability of topical sealing agents, such as fluoride varnish, to reduce hypersensitivity, but whose desensitizing effects were transient, with a progressive decrease in efficacy in the post-treatment controls [10,13].

Data obtained by EDX analysis of VF self-adhering composite validate the formula reported by Wej et al. [33]. Furthermore, this investigation detected Ca and Al in the elemental composition of VF. Si, Yt, F and Ba were the main elements and would be utilized as filler components in the resin [33]. This is in accordance with different studies that reported the use of ytterbium-fluoride and barium fillers with the purpose to increase radio-opacity [42,43], shorten the setting and increase hardness in composite matrices. Fillers of ytterbium-fluoride have been associated, moreover, to the fluoride release on the media due to the leach of surface-retained fluoride [44] with mineralization effects on the tooth's surface.

Morphologically, the application of VF formed a thick coating layer with particles that were tightly adapted to the ED surface and which completely masked the tubules. However, this SEM investigation was not able to show an inter-diffusion zone of VF in the dentine, possibly due to a very thin layer of resin–dentine infiltration (i.e. 200 nm) which could not be detected at the standardized magnifications used. Clinically, VF produced a significant drop of the VAS value in POST-1 compared with the baseline, presumably because the self-adhering flowable composite produced a tubular seal [44]. Our observations are in agreement with previous studies [45] that described the intimate interface between VF and dentine using transmission electron microscopy.

The evidence of particles in the thickness of the VF layer may be explained by (i) the acidic phosphate group of the self-etching composite, which could have raised ionized Ca and P ion concentration from the dentine, to a point where it exceeded the product's solubility constants [46]; and (ii) the consequent precipitation of Ca and P on the dentine [47]. Alternatively, the particles may simply have been insoluble fillers in a light-cured polymerized matrix.

The resinous layer formed by VF on the dentine showed the ability to resist 7 days in the oral environment, supporting our hypothesis that the coating remained on the dentine surface and in dentine tubules. In fact the composition of the material reflects longevity of tubular occlusions [5,17]. Furthermore, the interaction with saliva ions and the presence of F ions in the composite might have supported the growing of crystal-like precipitates on the ED surface and in the tubules exposed to oral environment conditions [6]. Regardless of the mechanism of tubule occlusion, this work suggests the ability of VF to occlude dentinal tubules in DH treatment. On the other hand, the evidence of crack and gap formations on the ED surface may imply instability of the polymer matrix under oral conditions. We related cracks on the ED in sub-group 1 to

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dehydration of the samples during the SEM procedure. Nevertheless, the presence of cracks and the formation of gaps may suggest a weakness of bonding between dentine and resin composite in an oral environment [48]. This speculation is supported by recent investigations that documented hydrolytic instability of VF in water [33]. The hydrolysis of the interface between nano-sized filler particles and polymer matrix may create diffusion paths for water. Thus, the evidence of cracks and gaps may indicate resin–filler interface degradation within 7 days of exposure to saliva and the oral environment [33].

Spectra in UDS treated teeth revealed Ca, Cl and Si as the elements in highest quantity in the matrix, which also contains Al peak and precipitates rich in Ca and Cl.

Morphologically the behaviour of the resin sealant was very different to that of the self-adhesive composite. A surface coating was clearly evidenced on the dentine under SEM. Plug-like structures of particles were also detected in the tubules. Both features may have contributed towards a significant decrease of VAS value in POST-1 compared with the baseline [14,22,23,34]. However, one of the most important outcomes of this study was that the 7 days of oral function strongly changed the morphology of UDS on the dentine, giving rise to a dense barrier-like structure with tag-like structures resembling demineralized tubular dentine. Thus, we believe that the 7 days of fluid contact and oral environment conditions would be essential for the morphological formation/expression of a dense seal into the exposed dentinal tubules.

As a result of this investigation, we observed morphological differences in the features of the seal and tubular dentine occlusion between VF and UDS, after 7 days of exposure to an oral environment. Thus, the null hypothesis that the resin-based material-treated dentine surfaces showed no morphological difference after 7 days in an oral environment was rejected.

Clinically, all the materials tested produced a reduction of dentine permeability. In addition, after 7 days, POST 2, there was no statistically significant difference in the decrease of the VAS, irrespective of the desensitizing agent employed. These considerations are in accordance with the literature, whereby significant differences among desensitizing effects may appear in longer term evaluations [10,12,13].

Further research in this field is needed to better clarify the effectiveness of FV and UDS in long-term clinical trials.

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Clinical evaluation of the efficacy of one self-adhesive composite in dental hypersensitivity.

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Abstract

Objectives To investigate the clinical effectiveness over 12 weeks of Vertise Flow™, a self-adhering composite, in dental hypersensitivity (DH).

Material and Methods The study was conduced as a split-mouth randomized clinical trial. Vertise Flow™ was compared to: 1) Universal Dentine Sealant, 2) Clearfil Protect Bond, and 3) Flor-Opal® Varnish. A total of 46 patients with 116 hypersensitive teeth were studied. Pain experience was generated by a cold stimulus and assessed using the Visual Analogue Scale (VAS) of pain. The response was recorded before the application of the materials (PRE-1), immediately after (POST-1), at 1 week (POST-2), 2 weeks (POST-3) and 12 week controls (POST-4). Statistical differences in VAS were performed using the Kruskall-Wallis analysis at the different time-points (P <0.05), adjusting statistical significances for multiple comparisons (Bonferroni correction).

Results All the materials showed any statistically significant differences at the baseline. After the application of each material, a VAS decrease was demonstrated at every post-control. VF showed significant hypersensitivity reduction in Post-1. Statistically significant relief was also observed in Post-2 while no significant differences were detected in Post-3 and Post-4 .

Conclusions After 12-week controls, there was no statistically significant hypersensitivity reduction using VF in respect to the other materials. On the other hand, any significant differences were detected in the decrease of the VAS irrespective of the desensitizing agent employed at the 12-week controls.

Clinical Relevance The significant increase in VAS scores within the 12-weeks of environment suggested there is instability of VF when used as desensitizing agent.

Key Words: dentine hypersensitivity, Vertise flow, self-adhering composite, desensitizing agents.

Introduction

Dentine hypersensitivity (DH) is a common and painful syndrome, predominately located on the cervical part of the tooth buccal surface. DH has a wide prevalence rate (3-98%) in the adult population, with a peak in 20–50 yy [1].

DH is characterized by a short and sharp sensation of pain arising from the tubular dentine exposure as a result of enamel loss and/or gingival root surface exposure due to attrition, abrasion, erosion, abfraction or gingival recession [2]. Any thermal, osmotic and mechanical stimuli induced by the application of tooth brushing, sweet and acid foods, hot or cold drinks may provoke pain referred to fluid shifts in the exposed dentinal tubules with activation of the pulp nerves, according to "Brännström's hydrodynamic theory" [2-5].

When reducing fluid movement by fully or partially occluding open dentine tubules, hypersensitivity could be diminished [6]. In fact most desensitizing agents have been designed to involve the dentine surface and occlude exposed tubules or penetrate the tubules, coating and sealing them [4,7-11].

Irrespective of the material used, the data demonstrated a decrease of sensitivity immediately after the application of materials in respect to the pre-treatment. However, the reported clinical outcome is quite variable in long term [7-11]. Data has been explained in the capacity of the material-dentine exposed surface to resist in face to interactions with saliva and oral ambient interferences. Moreover, differences in the efficacy were attributed to the different chemistries of the materials and application modalities required by the desensitizer itself [12-15].

Several different formulations of resin-based materials have being used in DH treatment. Four different kind can be summarized: 1) *varnishes*, usually with fluoride, creating a coat of calcium fluoride precipitates on the exposed surface and dentinal tubules [10,16-18]; 2) *adhesive monomeric systems*, with or without the etching phase, able to seal the exposed surface by a layer of interdiffusion in dentine and tubular resin plugs [12-14, 19]; 3) *resin sealants* and 4) *flowable resin composites* able to form covers on the dentine surface [20] which sealing capacity in the time is influenced by the resin composition and the coupling between filler and matrix [21].

Recently, new self-adhering flowable resins have been developed. According to manufacturers, these resins bond to tooth surfaces due to the presence of acidic monomers thus avoiding the need of adhesives [21, 22]. One of these, Vertise Flow (VF) has been suggested by the manufacturer (Kerr Corporation, Orange, CA, USA), in different fields of restorative dentistry including DH therapy.

VF consists of a new organic matrix of glycerol phosphate dimethacrylate (GPDM), proprietary methacrylate co-monomers, and nano-filler particles of barium glass, nano-sized colloidal-silica, nano-sized ytterbium-fluoride [21].

