# Efficacy of conventional fluoridated toothpastes containing arginine and high-fluoride toothpastes on the control of root caries in patients undergone radiotherapy of head-and-neck: a randomized controlled trial

**Marilia Velo**
Universidade de Sao Paulo Faculdade de Odontologia de Bauru
**Marina Giacominni**
Universidade de Sao Paulo Faculdade de Odontologia de Bauru
**Leticia Brianezzi**
Universidade de Sao Paulo Faculdade de Odontologia de Bauru
**Rafael Gonçalves**
Universidade de Sao Paulo Faculdade de Odontologia de Bauru
**Giovanna Zabeu**
Universidade de Sao Paulo Faculdade de Odontologia de Bauru
**Paulo Santos**
Universidade de Sao Paulo Faculdade de Odontologia de Bauru
**Sergio Ishikiriama**
Universidade de Sao Paulo Faculdade de Odontologia de Bauru
**Heitor Honório**
Universidade de Sao Paulo Faculdade de Odontologia de Bauru
**Linda Wang** ( wang.linda@usp.br )
Universidade de Sao Paulo Faculdade de Odontologia de Bauru

**Research Article**

**Keywords:** Arginine, High-fluoride toothpaste, Radiotherapy of head-and-neck, Root caries.

**Posted Date:** May 3rd, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-360231/v1

## Abstract

This parallel, triple-blind RCT evaluated the restorative performance of a resin-modified glass-ionomer-cement (RMGIC) in irradiated patients and the prevention of root caries lesions adjacent to restoration, comparing the effect of conventional (control) concentration, high-fluoride (F) containing fTCP and arginine-based toothpastes. A total of 63 lesions was screened and 60 were included into randomized distribution into three groups (N-participants in baseline/n- root caries lesions): G1 = 1,450 ppm F (N = 10/n = 17); G2 = 5,000 ppm F + fTCP (N = 7/n = 18) and G3 = 1,450 ppm F + arginine + CaCO3 (N = 6/n = 25). Based on eligibility criteria, all patients were mandatory enrolled after completed 3-month of radiotherapy of head-and-neck. Two calibrated operators performed the restorative procedures (RMGIC - Vitremer) and two calibrated examiners (Kappa = 0.94) evaluated the restorations based on modified USPHS criteria at baseline, 1, 3 and 6-month follow-up. Data was collected and statistically assessed with Kruskal-Wallis test ($p < 0.05$). There were no statistically significance differences among the performance of the restoration among the three groups regarding the criteria retention, marginal adaptation, marginal staining, post-operative sensitivity, adjacent caries, color alteration, anatomic form and surface texture ($p > 0.05$). Even with oral complications caused by radiation-therapy, if the restorations are properly performed and patients are under professional supervision, high-F presented similar efficacy of arginine and conventional-containing toothpastes to prevent secondary caries. *Clinical relevance*: This clinical trial brings new evidences about the regular use of high-F, arginine-based and conventional-F containing toothpastes in irradiated patients under supervision of a multidisciplinary team and the encouragement of self-cooperation.


## Introduction

While the decline in the prevalence and incidence of coronal dental caries has been observed worldwide in children and adults, an increase in the prevalence of root caries, especially in patients such as the elderly population and patients undergone radiotherapy of head-and-neck has been notable [1]. As life expectancy is increasing, older adults often retain a higher number of teeth in their oral cavity, which increases the risk of caries development and progression on their exposed root surfaces in the case of the presence of etiological factors [2]. In addition, though not at all subsites, head-and-neck cancer becomes more frequent with increasing age [2], although the incidence of oral cancer disease in people under the age of 45 appears to be increasing [3] and, these patients are also often submitted to radiation treatment.

Despite radiotherapy plays a vital role in curative and palliative cancer therapy [4], its adverse effects in the oral cavity are of clinical concern as usually complex oral complications are inevitable, including mucositis, hyposalivation, osteoradionecrosis, dentition breakdown, and radiation-related caries [5, 6]. Radiation-related caries lesions develop mainly in the cervical area, which include root caries as a notable clinical complication in these patients. As human dentin is highly soluble because of its less mineral and higher carbonate and magnesium content [7], dentin root caries rapidly progresses and the risk of radiation-related caries development with its sudden onset is a lifelong threat [8]. As consequence, it can develop as early as three-month post-radiotherapy resulting in a devastation of a healthy dentition within one year of treatment [9, 10].

The prevalence of dental caries has previously been estimated at 24% for cancer patients treated with radiotherapy and the etiology of this increased risk is multifactorial [2, 11]. Beside the factors that control the risk of dental caries development such as the presence of a cariogenic biofilm, fermentable carbohydrate intake and low fluoride exposure [12], radiotherapy-induced salivary gland acinar degeneration and interstitial fibrosis, which means that these patients present chronic hyposalivation and are at high-risk for radiation-related caries development and progression [2,]. Alterations in dental tissues and modification in the composition or structural pattern of root dentin may also be important contributing factors for radiation-related caries development [7, 13]. All these complications affect their feeding process, especially due to the sensitivity, difficult to mastication and dental cleaning [6]. Therefore, efforts should be focused from prevention to manage patients with severe caries, which can be accomplished by preventive and therapeutic strategies or reconstruction of caries lesion in these patients to reestablish their quality-of-life.

Resin-modified glass ionomer cements (RMGIC) are a great choice for restoration of root caries lesions [14]. However, restorative management of radiation-caries can be challenging, as the changes presented by radiation affect the bonding of adhesive materials [15]. Owing to the bonding capacity to both enamel and dentin substrates and ability to release fluoride (F), RMGIC is expected to be more resistant to avoid caries lesions adjacent to restorations. This restorative material is considered the gold standard material, but based on the current best of knowledge, the involvement of the patients and their self-cooperation is of great relevance to the successful approach overtime, since the effect of F-released can be replaced by F delivered from other sources, such as toothpastes [16, 17]. The mechanism of action of F toothpastes combines a mechanical disruption of tooth biofilm and F delivery, interfering with the demineralization and remineralization episodes, but this effect is influenced by F concentration [18].