The clinical behaviour and morphological aspect of VF, used as desensitizing agent within 7 days of oral exposure was investigated [20]. After 7 days of oral fluids, VF showed a thick, irregular coat on the surface of exposed dentine with crystal-like filler particles in the tubules leading to reduction of the Visual Analogue Scale (VAS) of pain in hypersensitive teeth. At the same time, the SEM evidence of cracks and gaps in VF/dentine surfaces suggested a low bond strength that could be related to a hydrolytic instability due to the presence of leachable ions and the subsequent substitution of environmental water [20,21]. An increase of adhesion performance was reported in other studies using VF after a pre-etching procedure with phosphoric acid, or self-etch adhesive systems [23,24].

In light of the considerations above and of the scarcity of studies on self-adhering composites evaluated clinically as desensitizing agents, the aim of the present study was to investigate clinically, the effectiveness of VF in hypersensitivity teeth in comparison to three other different materials.

The null hypotheses were:

- there will be some statistical differences in DH using VF in comparison to the other desensitizing agents at the 12-week control;
- VF will relieve DH at the 12-week treatment.

Materials and Methods

Partecipants

The study was designed as a split-mouth randomized clinical trial. The protocol and informed consent forms were approved by the ethics committee at the University of Sassari (n° 1000/CE). Subjects who had hypersensitive teeth were selected from an on-going program of evaluating desensitizing agents at the Dental Clinic of the University of Sassari, Italy.

Two examiners selected patients complaining about hypersensitivity and who had reported this to the Department of Periodontology at the Dental Clinic. The medical and dental history of the patients was collected, and sensitive teeth were differentiated from other clinical conditions that frequently interfere with DH. To participate in the study, the subjects had to have two or three teeth that were hypersensitive to the stimulation with a blast of air.

All the subjects were thoroughly informed about the study's purpose, risks, and benefits. A total of 86 patients with hypersensitive teeth were collected. The study inclusion/exclusion criteria were the following: 1) patients were considered suitable for the study if they had sensitive teeth showing abrasion, erosion or recession with the exposure of the cervical dentine; 2) teeth with subjective or objective evidence of carious lesions, pulpitis, restorations, premature contact, cracked enamel, active periapical infection, or which had received periodontal surgery or root-planning up to 6 months prior to the investigation were excluded from the study. Other exclusion criteria were professional desensitizing therapy during the previous 3 months, or use of 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). As a consequence, the total study population included in the program consisted of 46 patients, 27 females and 19 males who were randomly selected from the total population of 74 subjects who had hypersensitive teeth. A total of 116 teeth (52 incisors, 38 premolars, and 26 cuspidates) were included in the study.

Clinical Procedure

VF self adhering composite was compared to: Universal Dentin Sealant (UDS) (Ultradent Products Inc., South Jordan, UT, USA), a biocompatible, non-polymerizable, high molecular weight resin sealant in alcohol solvent, Clearfil Protect Bond (CPB), (Kuraray Noritake Dental, Osaka, Japan) a methacrilate-based resin, self-etching adhesive system, and Flor-Opal® Varnish (FOV), (Ultradent Products Inc., South Jordan, UT, USA), a fluoride-based varnish (Tab. 1).

A week before the experiment, patients received oral prophylaxis. Non-fluoride toothpaste (Biorepair, Coswell), soft toothbrush (Oral-B Sensitive Advantage, Procter & Gamble) and oral hygiene instructions were also provided in order to have standardized habits during the period of the study.

In view of the treatment with the desensitizing agents, teeth were randomly assigned in to four groups (N=29 per group) (Fig. 1). The level of sensitivity experienced by each patient was considered as independent of the position of the hypersensitive tooth in the oral cavity 11]. The pain experience was assessed using a Visual Analogue Scores (VAS) graded from 1 to 10, according to the same procedure of a previous study [20]. The pain stimulus was given by one examiner with the same equipment yielding similar air pressure each time, while the other one performed the treatments. The subject's response was considered before the application of the material (PRE-1), immediately after (POST-1), after 1 week (POST- 2), 4 weeks (POST- 3) and 12 weeks (POST-4) of 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.

Statistical Analysis

Shapiro-Wilk normality test was used to assess the normality distribution of the collected variables. Median and inter-quartile ranges were used as measures of central tendency and variability to describe quantitative variables. Statistical differences in the Visual Analogue Scale (VAS) values of VF, UDS, CPB and FOV were performed using the Kruskall-Wallis analysis at the different time-points, adjusting statistical significance for the multiple comparisons (Bonferroni correction). Statistical differences at the baseline VAS value and the other time-points were calculated performing the Mann–Whitney U test. 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

The sample size based on the initial assumptions showed a statistical power higher than 80%.

Table 2 shows the median VAS scores at the different time-points.

At baseline (VAS score), no significant statistical differences were observed (p-value >0.05) among the groups (Fig. 2). After the applications of the materials, statistical significant decrease of the VAS values was observed proceeding from Post-1 to Post-4 control.

Teeth treated with VF showed lower VAS scores at Post-1 control when compared to UDS (p-value >0.001), CPB (p-value =0.001), and FOV (p-value >0.001) (Fig. 3), while at Post-2, a significant statistical reduction of the value was demonstrated in VF in comparison to UDS (p-value =0.001) and FOV (p-value =0.001) (Fig. 4). As far as the Post-3 and Post-4 controls, no significant differences were detected in VF efficiency in respect to any other materials (Fig. 5 and 6). Also, post-treatment values showed a significant decrease in the VAS score in all of the groups in comparison to the baseline values (Tab. 3).

Discussion

VAS has been accepted as a method to evaluate pain in DH and thus, the effectiveness of desensitizing agents in pain reduction. In clinical trials, the VAS value has been assessed thought different stimuli, among which the cold stimulation, via an air dental syringe, is largely accepted [8,9,11]. Thus, in the present study, a cold stimulus was used as measure of the VAS value both to select the study population of hypersensitive teeth as well as, in the reassessment of sensitivity prior the material applications, and in the post-treatment clinical outcomes.

A 12-week evaluation was kept in consideration due to the fact that significant differences among the desensitizer effects may appear in long-term estimation of the agents [8,9,11]. Factors involved in the efficiency of the desensitizers are first of all the intrinsic material performance, strictly related to the different formulation [16] and the active ingredient of the materials [9,19]. The leach of ions by resins may affect the sealing capacity of the desensitizing agents in oral fluids [25,26]. Another factor is the stability of the tubular occlusions produced by the agents, which is related to the composition of the blocks [17] finally derived by the interaction of the material components with the oral fluids [17,27]. In view of the consideration above, the efficiency of VF, which seal was questionable after 7 days of *in vivo* evaluation [20], was compared to other resin-based materials, testing the seal within 12-week treatment controls. VF was matched to 1) UDS resin sealant as the sealing performances of resin flow composites may be comparable to those of resin-based sealants, as *in vivo* as well as *in vitro* [28-30]; 2) PB self etching adhesive system and FOV varnish to assess the VF's desensitization effect in a range of efficiency of known classes of resins just reported in DH treatment [13].

Data obtained in this study demonstrated that of the VAS value was reduced after the application of VF and the other desensitizing agents when compared to the baseline. However, different responses could be