Some *in situ* and *in vivo* evidences demonstrated the benefit of high-F containing toothpastes (5,000 ppm F) to prevent initial caries development and to repair root caries lesions when compared with the use of conventional-F toothpastes [19–21]. When high-F concentration toothpaste is applied, beside its mechanism of action, F also develop a calcium (Ca)-fluoride reservoir ($CaF_2$-like particles) and provides a physical barrier on the substrate, inducing remineralization by maintaining high concentrations of F in the oral environment [22]. The common protocol used to reduce post radiation-related caries is the daily topical application of 1% neutral sodium F gel (5,000 ppm F) with custom-made F carriers [23]. However, compliance of patients is frequently poor because of the inconvenient method of application and many patients with head-and-neck cancer may be debilitated to use both conventional toothpaste and topical gel application [24]. Whereas toothbrushing with fluoridated toothpastes is the most cost-

effective tool to prevent dental caries [25], in patients undergoing radiotherapy of head-and-neck, the daily use of high-F toothpaste could be a great choice to prevent new caries development around restorations with RMGIC.

Furthermore, attempts to improve remineralization efficacy from toothpastes include the calcium phosphate-based delivery systems such as functionalized tri-calcium phosphate (fTCP), calcium phosphate nanocomplexes (CPP-ACP) or insoluble Ca compound associated with arginine. Some *in vitro* studies demonstrated that toothpastes containing fTCP prevented Ca from prematurely interacting with ionic F, enhancing their effect [26, 27]. However, even available as a commercial product, the remineralization efficacy regarding fTCP products are limited to *in vitro* researches and focused on enamel substrate [28]. A previous *in situ* design showed that toothpaste containing fTCP presented similar effect to prevent early root caries lesions, although it could be interesting to repair active dentin caries lesions and should be evaluated in patients at high-risk of caries [19].

The toothpaste containing an insoluble Ca compound, 1.5% arginine and conventional-F concentration was also introduced to prevent caries development at an earlier stage targeting the residual biofilm through arginine metabolism [29]. The association with Ca ions provided by $CaCO_3$ compound inhibits mineral loss during low-pH periods and repair it when pH returns to neutral condition. An *in vivo* study demonstrated that patients who used arginine-based toothpaste had significantly higher plaque pH values before and after the sucrose challenge [30]. Other investigations have shown positive benefits by using arginine-based pastes to manage root caries when compared to conventional ones [31], which boost for new evidences of this technology in post-radiation caries in patients undergone radiotherapy of head-and-neck.

Thus, the purpose of this clinical trial was to test the effectiveness of high-F toothpaste (5000 ppm F) and arginine-based toothpaste on root caries lesions around RMGIC evaluating the performance of the restorations.

# Methods

### Trial design

This single-center, interventional, parallel, triple-blind 6-month randomized controlled clinical trial was conducted in the Clinical Research Center of the Bauru School of Dentistry, University of São Paulo, Brazil (44944915.4.0000.5417). The study was approved by Human Ethics in Clinical Research Committees of the Bauru School of Dentistry and registered at the Registro Brasileiro de Ensaios Clínicos – REBEC website under the registration number U1111-1171-2738. This randomized controlled trial is reported in accordance with the CONSORT (Consolidated Statement Of Reporting Trials) statement [32] (Fig. 1). A consent form was shown for the participants that explained the nature of the study and only after they assigned it the study has initiated.

### Study population and sampling procedure

Based on eligibility criteria, all patients were enrolled after at least 3-month completed the radiotherapy. Adult patients diagnosed with untreated root caries were selected to be included in the trial. The sample size was determined considering the 80% of power, 25% of drop out and significance level and statistical power were adopted at 5%. The main response variables were related to the caries adjacent to the restoration and marginal leakage, considering the difference of 1 level of USPHS system recording. The randomly allocated sequence was implemented using Microsoft Excel for Mac 2011, Version 14.3.5 (Microsoft, Chicago, IL, USA) based on simple randomization strategy.

To compensate for the expected number of drop-outs over 6-month the Intention-to-Treat (ITT) analysis was performed to include every patient in the primary analysis within the respective treatment group they have been assigned to at randomization. The experimental unit was the restored tooth.

At baseline, participants were from 18 to 80 years old. The eligibility criteria for the recruitment are listed in Table 1. Before inclusion and exclusion criteria evaluation, all patients were clinical analyzed by a multidisciplinary team, including nutritionist, speech therapist and dentist. Patients presenting post-radiation root caries were recruited and the included subjects received instructions on oral health, particularly regarding oral hygiene and sugar consumption. Their oral cavity was evaluated and if they presented active coronal decay or other disease, they were treated accordingly.

Table 1
Inclusion and exclusion criteria for the recruitment of subjects

| *Inclusion criteria* |
|---|
| Age group minimum of 18 years |
| Must have at least one root caries lesion with pulp vitality |
| Teeth included must be not be compromised or crowned |
| Patients who have their teeth treated before radiotherapy sections |
| Exclusion criteria |
| Patients undergoing radiation therapy |
| Patients ongoing fixed orthodontic appliance therapy, with acute periodontitis, severe bruxism and other parafunctional habits |
| Patients with serious systemic complications |
| Pregnancy, lactating or hypersensitive to the trial test products or ingredients |
| Undergone high-F therapy 3-month prior to this trial |
| Local or systemic antibiotic therapy 3-month prior to this trial or within the 6-month of the trial |

**Interventions**

The selected patients were allocated to one of three groups using a sequence of codes randomly generated by the blind-study administrator in an Excel program. The control group participants (Group 1) were administered with conventional-F toothpaste: G1 = 1,450 ppm F (Colgate Total 12®; Colgate-Palmolive Company, São Paulo, SP, Brazil). The tested groups (Groups 2 and 3) used toothpastes containing: G2 = 5,000 ppm F + fTCP (Clinpro® 5000; 3M, Sumaré, SP, Brazil) and G3 = 1,450 ppm F + arginine + $CaCO_3$ (Neutraçucar®, Colgate-Palmolive Company, São Paulo, SP, Brazil).

The compositions of toothpastes and all material used in this study are better described in Table 2. To blind the volunteers and examiners, the toothpastes were packed in blank tubes and labeled with colors to identify them only for the study administrator. All patients received separate packets containing two tubes of toothpastes and a standard soft bristled adult toothbrush (CS 5460B, Curaprox). Participants were instructed to brush at least twice daily with their assigned toothpaste. Two tubes of toothpastes, and a new toothbrush were supplied to each patient after 45 days, but additional tubes of toothpaste were available upon their request.

Table 2
Composition and classification of all materials used in this study.

| MATERIAL | COMPOSITION | MANUFACTURER | CLASSIFICATION |
|---|---|---|---|
| Vitremer® | Primer: polyalkenoic acid, methacrylate groups, water, HEMA, camphorquinone. Powder: fluoraluminium silicate crystals, potassium persulfate, ascorbic acid, pigments. Liquid: polyalkenoic acid, methacrylate groups, water, HEMA, camphorquinone | 3M ESPE, St Paul, MN, USA | Resin-modified glass ionomer cement |
| Colgate Total 12® | 1,450 ppm F (sodium fluoride-NaF) | Colgate-Palmolive®, São Paulo, SP, Brazil | Dentifrice 1,450 ppm F (conventional concentration) |
| Clinpro 5000® | 1.1% sodium fluoride, water, sorbitol, hydrated silica, glycerin, polyethylene-polypropylene glycol, flavor, polyethylene glycol, sodium lauryl sulfate, titanium dioxide, carboxymethyl cellulose, sodium saccharin and tri-calcium phosphate | 3M ESPE, St Paul, MN, USA | High-fluoride tootpaste (5,000 ppm F) plus functionalized tri-calcium phosphate (fTCP) |
| Neutraçucar® | 1,450 ppm F (Sodium Monofluorphosphate - MFP), calcium carbonate, sodium lauryl sulfate, sodium saccharin, tetrasodium pyrophosphate, sodium silicate, polyethylene glycol, sorbitol, carboxymethyl cellulose, methylparaben, propylparaben, aromatic composition and water | Colgate-Palmolive®, São Paulo, SP, Brazil | Dentifrice (conventional F concentration) plus 1.5% arginine plus CaCO3 |

**Restorative procedure**

One or more active root caries lesion for each subject was selected for inclusion in the study and restorations were performed by two calibrated dentist operators (MMACV and RSG).

All selected patients received a prophylaxis with pumice stone and distilled water, applied with a Robinson brush prior to the intervention. Firstly, carious tissue was carefully removed using spherical bur nos. 1, 2, and 3 (KG Sorensen, Cotia, SP, Brazil) at low speed and hand excavators removing all demineralized dentin on lateral walls. Cavity preparation was limited to carious tissue removed, based on the selective carious dentin removal. Manual instruments (gingival margin cutters) were used for finishing the cervical and extern margins. All surfaces were cleaned, and the cavities restored using a RMGIC (Table 2) based on the manufacturer's instructions. Calcium hydroxide (Dycal, Dentsply Caulk, Germany) was inserted when deep cavities were presented. The exposed dentin surface was kept visibly moist for the primer application (30s of application followed by 15s of soft air jet), and then it was photo-activated for 30s. (1: 1 ratio), The restorative material (1:1 ration) was positioned over lesions using an applied syringe (Centrix) and photo-activated by 40 s. A layer of the Finishing Gloss component was applied to the restored surface, preventing the occurrence of synergy and imbibition. Possible excesses of restorative material were removed with a scalpel blade and after 7 days, finishing and polishing were performed in the restorations. Then, participants received their packets with respective toothpastes to beginning the study.

**Clinical examination methods**

The restorations were examined at baseline, 1, 3 and 6 months by two calibrated examiners (LW and SKY, Kappa = 0.94). Mouth mirrors, wooden spatulas, and the CPI (Community Periodontal Index) probe were the dental instruments used. The clinical assessment has begun with an examination of the soft and hard tissues of the mouth and then, the modified USPHS criteria was used for restorations evaluation (Table 3). All restorations were scored as follows: alpha as the ideal clinical situation; Bravo was clinically acceptable (satisfactory success); Charlie represented clinically unacceptable situations where the restoration had to be replaced or lost retention (unsatisfactory fail) (Table 3).