observed in the post-treatment controls as a consequence of the material composition and interaction capacity in dentine under oral environment (Fig. 7).
Compared with the baseline, VF showed the ability to significantly reduce the sensitivity immediately after the application, however lowering its efficiency within the 12-week post-treatments, as a possible loss of the resin sealing in dentine under oral fluids exposure.
The significant decrease of the VAS in POST-1 may be attributed to the intimate particles rich layer formed by the self-adhering composite on the dentine [20]. Under SEM, VF layer covered the exposed surface of dentine leading to tubular seals and reduction of sensitivity. The particle layer might establish a high chemical and physical bonding in dentine due to the acidic monomer composition of the self-adhering composite and the present of specific ions in the mass, along with Si, Yt and F. The acidic monomer in VF might raise the concentration of Ca and P from the dentine to a point where it exceeded the product's solubility constants [31], thus allowing for the subsequent precipitation of Ca-P complexes [28] with micromechanical interactions in tubular dentine [20]. The reduction of the tubular orifices can explain the significant decrease of DH, as any substance that causes a decrease of tubular radius is able to reduce clinical symptoms of DH by reducing fluid conductance [32].
It is like, however, that the same chemical components of the composite mass might be responsible for the deterioration of the physico-mechanical properties of the resin cover within the 12-week controls. Indeed, it has been stated that the resin-based materials absorb water in an aqueous environment mainly due to a hydrolytic breakdown of the bond between the silane and filler particles, filler-matrix debonding or even hydrolytic degradation of the fillers [33]. A hydrolytic breakdown has been supposed in VF in water mostly related to the presence of leachable ions of Si, Yt, F, and Ba [21]. The high presence of Si, Yt, F, and Ba, identified in VF by the EDX [20], may have allowed the permeation of water molecules into the spaces previously occupied by these ions [33, 34]. This process may explain a possible reduction of the strength of resin–filler interface, a weakening of the mechanical properties, and the chemical bond of VF in dentine.
UDS revealed Ca, Cl, and Si as the highest ions in the resin matrix, also containing Al ion peaks [20]. Clinically, the behaviour of the resin sealant was different to that of the self-adhesive composite. In comparison to VF, UDS produced a slowly but continue decrease of the VAS showing the higher most stable desensitizing effect at the 12-week controls. Results may be related to the different composition and filler treatment in UDS in respect to VF [20], leading to a filler-polymer bond probably less attackable by water degradation under oral exposure. Moreover, the different behavior of UDS in respect to VF, may suggest that the 12-weeks of oral environment would be essential for the sealant expression.
In the case of CPB, the presence of Si, P, Al and F ions are explained in the acidic methacrylate composition of the self-etching adhesive, which is also enriched by polysiloxane-encapsulated sodium fluoride fillers as a source of fluorine ions release [35]. Clinically, CPB showed a significant decrease of the VAS in POST-1, that remained stable within the 12-week controls. The significant decrease in DH immediately after CPB application may be related to the high bonding capacity in tubular dentine. The strong adhesion in dentine may be the result of the 1) chemical bonding of the acidic functional monomer MDP contained in the CPB allowing for a ionic interaction to the calcium in dentine [36], and 2) micromechanical bonding due to the fluoro-alumino-silicate glasses in the filler capable to react with the acidic monomer following a typical glass-ionomer acid–base reaction [35]. Still, the reduction in efficiency observed within the 12-week controls may be explained in the incapacity of the resin adhesive to resist in face to the fluid exposure unless a composite cover is performed [37].
FOV, a resin varnish rich in Na and F, and Si and P traces [20], clinically demonstrated low efficiency in DH when compared to the other materials. FOV showed a higher VAS score after the 12-week control.
The initial reduction of VAS value by FOV may be explained by the presence of a cover of varnish on dentine with precipitation of crystallites of calcium fluoride or phosphate containing calcium fluoride in the opening of the tubules [7,17]. This mechanism of covering, previous observed *in vivo* [20], is able to reduce the tubular apertures in exposed dentine with a decrease of tubular fluid conductance and DH [32],

as was observed in POST-1. However, the progressive decline in effectiveness demonstrated the inability of the resin varnish to produce a firm seal in dentine [17,38] within the 12-week controls under environment.

Conclusion

As a result of this investigation, all the materials tested produced a reduction of dentine permeability. However, after 12-week controls, there was no significant statistical difference in the decrease of the VAS irrespective of the desensitizing agent employed.

Even if VF produced a significant reduction of DH in Post-1, the chemical components of the resin, mostly related to the presence of leachable species, may have interfered with the stability of the seal under oral environment exposure. A significant increase was observed in scores within the 12-week controls as a possible consequence of deterioration of the physical-mechanical properties of the resin cover in dentine. Thus, the null-hypotheses was accepted.

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Disclosure

The author reports no conflicts of interest in this work.

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Table 1. Desensitising 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	3391829	1. Thoroughly brush, rubber cup polish and air dry at maximum air pressure for 5 seconds. 2. Etch for 15 s 3. Rinse thoroughly for 15 s 4. Gently air dry for 3 s 5. Dispense with a dispensing tip 6. Brush a thin layer and beveled area with moderate pressure for 15-20 s. 7. Light-cure for 40 s* 8. Saliva contact
Universal Dentin Sealant	Ultradent Products Inc.	Resin, Ethyl alcohol	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 placer 2. With syringes connected, push varnish back and forth from syringe to syringe, 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

*[illegible]uring time suggested by the manufacturer for A3,5 VF.

Table 2. Descriptive and inferential analysis of Visual Analogue Scale (VAS) values measured in patients at baseline and post-treatment.

Material	**n**	**VAS PRE1** Median (IQR)	**VAS POST1** Median (IQR)	**VAS POST 2** Median (IQR)	**VAS POST3** Median (IQR)	**VAS POST 4** Median (IQR)
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: Inter-Quartile Range
**Kruskall-Wallis* test

Table 3. Differences of Visual Analogue Scale (VAS) between baseline and post-treatment values.

	VAS PRE1 - VAS POST1 Difference (*p-value*)	**VAS PRE1 - VAS POST2** Difference (*p-value*)	**VAS PRE1 - VAS POST3** Difference (*p-value*)	**VAS PRE1 - VAS POST 4** Difference (*p-value*)
Vertise Flow TM	3.0 (<0.001)	3.0 (<0.001)	2.5 (<0.001)	2.0 (<0.001)
Universal Dentine Sealant	3.0 (<0.001)	3.0 (<0.001)	3.0 (0.001)	3.0 (<0.001)
Clearfil Protect Bond	2.0 (<0.001)	2.0 (<0.001)	2.0 (<0.001)	2.0 (<0.001)
Flor-Opal® Varnish	2.0 (<0.001)	2.0 (<0.001)	2.0 (<0.001)	1.0 (<0.001)

Difference: Difference between median Visual Analogue Scale (VAS) values.

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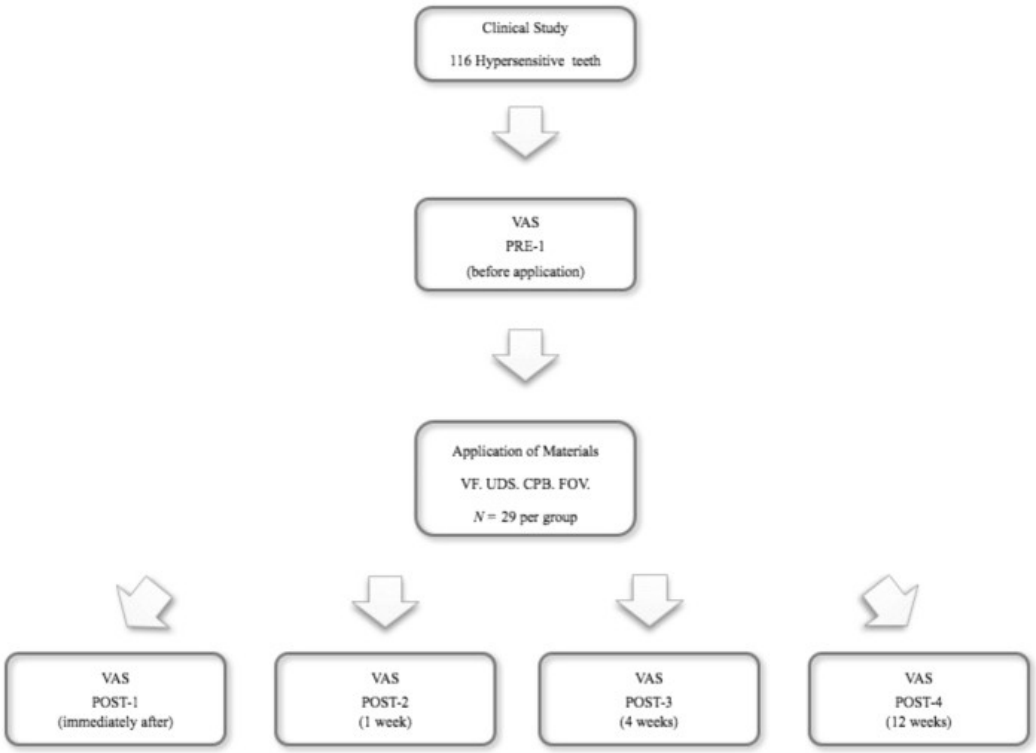

Fig. 1 - Summary of the experimental design to collect hypersensitivity teeth to test the efficiency of desensitising materials during the clinical study.