Table 3
Modified USPHS criteria

| Criterion | Code | Description |
|---|---|---|
| Anatomic form | Alpha (A) | Restoration maintains continuity with dental surface |
| | Bravo (B) | Presence of sub-contour without dentin exposure |
| | Charlie (C) | Loss of material exposing dentin |
| Marginal adaptation | Alpha (A) | Continuity at the margin (without protrusion or gap) |
| | Bravo (B) | Small discontinuity detectable with explorer probe, but does not require replacement |
| | Charlie (C) | Marginal gap that requires replacement |
| Color alteration | Alpha (A) | The restoration appears to match the shade and translucency of adjacent tooth structure |
| | Bravo (B) | The restoration does not match the shade and translucency of adjacent tooth structure, but the mismatch is within the normal range of tooth shades |
| | Charlie (C) | The restoration does not match the shade and translucency of adjacent tooth structure, and the mismatch is outside the normal range of tooth shades and translucency |
| Marginal staining | Alpha (A) | There was no visual evidence of marginal discoloration different from the color of the restorative material and from the color of the adjacent tooth structure |
| | Bravo (B) | There was visual evidence of marginal discoloration at the junction of the tooth structure and the restoration that has not penetrated along the restoration |
| | Charlie (C) | There was visual evidence of marginal discoloration at the junction of the tooth structure and the restoration, and the discoloration has penetrated along the restoration |
| Retention | Alpha (A) | No loss of restorative material |
| | Bravo (B) | Restorative material was partially lost |
| | Charlie (C) | Absence of restorative material |
| Sensibility | Alpha (A) | Not present |
| | Charlie (C) | Present (constant sensitivity, not diminishing in intensity) |
| Adjacent caries | Alpha (A) | The restoration is a continuation of existing anatomic form adjacent to the restoration and there was no caries evidence |
| | Charlie (C) | There is visual evidence of dark, deep discoloration adjacent to the restoration |

Photographic documentation with a Digital Camera (EOS 60D Macro-Lens EF 100 mm f/2.8 USM) and Canon Flash Macro Ring Lite MR-14EX (Canon do Brasil Indústria e Comércio, São Paulo, SP, Brazil) with the aid of a photo mirror was performed before and after treatment and at all evaluation points.

### Statistical methods

The results were analyzed using SPSS software (Statistical Package for Social Sciences, IBM Inc., USA).

To analyze the distribution of the scores according to the modified USPHS criteria, the Kruskal-Wallis test was used ($p < 0.05$). Intention to treat analysis (ITT) was used to analyze the results.

## Results

A total of 68 subjects was examined and 26 was screened for the study. As root caries lesion was considered the experimental unit, a total of 63 lesions was screened but only 60 were included to randomization (Fig. 1). After allocation, they were distributed into the 3 groups: G1 = 10 participants in the baseline (n = 17 root caries lesions); G2 = 7 participants (n = 18 root caries lesions) and G3 = 6 participants (n = 25 root caries lesions). There were no observed or reported adverse reactions to the use of either product.

The changes in the modified USPHS are tabulated in Table 4. There were no statistically significance differences among the performance of the restoration among the three groups regarding the criteria retention, marginal adaptation, marginal staining, post-operative sensitivity, adjacent caries, color alteration, anatomic form and surface texture ($p > 0.05$).

Table 4
Distribution of scores according to the modified USPHS criteria for RMGIC restorations at all points evaluation

| Criteria | 1 month | | | 3 months | | | 6 months | | |
|---|---|---|---|---|---|---|---|---|---|
| | Control | Arginine | High-F | Control | Arginine | High-F | Control | Arginine | High-F |
| Anatomic form | | | | | | | | | |
| Satisfactory | 13 | 14 | 10 | 12 | 14 | 9 | 17 | 25 | 18 |
| Unsatisfactory | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 2 | 1 |
| p | *p = 0.440* | | | *p = 0.981* | | | *p = 0.941* | | |
| Marginal adaptation | | | | | | | | | |
| Satisfactory | 12 | 11 | 9 | 12 | 11 | 8 | 17 | 25 | 18 |
| Unsatisfactory | 1 | 4 | 1 | 1 | 4 | 2 | 4 | 6 | 1 |
| p | *p = 0.269* | | | *p = 0.562* | | | *0.282* | | |
| Color alteration | | | | | | | | | |
| Satisfactory | 13 | 12 | 9 | 13 | 12 | 8 | 17 | 25 | 18 |
| Unsatisfactory | 0 | 1 | 1 | 0 | 1 | 2 | 0 | 2 | 1 |
| p | *p = 0.555* | | | *p = 0.257* | | | *p = 0.826* | | |
| Marginal staining | | | | | | | | | |
| Satisfactory | 13 | 14 | 10 | 12 | 14 | 9 | 17 | 25 | 18 |
| Unsatisfactory | 0 | 1 | 0 | 1 | 1 | 1 | 2 | 2 | 1 |
| p | *p = 0.440* | | | *p = 0.981* | | | *p = 0.506* | | |
| Retention | | | | | | | | | |
| Satisfactory | 12 | 14 | 10 | 12 | 14 | 9 | 17 | 25 | 18 |
| Unsatisfactory | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 2 | 1 |
| p | *p = 0.751* | | | *p = 0.255* | | | *p = 0.941* | | |
| Sensibility | | | | | | | | | |
| Satisfactory | 13 | 15 | 10 | 13 | 15 | 9 | 17 | 25 | 18 |
| Unsatisfactory | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| p | *p = 1.00* | | | *p = 0.287* | | | *p = 0.941* | | |
| Caries adjacent restorations | | | | | | | | | |
| Satisfactory | 13 | 15 | 10 | 13 | 15 | 9 | 17 | 25 | 18 |
| Unsatisfactory | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| p | *p = 1.00* | | | *p = 0.287* | | | *p = 0.941* | | |

| Criteria | 1 month | | | 3 months | | | 6 months | | |
|---|---|---|---|---|---|---|---|---|---|
| | Control | Arginine | High-F | Control | Arginine | High-F | Control | Arginine | High-F |
| Anatomic form | | | | | | | | | |
| Satisfactory | 13 | 14 | 10 | 12 | 14 | 9 | 17 | 25 | 18 |
| Unsatisfactory | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 2 | 1 |

| Criteria | 1 month | | | 3 months | | | 6 months | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Arginine | High-F | Control | Arginine | High-F | Control | Arginine | High-F | | | | |
| p | *p = 0.440* | | | | | *p = 0.981* | | | | | *p = 0.941* | | |
| Marginal adaptation | | | | | | | | | | | | | |
| Satisfactory | 12 | | 11 | 9 | 12 | | 11 | | 8 | 17 | 25 | 18 | |
| Unsatisfactory | 1 | | 4 | 1 | 1 | | 4 | | 2 | 4 | 6 | 1 | |
| p | *p = 0.269* | | | | *p = 0.562* | | | | | *0.282* | | | |
| Color alteration | | | | | | | | | | | | | |
| Satisfactory | 13 | | 12 | 9 | 13 | | 12 | | 8 | 17 | 25 | 18 | |
| Unsatisfactory | 0 | | 1 | 1 | 0 | | 1 | | 2 | 0 | 2 | 1 | |
| p | *p = 0.555* | | | | *p = 0.257* | | | | | *p = 0.826* | | | |
| Marginal staining | | | | | | | | | | | | | |
| Satisfactory | 13 | | 14 | 10 | 12 | | 14 | | 9 | 17 | 25 | 18 | |
| Unsatisfactory | 0 | | 1 | 0 | 1 | | 1 | | 1 | 2 | 2 | 1 | |
| p | *p = 0.440* | | | | *p = 0.981* | | | | | *p = 0.506* | | | |
| Retention | | | | | | | | | | | | | |
| Satisfactory | 12 | | 14 | 10 | 12 | | 14 | | 9 | 17 | 25 | 18 | |
| Unsatisfactory | 1 | | 1 | 0 | 1 | | 1 | | 1 | 1 | 2 | 1 | |
| p | *p = 0.751* | | | | *p = 0.255* | | | | | *p = 0.941* | | | |
| Sensibility | | | | | | | | | | | | | |
| Satisfactory | 13 | | 15 | 10 | 13 | | 15 | | 9 | 17 | 25 | 18 | |
| Unsatisfactory | 0 | | 0 | 0 | 0 | | 0 | | 1 | 0 | 0 | 1 | |
| p | *p = 1.00* | | | | *p = 0.287* | | | | | *p = 0.941* | | | |
| Caries adjacent restorations | | | | | | | | | | | | | |
| Satisfactory | 13 | | 15 | 10 | 13 | | 15 | | 9 | 17 | 25 | 18 | |
| Unsatisfactory | 0 | | 0 | 0 | 0 | | 0 | | 1 | 0 | 0 | 1 | |
| p | *p = 1.00* | | | | *p = 0.287* | | | | | *p = 0.941* | | | |

## Discussion

A daily topical application of 1% neutral sodium F gel (5,000 ppm F) with custom-made F carriers and the use of neutral F-containing mouth rinses have demonstrated to be beneficial in preventing caries occurrence in irradiated patients [9, 28]; however, the compliance of patients to these protocols is poor because of the inconvenient method of application. The preference for any effective approach usually relies on a simpler, feasible preventive intervention that is easily applied at-home. Moreover, many patients with head-and-neck cancer are frequently debilitated [24] to use conventional toothpastes to brush their teeth followed by topical application of fluoride. On the other hand, toothbrushing with fluoridated toothpastes has been considered the most cost-beneficial tool as it combines the mechanical disruption of dental biofilm with additional F delivery that will act in demineralization and remineralization process [25].

Literature has shown benefits of using conventional fluoridated toothpastes in the prevention and treatments for dental caries in children and young adults [18]. Despite such advantages, its effect is influenced by F concentration and evidences until now suggest that high-F toothpaste provides better control on root caries lesions than conventional F-containing toothpaste [18]. According to Duane (2012), high-F toothpaste has a greater

impact on individuals at high-risk who do not use toothpaste regularly or do not brush their teeth twice a day, which highlights the importance to evaluate their effect in patients undergone radiotherapy [33]. The current clinical trial found no difference among the treatment groups ($p < 0.05$), i.e, our findings suggest that the use of 5,000 ppm F-containing toothpaste is similar to the remineralizing dentifrice (containing 1.5% arginine, Ca compound and conventional-F concentration) and conventional containing-toothpaste on preventing the development of root caries lesions around restorations in patients undergone radiotherapy, but reasons could influence such results.

Although all careful have been done to design this clinical trial, the course of the research showed a dropout rate of 24% after 6-month. Notwithstanding, we have performed the analysis considering the surface level to increase the power of the study. All efforts were made by the team to evaluate all participants and to find some of them who not returned for the evaluation points. Unfortunately, loss of follow-up was due to the worsening of the initial condition in relation to the cancer disease or death of the participants. For this reason, our follow-up period was limited to this feasible follow-up times. The effects of fluoride toothpaste are usually underestimated in 'short-term' clinical trials since the greater cumulative effect is conferred over time as fluoride toothpastes are used throughout life [34]. In addition, some authors believe that the use of fluoridated toothpaste in areas with community water fluoridation offers more protection than either alone [34].

To preserve a balance in prognostic factors achieved by randomization, which is important for avoiding selection bias and establishing causation, an intention-to-treat analysis (ITT) was conducted in the statistical analysis of this study. ITT keeps participants in the treatment groups to which they were randomized regardless of whether they withdraw following randomization as a strategy to maintain the integrity of randomization and strengthening the trial's internal validity [35].

Another point that should be addressed is that participants had all cavitated lesions restored at baseline, removing the present biofilm accumulated onto surfaces surrounding the cavities. Unlike some previous studies that evaluated primary root caries lesions, the objective of our clinical trial was to test the effectiveness the toothpastes on root caries lesions around RMGIC evaluating the performance of the restorations, which difficult comparisons with other studies. The current evidences shown that daily use of dentifrice containing 5,000 ppm F should be recommended for elderly patients as it presents more efficacious in reducing active root caries lesions than dentifrice containing 1,100 to 1,450 ppm F [36].