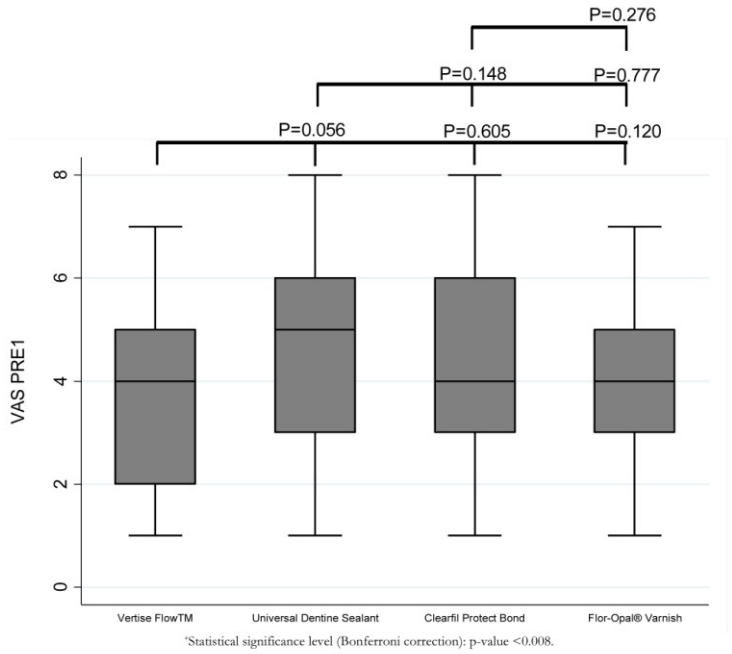

Fig. 2 - Pairwise comparisons between VAS values in Pre-1.

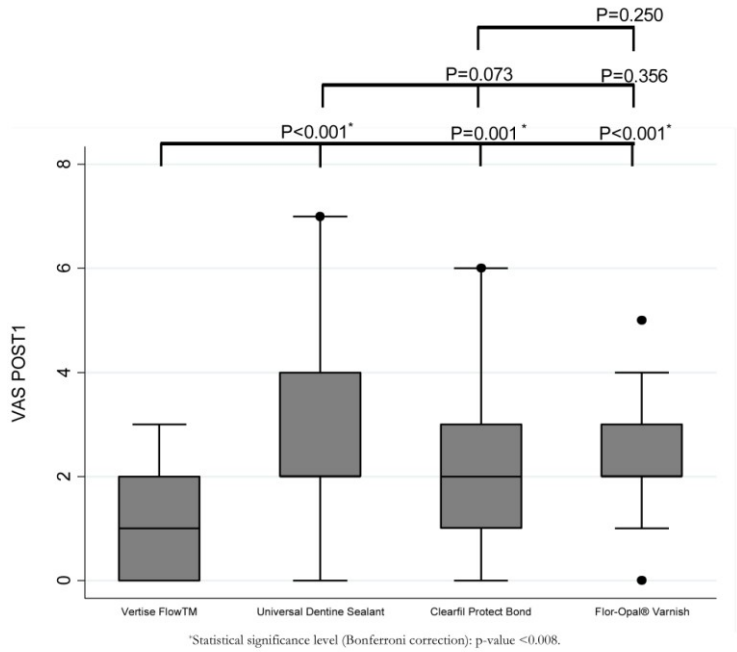

Fig. 3 - Pairwise comparisons between VAS values in Post-1.

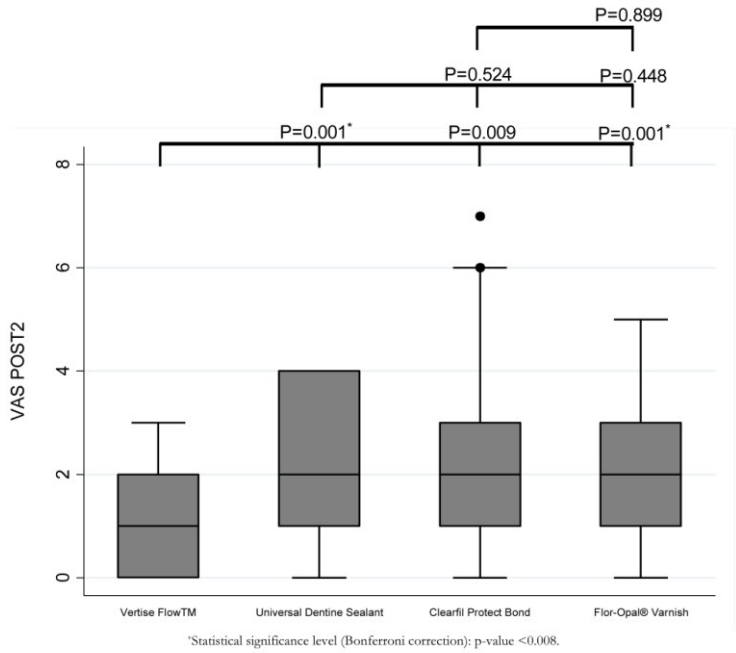

Fig. 4 - Pairwise comparisons between VAS values in Post-2.

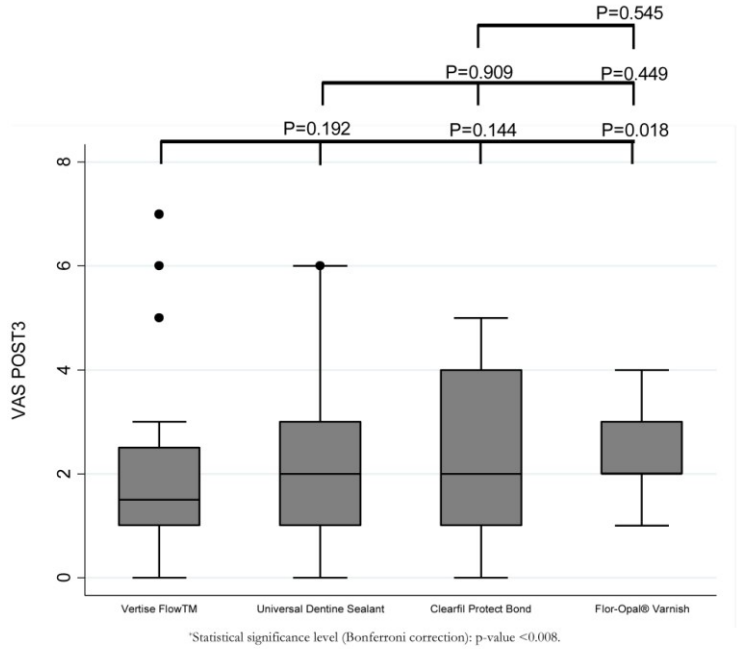

Fig. 5 - Pairwise comparisons between VAS values in Post-3.

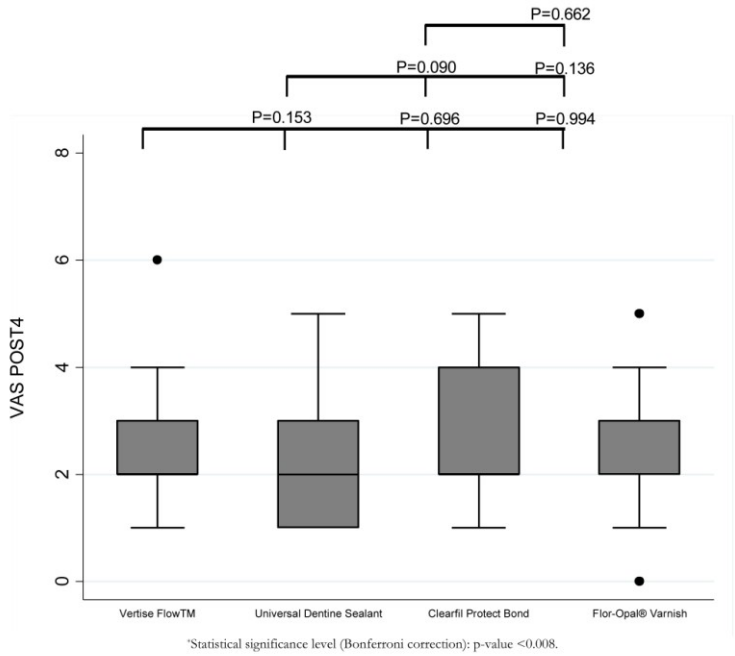

Fig. 6 - Pairwise comparisons between VAS values in Post-4.