Similarly, a systematic review has also demonstrated that daily use of dentifrices containing 1.5% arginine plus 1,450 ppm F inactivates 21% more root caries lesions than patients using dentifrice containing 1,100 to 1,450 ppm F, although evidence level was graded as very low [36]. The main act mechanism of arginine-based toothpastes it to prevent caries development at an earlier stage, targeting the residual biofilm. Arginine metabolism is converted in ammonia, carbon dioxide and acetate which, in turn, neutralize biofilm acids after sugar challenge. Such effect in association with Ca ions provided by $CaCO_3$ presented in toothpaste composition inhibits mineral loss during low pH periods and repair it when pH returns to neutral conditions [37]. As mentioned elsewhere, despite such evidences regarding arginine-based toothpastes, it is difficult to compare the present trial with other studies, as they did not evaluate the development of root caries around restorations but focused on primary root caries lesions.

In this clinical trial, RMGIC was the restorative material of choice since it has been indicated to restore cervical and root caries lesions [14]. RMGIC presents bonding ability to the substrate, excellent coefficient of linear thermal expansion and of modulus of elasticity which is similar to that of the tooth [38]. They are also biocompatible, bioactive and releases F, besides of the formation of a good seal around the restoration, which provide an advantage in reducing the development of caries lesions adjacent to the restoration [38, 39]. Despite these properties of RMGIC, it is known that the effect of F-released and cariostatic action is as a result of its sustained release of F from other sources, such as toothpastes, since F toothpastes can interfere with caries lesion progression adjacent to dental materials [16]. In the present study, we expected that the constant use of high-F toothpaste would present better results in terms of retention, marginal staining, sensibility and caries adjacent to restorations since the ability of a restoration to act as a F reservoir is dependent on the type and permeability of filling material, the frequency of F exposure and concentration of F product [40].

Although the addition of fTCP to F toothpaste occurred to increase F-retention in the substrate and facilitate remineralization, the present results did not show more efficiency of this toothpaste for prevent root caries lesions in patients at high-risk. Other *in vitro* and *in situ* studies have also demonstrated that the effect of topical fluoride varnishes added or not with fTCP in enamel [41] or in high-F toothpastes in dentin presented similar results than conventional products to control dental caries [19]. This is relevant as the inclusion of biomaterials such as fTCP on toothpaste might not be a cost-benefit strategy. However, it was shown that toothpastes containing fTCP could be beneficial to repair active dentin caries lesions as these toothpastes act mainly in the subsurface layer [42] and, in a long-term process, their continuous using can be an interesting tool to patients at high-risk, but further clinical trials with greater follow-up than 6-month is need to evaluate it.

Finally, other factors may also have contributed to our findings. As patients were under treatment with a multidisciplinary team, they were constant instructed for diet by nutritionists to reduce the frequency of sugar intake. It should be noted that only the reestablishment of the habits in patients undergone radiotherapy of head-and-neck is not sufficiently able to control carious process as besides the indirect changes caused by radiation, radiation also leads to direct changes in biological and mechanical structures, which can imply in deleterious consequences to future tooth restorations.

Therefore, the interpretation of our results must be done with caution taking into consideration all these conditions related herein. Nevertheless, it is certainly that even with oral complications caused by radiotherapy of head-and-neck, if the restorations are properly performed and patients are

under professional control and supervised, conventional concentration toothpaste can be as effectiveness as high-F and arginine-based toothpastes to prevent secondary caries.

## Conclusion

High-fluoride toothpaste (5,000 ppm F) containing fTCP presented similar efficacy of arginine-based and conventional toothpastes to prevent the development of secondary caries around RMGIC ionomer cements restorations in patients undergone radiotherapy of head-and-neck in a 6-month follow-up.

## Declarations

**Funding:** 'N/A'

**Conflicts of interest/Competing interests:** Authors declare that there is no conflict of interest in this study.

**Availability of data and material:** The authors thank the volunteers for their participation, Audria Veronez, Sueli Ribeiro, Anderson Prestes and all team of the Clinical Research Center of the Bauru School of Dentistry for their technical support during the study. We also thank 3M-ESPE for the donation of all soft bristled adult toothbrush (CS 5460B, Curaprox) and Clinpro 5000 toothpastes used in this study.

**Code availability:** 'N/A'

**Ethics approval:** The study was approved by Human Ethics in Clinical Research Committees of the Bauru School of Dentistry and registered at the Registro Brasileiro de Ensaios Clínicos – REBEC website under the registration number U1111-1171-2738.