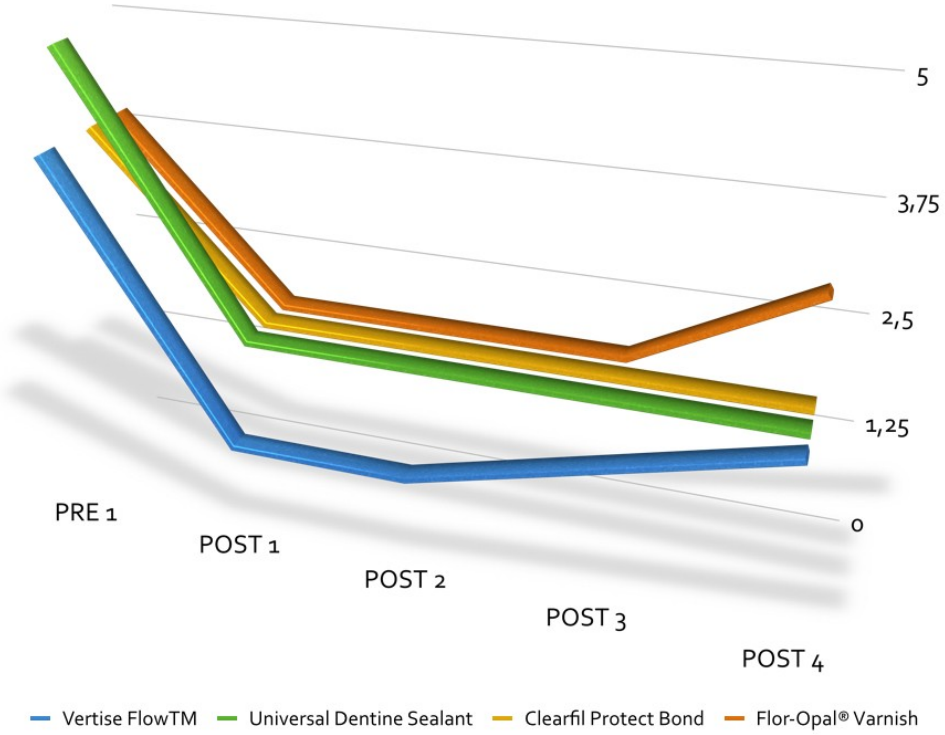

Fig. 7 – Trend of VAS Scores.

IV

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Tesi di Dottorato in Odontostomatologia preventiva,
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Clinical evaluation of a self-adhering material as desensitizing agent in xerostomic patients for head and neck cancer.

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Abstract

Aim: To evaluate the desensitizing capacity of four different materials to treat dentine hypersensitivity (DH) in xerostomic patients due to radiotherapy for head and neck cancer.
Methods: A total of 24 patients underwent to radiotherapy were selected for the study. The study was conducted as a split-mouth randomized clinical trial, comparing: 1) Vertise FlowTM (VF), 2) Universal Dentine Sealant (UDS), 3) Clearfil Protect Bond (CPB), and 4) Flor-Opal® Varnish (FOV). Basal and stimulated salivary flow was recorded for each patient according to European classification criteria (1993). The pain experience was generated by a cold stimulus directly to sensitive tooth surface and assessed using the Visual Analogue Scale (VAS). The response was recorded before the application of the materials (PRE-1), immediately after (POST-1), at 1 week (POST-2), 4 weeks (POST-3) and 12 week controls (POST-4).
Results: The number of patients meeting the inclusion criteria was eight. The mean basal salivary flow rate was 0.24 ml/min (minimum 0.06 – maximum 0.42), while the stimulated rate was 0.54 ml/min (minimum 0.29 – maximum 0.86). . At POST-4, UDS showed the best desensitizing capacity in comparison to the other materials agents, while FOV was the less effective in the reduction of VAS values.
Conclusion: As a result of this investigation, all the materials tested produced a reduction of dentine hypersensitivity. However, after 12-week controls, there was no significant difference in the decrease of the VAS irrespective of the desensitizing agent employed.

Key words: Xerostomia, head and neck cancers, radiotherapy, dentine hypersensibility, desensitising agents.

Introduction

Xerostomia is a term used to describe the subjective symptoms of "dry mouth" frequently deriving from a lack of saliva (1,2). Most patients with head and neck cancer (HNC) usually receive radiotherapy as a part of their cancer treatment. As a radiation dose to destroy malignant cells, HNC patients routinely have a total of 50-70 Gythat very often leads to the onset of salivary gland hypofunction and chronic xerostomia (3). In fact, during and following the full course of radiotherapy, xerostomia and hyposalivation rise as the most common complications and occur to some degree in up to 100% of patients, severely impairing their quality of life (QOL) (4-8).

The salivary glands are superficially located compared to most head and neck tumors, and thus, the ionizing radiation has to pass through the salivary glands to effectively treat the tumor (9).The reduced secretion rates and the alteration in the quality of saliva in irradiated patients are due to irreversible fibrosis and atrophy of the gland parenchyma (11), as well as damage to extra glandular blood vessels or nerve structures (12).

Saliva plays an essential role for the health condition of the oral cavity (11). Thanks to the properties to humidify and lubricate the soft and hard tissue, saliva plays protective effects of the tissues, among which the preventing of mechanical damage. As regard to the tooth structural integrity, the buffering effect of the saliva is very important in the control of demineralization/remineralization process (11-13). Physiologically saliva is supersaturated with respect to the tooth mineral content. Among the inorganic components, bicarbonate is related to saliva buffering capacity, while calcium, fluoride and phosphate are necessary for remineralization allowing for the maintenance of tooth mineral integrity (14).

As a consequence of a reduction in the rate of saliva flow, which is correlated to the amount of radiation given to the patients, oral complications will occur (15). An increase of dentine hypersensitivity (DH) may represent one of the most common manifestations that affects patients after radiotherapy (16-19).

DH is characterized by a short and sharp sensation of pain arising from the tubular dentine exposure as a result of enamel loss and/or gingival root surface exposure due to attrition, abrasion, erosion, abfraction or gingival recession (20). Any thermal, osmotic and mechanical stimuli induced by the application of tooth brushing, sweet and acid foods, hot or cold drinks may provoke pain referred to fluid shifts in the exposed dentinal tubules with activation of the pulp nerves, according to "Brännström's hydrodynamic theory" (2-23). Therefore, the occlusion of the tubules by different materials may reduce the fluid movement inside the dentinal tubules and the clinical symptoms of DH (24). When reducing fluid movement by fully or partially occluding open dentine tubules, hypersensitivity could be diminished (25). Consequently, most desensitizing agents have been designed to ?? cover the dentine surface with occlusion of the exposed tubules or penetration in the tubules, coating and sealing them (22,26-30).

However, the efficacy of desensitizing agents is quite variable in long term, as reported in our previous studies and other clinical outcomes conditions (26 – 31. The desensitizing capacity has been correlated to the ability of the material to resist in front of the interactions of saliva and other oral ambient interferences (31).

In light of the considerations above and of the scarcity of clinical studies on the effectiveness of desensitizing agents in xerostomic patients due to radiotherapy for HNC, the aim of the present study was to investigate clinically, the efficacy of four different kind of materials in the relief of DH.

The null hypotheses were:

- There will be no statistical differences in DH reduction among the desensitizing agents at the 12-week control,
- There will be no statistical differences in effectiveness of desensitizing agents among xerostomic patients and patients with normal salivary flow.

Materials and Methods

Partecipants

The study was designed as a split-mouth randomized clinical trial. The protocol and informed consent forms were approved by the ethics committee at the University of Sassari (n° 1000/CE). Radio-therapeutic patients who had hypersensitive teeth were selected from an on-going program of evaluating desensitizing agents at the Dental Clinic of the University of Sassari, Italy.

During 2013, a total of 48 patients were visited at the Department of Radiology. 24 patients, which needed radiotherapy for HNC were collected. These groups of patients were subjected to a dental check-up with eventual teeth treatments, during and after the radiotherapy. Few months later the end of the radio-exposition, 8 patients began to complain HD.

To participate in the study all the subjects were thoroughly informed about the study's purpose, risks, and benefits.

The study inclusion criteria were the following:

- A relative good general health status;
- A clinical reduction of salivary flow;
- Two or three teeth that were hypersensitive to the stimulation with a blast of air.

In addition, patients were considered suitable for the study if they had sensitive teeth showing abrasion, erosion or recession with the exposure of the cervical dentine.

The study exclusion criteria were:

- teeth with subjective or objective evidence of carious lesions, pulpitis, restorations, premature contact, cracked enamel, active periapical infection;
- received periodontal surgery or root-planning up to 6 months prior to the investigation;
- professional desensitizing therapy during the previous 3 months
- use of 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).