**Consent to participate:** all volunteers assigned for participate in this study

**Consent for publication:** 'N/A'

## References

1. Tan H, Richards L, Walsh T, Worthington HV, Clarkson JE, Wang L, Mattar de Amoedo Campos Velo M (2017) Interventions for managing root caries. The Cochrane Database of Systematic Reviews 2017(8):CD012750. https://doi.org/10.1002/14651858.CD012750
2. Ismail AI, Pitts NB, Tellez M, Benerjee A, Deery C, Douglas G et al (2015) The International Caries Classification and Management System (ICCMS™) an example of a caries management pathway. BMC Oral Health 15(Suppl 1):S9
3. Hussein AA, Helder MN, de Visscher JG et al (2017) Global incidence of oral and oropharynx cancer in patients younger than 45 years versus older patients: A systematic review. Eur J Cancer 82:115–127. doi:10.1016/j.ejca.2017.05.026
4. Smith GL, Smith BD (2014) Radiation treatment in older patients: a framework for clinical decision making. J Clin Oncol 32:2669–2678
5. Craddock HL (2006) Treatment and maintenance of a dentate patient with 'radiation caries'. Dent Update 33:462–468
6. Campos Velo MMA, Farha ALH, da Silva Santos PS, Shiota A, Sansavino SZ, Souza ATF, Honório HM, Wang L (2017) Gamma radiation increases the risk of radiation-related root dental caries. Oral Oncol 71:184–185. doi:10.1016/j.oraloncology.2017.06.007
7. Velo MMAC, Farha ALH, da Silva Santos PS et al (2018) Radiotherapy alters the composition, structural and mechanical properties of root dentin in vitro. Clin Oral Investig 22:2871–2878. doi:10.1007/s00784-018-2373-6
8. Kielbassa AM, Hinkelbein W, Hellwig E, Meyer-Lückel H (2006) Radiation-related damage to dentition. Lancet Oncol 7:326–335
9. Dreizen S, Daly TE, Drane JB, Brown LR (1977) Oral complications of cancer radiotherapy. Postgrad Med 61:85–92
10. Hong CH, Napeñas JJ, Hodgson BD et al (2010) A systematic review of dental disease in patients undergoing cancer therapy. Support Care Cancer 18:1007–1021
11. Kumar N (2019) The oral management of oncology patients requiring radiotherapy, chemotherapy and/or bone marrow transplantation – Clinical guidelines. R Coll Surg Engl/Br Soc Disabil Oral Heal 1–82
12. Fejerskov O (2004) Changing paradigms in concepts on dental caries: consequences for oral health care. Caries Res 38:182–191
13. Springer IN, Niehoff P, Warnke PH, Böcek G, Kovács G, Suhr M, Wiltfang J, Açil Y (2005) Radiation caries-radiogenic destruction of dental collagen. Oral Oncol 41:723–728
14. McComb D, Erickson RL, Maxymiw WG, Wood RE (2002) A clinical comparison of glass ionomer, resin-modified glass ionomer and resin composite restorations in the treatment of cervical caries in xerostomic head and neck radiation patients. Oper Dent 27:430–437
15. Rodrigues RB, Soares CJ, Junior PCS, Lara VC, Arana-Chavez VE, Novais VR (2018) Influence of radiotherapy on the dentin properties and bond strength. Clin Oral Investig 22:875–883
16. Hara AT, Turssi CP, Ando M, Gonzalez-Cabezas C, Zero DT, Rodrigues AL Jr et al (2006) Influence of fluoride-releasing restorative material on root dentine secondary caries in situ. Caries Res 40:435–439

17. Cury JA, de Oliveira BH, dos Santos AP, Tenuta LM (2016) Are fluoride releasing dental materials clinically effective on caries control? Dent Mater 32:323–333. doi:10.1016/j.dental.2015.12.002
18. Walsh T, Worthington HV, Glenny AM, Appelbe P, Marinho VC, Shi X (2010) Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. Cochrane Database Syst Ver:CD007868. https://doi.org/10.1002/14651858. CD007868
19. de Amoêdo Campos Velo MM, Agulhari MAS, Rios D, Magalhães AC, Honório HM, Wang L (2020) Root caries lesions inhibition and repair using commercial high-fluoride toothpastes with or without tri-calcium phosphate and conventional toothpastes containing or not 1.5% arginine $CaCO_3$: an in situ investigation. Clin Oral Investig 24:2295–2304. doi:10.1007/s00784-019-03084-8
20. Baysan A, Lynch E, Ellwood R, Davies R, Petersson L, Borsboom P (2001) Reversal of primary root caries using dentifrices containing 5,000 and 1,100 ppm fluoride. Caries Res 35:41–46
21. Ekstrand KR, Poulsen JE, Hede B, Twetman S, Qvist V, Ellwood RP (2013) A randomized clinical trial of the anti-caries efficacy of 5,000 compared to 1,450 ppm fluoridated toothpaste on root caries lesions in elderly disabled nursing home residents. Caries Res 47:391–398
22. Buzalaf MA, Pessan JP, Honório HM, ten Cate JM (2011) Mechanisms of action of fluoride for caries control. Monogr Oral Sci 22:97–114
23. Jansma J, Vissink A, Gravenmade EJ, Visch LL, Fidler V, Retief DH (1989) In vivo study on the prevention of postradiation caries. Caries Res 23:172–178
24. Thariat J, Ramus L, Darcourt V et al (2012) Compliance with fluoride custom trays in irradiated head and neck cancer patients. Support Cancer Care 20:1811–1814
25. Rølla G, Ogaard B, Cruz RA (1991) Clinical effect and mechanism of cariostatic action of fluoride containing toothpastes: a review. Int Dent J 11:442–447
26. Karlinsey RL, MacKey AC, Walker ER, Frederick KE (2010) Surfactant-modified -TCP: structure, properties, and in vitro remineralization of subsurface enamel lesions. J Mat Sci 21:2009–2020
27. Karlinsey RL, Pfarrer AM (2012) Fluoride plus functionalized b-TCP: a promising combination for robust remineralization. Adv Dent Res 24:48–52
28. Philip N (2019) State of the art enamel Remineralization systems: the next frontier in caries management. Caries Res 53:284–295
29. Cummins D (2016) The superior anti-caries efficacy of fluoride toothpaste containing 1.5% arginine. J Clin Dent 27:27–38
30. Wolff M, Corby P, Klaczany G et al (2013) In vivo effects of a new dentifrice containing 1.5% arginine and 1450 ppm fluoride on plaque metabolism. J Clin Dent 24 Spec no A:A45-A54
31. Souza ML, Cury JA, Tenuta LM et al (2013) Comparing the efficacy of a dentifrice containing 1.5% arginine and 1450 ppm fluoride to a dentifrice containing 1450 ppm fluoride alone in the management of primary root caries. J Dent 41(Suppl 2):S35–S41
32. Schulz KF, Altman DG, Moher D (2010) Consort 2010 statement:updated guidelines for reporting parallel group randomized trials. Ann Intern Med 152:726–732
33. Duane B (2012) 5,000 ppm F dentifrice for caries prevention in adolescents. Evid Based Dent 13:43–44
34. Walsh T, Worthington HV, Glenny AM, Marinho VC, Jeroncic A (2019) Fluoride toothpastes of different concentrations for preventing dental caries. Cochrane Database Syst Rev 3(3):CD007868. doi:10.1002/14651858.CD007868.pub3 Published 2019 Mar 4.
35. Polit DF, Gillespie BM (2010) Intention-to-treat in randomized controlled trials: recommendations for a total trial strategy. Res Nurs Health 33:355–368
36. Wierichs RJ, Meyer-Lueckel H (2015) Systematic review on noninvasive treatment of root caries lesions. J Dent Res 94:261–271
37. Cummins D (2013) The development and validation of a new technology, based upon 1.5% arginine, an insoluble calcium compound and fluoride, for everyday use in the prevention and treatment of dental caries. J Dent 41:S1–S11
38. Wilson AD (1990) Resin-modified glass-ionomer cements. Int J Prosthodont 3(5):425–429
39. Sidhu SK, Nicholson JW (2016) A review of glass-ionomer cements for clinical dentistry. J Funct Biomater 7:16
40. Wiegand A, Buchalla W, Attin T (2007) Review on fluoride-releasing restorative materials-fluoride release and uptake characteristics, antibacterial activity and influence on caries formation. Dent Mater 23:343–362
41. Mohd Said SN, Ekambaram M, Yiu CK (2017) Effect of different fluoride varnishes on remineralization of artificial enamel carious lesions. Int J Paediatr Dent 27:163–173
42. Balakrishnan A, Jonathan R, Benin P, Kuumar A (2013) Evaluation to determine the caries remineralization potential of three dentifrices: an in vitro study. J Conserv Dent 16:375–379. doi:10.4103/0972-0707.114347

## Figures

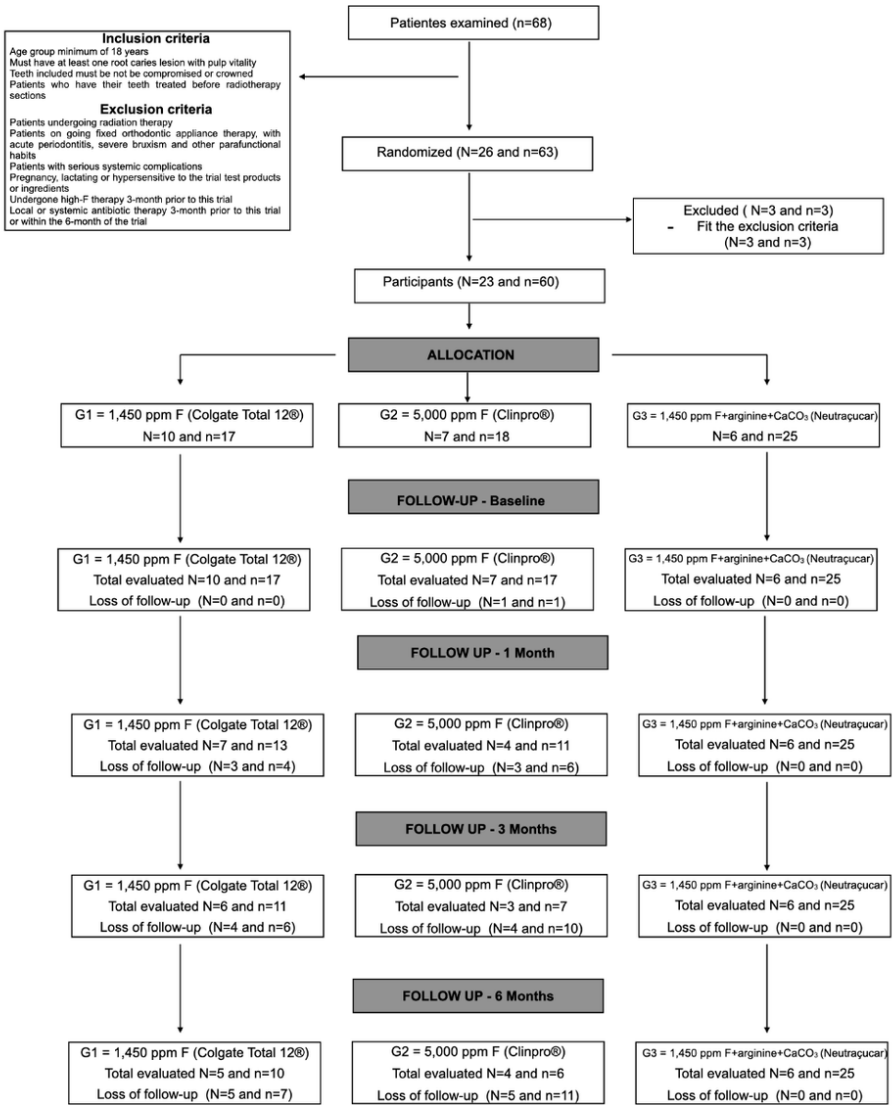


**Figure 1**

A flowchart of the study based on CONSORT for clinical trials. N= individuals; n= root caries. Note: Reasons for loss or follow-up: participants who changed status or gave up participating in the survey.