Clinical Procedure

Saliva collection

All salivary assessments were performed in the absence of acute sialadenitis. The flow rate was determined in every person according to the method described by Sreebny (32). Saliva was collected in a standardised manner. Patients were instructed not to eat, drink, or smoke for 90 minutes before the sialometric assessment. All assessments were performed at a fixed time of the day, between 10 am and 1 pm, in order to minimise fluctuations related to a circadian rhythm of salivary secretion and composition. All assessments were performed by the same observer. Whole saliva was collected in pre-weighed plastic tubes using an electronic scale.

Unstimulated salivary secretions were collected for 5 min with the patient seated in an upright position and with the tilted head. When possible the tongue, cheeks and lips movements were limited during the procedure. At the end of the collection period, the patient had to expectorate saliva into the test-tube.Stimulated whole saliva was collected asking to patients to chew a small block of paraffin wax or chewing gum. All the saliva secreted for 5 min was then collected in the test-tube.Measuring vessels were weighed after each collection using an electronic scale, and salivary flow rate was expressed in ml/min, which is nearly equivalent to g/min (33). A secretion rate < 0.1-0.2 ml/min for unstimulated flow and < 0.5-0.7 ml/min for stimulated flow was considered as an objective sign of hyposalivation.

Assessment of hypersensitivity and desensitizing agents application.

A week before the experiment, patients received oral prophylaxis. Non-fluoride toothpaste (Biorepair, Coswell), soft toothbrush (Oral-B Sensitive Advantage, Procter & Gamble) and oral hygiene instructions were also provided in order to have standardized habits during the period of the study. The level of sensitivity experienced by each patient was considered as independent of the position of the hypersensitive tooth in the oral cavity (30). The pain experience was assessed using a Visual Analogue Scores (VAS) according the methodology described in the previous studies (34)

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

All 8 patients were considered eligible and agreed to take part in the study. In view of the treatment with the desensitizing agents, teeth were randomly assigned into four groups (N= per group) (Fig. 1). None of the participants failed to complete the study neither reported any adverse reactions.

Statistical Analysis

Shapiro-Wilk normality test was used to assess the normality distribution of the collected variables. Median and inter-quartile range were used as measures of central tendency and variability to describe quantitative variables. Statistical differences between Visual Analogue Scale (VAS) values of Vertise FlowTM, Universal Dentine Sealant, Clearfil Protect Bond and Flor-Opal® Varnish were evaluated performing Kruskall-Wallis analysis at different time points, adjusting statistical significance for the multiple comparisons (Bonferroni correction). Statistical differences between baseline VAS values and those obtained at other time-points were calculated performing the Mann–Whitney U test. 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).

Statistical differences between VAS values of xerostomic group and normo-salivation group were calculated performing the Mann–Whitney U test. Statistical analysis was carried out using STATA®13 (StataCorp, College Station, TX, USA).

Results

The mean basal salivary flow rate was 0.24 ml/min (minimum 0.06 – maximum 0.42) while the stimulated rate was of 0.54 ml/min (minimum 0.29 – maximum 0.86).

The median VAS scores at different time-points is shown in Table 1. No statistically significant differences between the baseline VAS scores were observed (p-value >0.05) (Fig. 2). Following the exposure to the materials, a statistically significant VAS decreases was observed from Post-1 to Post-3; no statistical differences were detected in the final point. Teeth treated with Vertise FlowTM and Universal Dentine Sealant showed lower VAS scores at Post-1 in in comparison to those treated with Clearfil Protect Bond (p-value <0.0001), and Flor-Opal® Varnish (p-value <0.0001) (Fig. 3). On the other hand, statistically significant lower VAS values were showed for Vertise FlowTM and Universal Dentine Sealant in Post-2 when compared to Flor-Opal® Varnish (p-value =0.0002 and p-value<0.0001, respectively) (Fig. 4). Significantly higher VAS values were reported in regard to Flor-Opal® Varnish, Universal Dentine Sealant (p-value =0.0003) and Clearfil Protect Bond (p-value =0.0002) (Figure 5). Conversely, no significant differences were detected at Post-4 (Fig. 6). In the case of Universal Dentine Sealant and Clearfil Protect Bond, the baseline, Pre-1, and the post-treatment values Post-4 showed

significant VAS score decreases, This wasn't in the case of Vertise FlowTM and Flor-Opal® Varnish (Tab. 2).
Moreover, no statistically significant differences (p-value >0.05) were detected at the baseline VAS when the xerostomic group was compared to the healthy (Tab. 3). Statistically lower VAS values were showed in the normo-salivation group treated with Vertise FlowTM , Clearfil Protect Bond and Flor-Opal® Varnish at Post-4 (p-value <0.05) (Tab. 4).

Discussion

DH arises from the tubular dentine exposure and represent a common, painful and subjective symptom that is difficult to quantify (35-37). Nevertheless, the VAS scale is an accepted method of pain measurement (38). Sealing the dentine tubules by the use of adhesive materials and varnishes has been considered the primary choice in DH treatment, according to *Hydrodynamic Theory* (39-44).
Adhesive materials which contain acidic monomers as part of their chemicall formula, might raise the concentration of Ca and P from the dentine to a point where it exceeded the product's solubility constants (45). In this way, precipitation of Ca-P complexes will be allowed at the dentine surface (46) with consequent micromechanical interactions in tubules (47). The reduction of tubular orifices can explain the significant decrease of DH, as any substance that causes a decrease of tubular *radius* is able to reduce clinical symptoms of DH by reducing fluid conductance (47).
The therapeutic mechanism of varnish in DH is caused by the reaction of NaF or Oxalates at the surface of dentine (?) that results in the precipitations of insoluble calcium crystallites at the opening of the tubules (26,42-44,48-50). This mechanism, observed both in vitro (51, 52) and in vivo (34), is able to reduce the tubular apertures in exposed dentine with a decrease of tubular fluid conductance and DH (47).
However, the efficacy of different desensitizers is still a concern. This is because significant differences among the materials could appear in long-term estimation of the agents (30,57,58), Conversely, most of the clinical data were reported at short-term evaluation (53-56) and yielded poor results (53-56).
Consequently, it is no gold standard for the treatment of DH available today (59). Factors involved in the efficiency of the desensitizers are particularly related to the intrinsic material performance, strictly connected to the own formulation of the agent (60), as well as the active ingredient of the material (28,61). Moreover, in this view the stability of tubular occlusions must be considered, , which has been related to the composition of the blocks [48] finally derived by the interaction of the material components within the oral environment (28,62).
Due to the lack of information about DH in radiotherapeutic xerostomia, this study was undertaken to investigate the effectiveness of four different desensitizing agents with the purpose to identify the material of choice . Also, the response of the hyposalivary group was compared to a group of normosalivary patients in order to understand differences between the two groups. All the eight patients (101 teeth) completed the 12-week evaluation study. Data obtained in demonstrated that of the VAS value was significantly reduced after the application of all the materials (Tab 1). This is really evident for VF and CPB, both showing an overall specular behaviour (Fig. 7). It could be speculated that the reduced presence of saliva, as found among the patients, was a determinant factor in this result. In fact, one of the major factor in the reduction of the adhesive bond in dentine is the hydrolysis of the adhesive material within water exposure (63). In an oral environment with low saliva volume these materials could be able to increase their performance.At the same time, it could be speculated that the clinical condition of xerostomia, may lower the bonding in time.. The occlusal stress, thermal stress and chemical attack by acid and enzymes may affect the adhesive sealing, compromising the integrity of the adhesive restoration (63). Consequently, comparing the data with those obtained in our previous evaluation (31), both the materials may have behaved overall in a less stable manner (Fig. 7). However, after 12-week controls, both VF and CPB showed a dramatically decrease of performance with reduction of the VAS scores in a similar manner to those observed at PRE-1 (Fig. 7).

As reported in the previous study (31) (Fig. 7), UDS produced a slow but continue decrease of the VAS scores (Fig. 7). The results may be related to the proper composition of UDS and the presence of fillers in the resin mass of [34]. Unlike it was previously reported, at 12-week controls UDS VAS decreases showing similar values to those noted at PRE-1, similarly to VF and CPB (Fig. 7).
As regard to FOV, it demonstrated the lower efficiency in DH when compared to the other materials (Fig. 7). As previous observed in vivo [34], the reduction of VAS scores in FOV is due to precipitation of crystallites of calcium fluoride or phosphate containing calcium fluoride in the opening of the tubules. In this study, FOV showed the higher VAS scores after the 12-week control. It could be speculated that the reduction of saliva might have affected the performance of the varnish as in the case of UDS and FOV.
In light of these data, the first null hypothesis has been accepted: after 12-week controls there is no statistically significant difference among all desensitizers (Tab 1). Conversely, the second null hypothesis was rejected except in the case of UDS, which didn't show an evident statistically significant difference (Tab 4).

Conclusions

As a result of this investigation, in xerostomic patients all materials tested produced a significant reduction in the dentine sensibility when compared to the baseline. All agents were effective immediately after the application, whereas a significant increase of DH was observed within the 12-week controls as a possible consequence of deterioration of the physical-mechanical properties of the materials. The lack of information about the DH treatment in radiotherapeutic xerostomic patients ensure that further studies should be carried out. Anyway, within the limits of this study, it is not possible to indicate a material as a gold standard of care, as there are no significant differences in efficacy among the desensitizing agents in the 4-weeks control .

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Table 1. Descriptive and inferential analysis of Visual Analogue Scale (VAS) values measured in patients at baseline and post-treatment.
IQR: Inter-Quartile Range

	n	VAS PRE1 Median (IQR)	VAS POST1 Median (IQR)	VAS POST 2 Median (IQR)	VAS POST3 Median (IQR)	VAS POST 4 Median (IQR)
Vertise Flow™	29	4 (3-6)	0 (0-0)	0 (0-1)	2 (2-3)	3 (3-5)
Universal Dentine Sealant	21	4 (3-5)	2 (0-2)	1 (0-2)	1 (1-2)	3 (2-3)
Clearfil Protect Bond	27	4 (3-6)	0 (0-0)	0 (0-1)	2 (1-2)	3 (2-5)
Flor-Opal® Varnish	24	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*

**Kruskall-Wallis* test

Table 2. Differences ofVisual Analogue Scale (VAS) between baseline and post-treatment values.

	VAS PRE1 - VAS POST1 Difference (*p-value*)	VAS PRE1 - VAS POST2 Difference (*p-value*)	VAS PRE1 - VAS POST3 Difference (*p-value*)	VAS PRE1 - VAS POST4 Difference (*p-value*)
Vertise FlowTM	4(<0.001)	4 (<0.001)	2 (0.003)	1 (0.251)
Universal Dentine Sealant	2 (<0.001)	3 (<0.001)	3 (0.001)	1 (0.008)
Clearfil Protect Bond	4 (<0.001)	4 (<0.001)	2 (<0.001)	1 (0.018)
Flor-Opal® Varnish	2 (<0.001)	2.5 (<0.001)	1 (0.030)	0 (0.193)

Difference: Difference between median Visual Analogue Scale (VAS) values.

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Table 3. Comparison ofVisual Analogue Scale (VAS) between groups at baseline.

	Normo-salivation group		Xerostomic group		
	n	VAS PRE1 Median (IQR)	n	VAS PRE1 Median (IQR)	p-value
Vertise Flow™	28	4 (2-5)	29	4 (3-6)	0.329
Universal Dentine Sealant	27	5 (3-6)	21	4 (3-5)	0.167
Clearfil Protect Bond	30	4 (3-6)	27	4 (3-6)	0.961
Flor-Opal® Varnish	31	4 (3-5)	24	4 (3-6)	0.530

Table 4. Comparison ofVisual Analogue Scale (VAS) between groups at the end of treatment.

	Normo-salivation group		Xerostomic group		
	n	VAS POST 4 Median (IQR)	n	VAS POST 4 Median (IQR)	p-value
Vertise Flow™	28	2 (2-3)	29	3 (3-5)	0.003
Universal Dentine Sealant	27	2 (1-3)	21	3 (2-3)	0.059
Clearfil Protect Bond	30	2 (2-4)	27	3 (2-5)	0.012
Flor-Opal® Varnish	31	3 (2-3)	24	4 (2-5)	0.003

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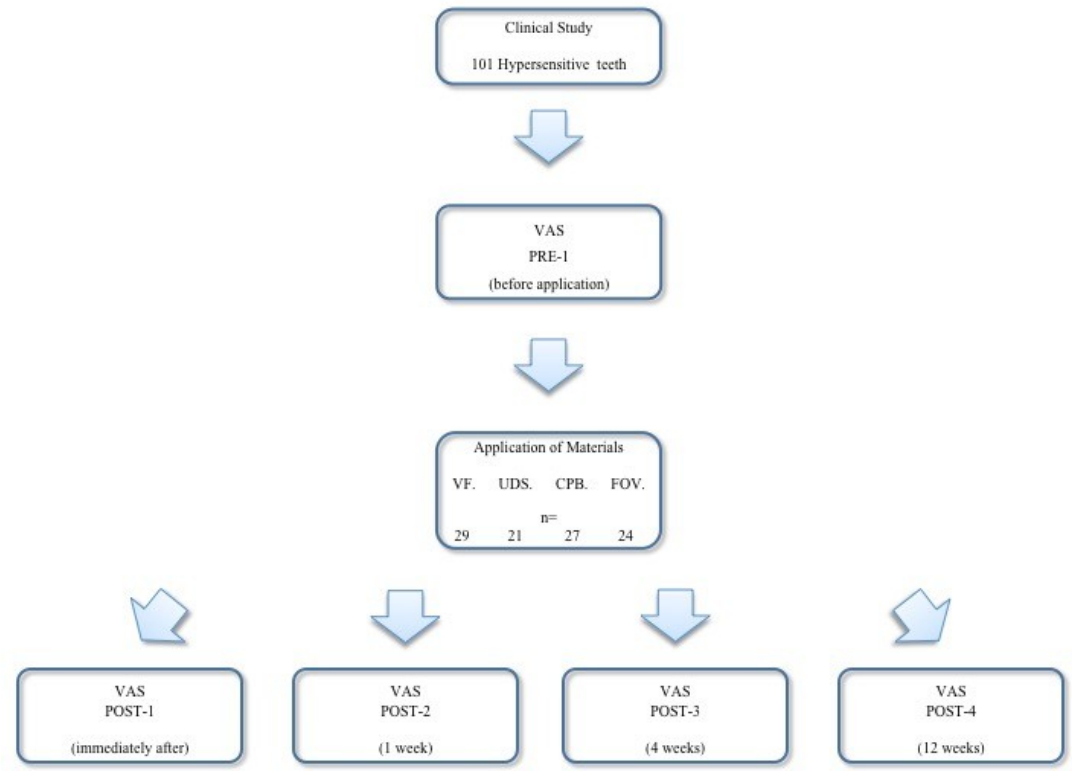
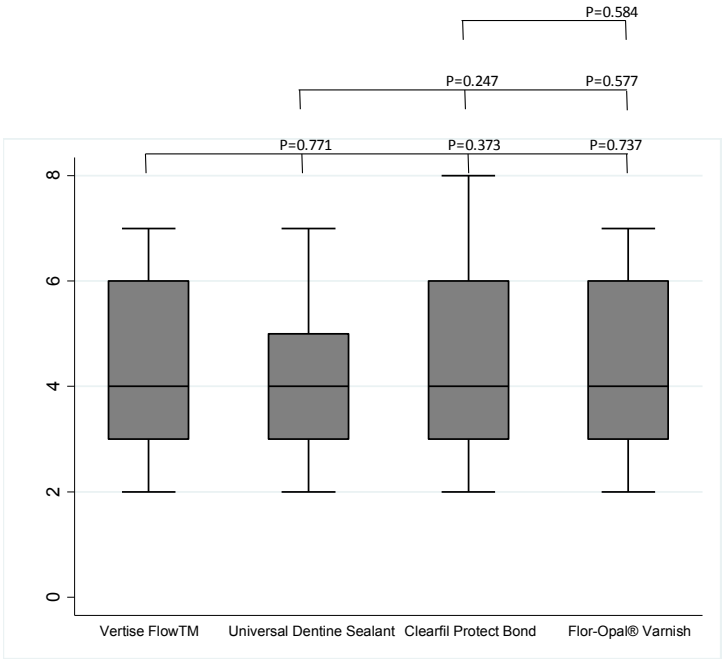
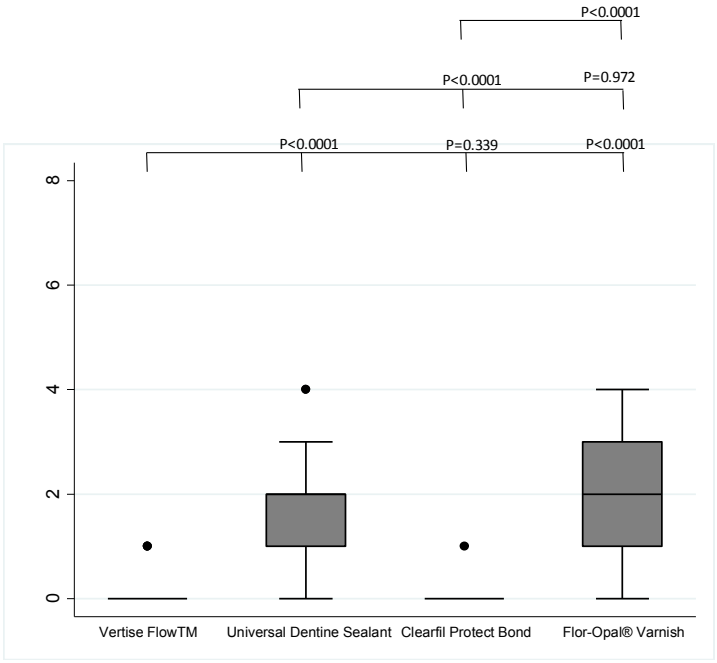


Fig. 1. Summary of the experimental design to collect hypersensitivity teeth to test the efficiency of desensitising materials during the clinical study.



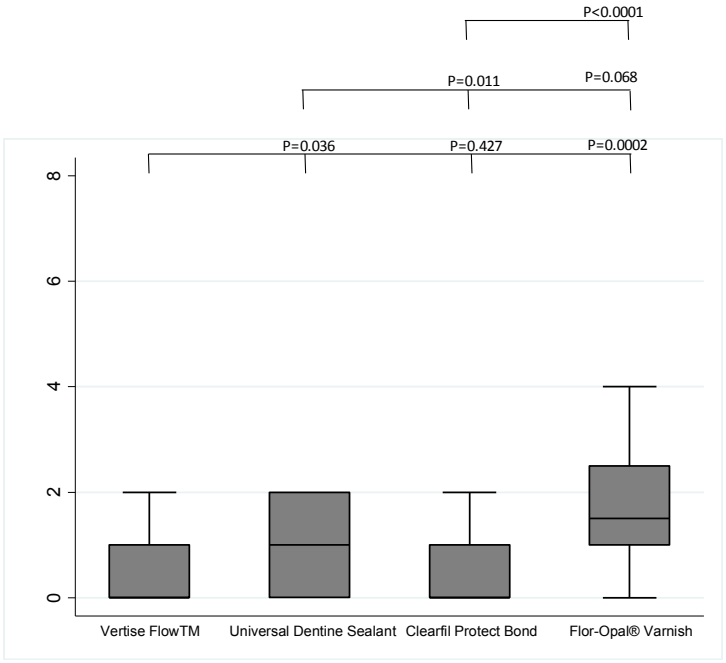
*Statistical significance level (Bonferroni correction): p-value <0.008.

Fig. 2. Pairwise comparisons between VAS values in Pre-1.



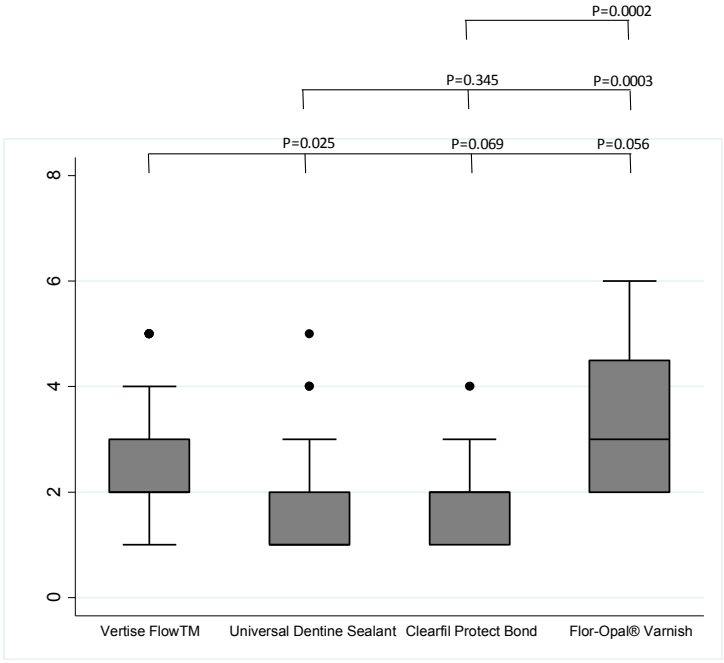
*Statistical significance level (Bonferroni correction): p-value <0.008.

Fig. 3. Pairwise comparisons between VAS values in Post-1.



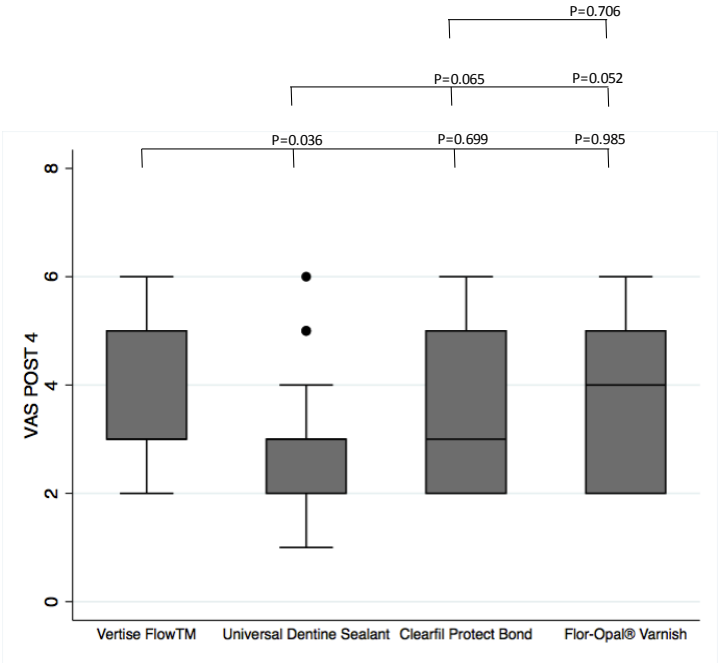
*Statistical significance level (Bonferroni correction): p-value <0.008.

Fig. 4. Pairwise comparisons between VAS values in Post-2.



*Statistical significance level (Bonferroni correction): p-value <0.008.

Fig. 5. Pairwise comparisons between VAS values in Post-3.



*Statistical significance level (Bonferroni correction): p-value <0.008.

Fig. 6. Pairwise comparisons between VAS values in Post-4.

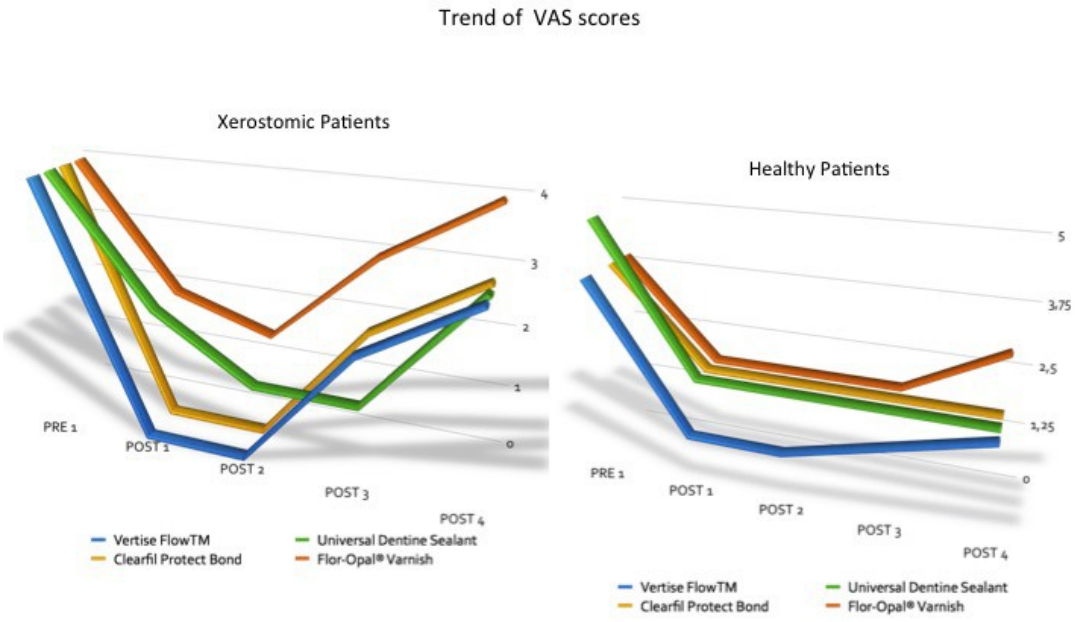


Fig. 7. Trend of VAS Scores.

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